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HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution

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Special Report 23

Health Effects Institute

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ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the Institute

- Identifies the highest-priority areas for health effects research
- Competitively funds and oversees research projects
- Provides intensive independent review of HEI-supported studies and related research
- Integrates HEI's research results with those of other institutions into broader evaluations
- Communicates the results of HEI's research and analyses to public and private decision makers.

HEI typically receives balanced funding from the U.S. Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 340 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 260 comprehensive reports published by HEI, as well as in more than 2,500 articles in the peer-reviewed literature.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Review Committee (or in this case, the HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution) are widely disseminated through HEI's website (*www.healtheffects.org*), reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

CONTRIBUTORS

In 2018, the Board of Directors of the Health Effects Institute (HEI) appointed an expert Panel to review the scientific literature on traffic-related air pollution and health. The Panel consisted of scientists from a variety of disciplines and was co-chaired by Francesco Forastiere, Imperial College London, and Frederick Lurmann, Sonoma Technology, Inc., Petaluma, California. During the course of the review, consultants to the Panel were added. In addition, HEI hired a contractor team at the Swiss Tropical and Public Health Institute, Switzerland, to execute certain parts of the review. HEI is indebted to the Panel, the consultants to the Panel, and contract team for their expertise, cooperation, and enthusiasm. A draft of the resulting report was submitted for outside peer review.

HEI PANEL ON THE HEALTH EFFECTS OF LONG-TERM EXPOSURE TO TRAFFIC-RELATED AIR POLLUTION

Francesco Forastiere (co-chair) *Visiting Professor, Environmental Research Group, School of Public Health, Faculty of Medicine, Imperial College London, United Kingdom*

Frederick Lurmann (co-chair) *Manager of Exposure Assessment Studies, Sonoma Technology, Inc., Petaluma, California*

Richard Atkinson *Professor of Epidemiology, Population Health Research Institute, St. George's, University of London, United Kingdom*

Jeffrey Brook *Assistant Professor, Occupational and Environmental Health Division, Dalla Lana School of Public Health, University of Toronto, Canada; HEI Research Committee*

Howard Chang *Professor, Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, Georgia*

Gerard Hoek *Associate Professor, Institute for Risk Assessment Sciences, Environmental Epidemiology, Utrecht University, the Netherlands*

Barbara Hoffmann *Professor of Environmental Epidemiology, Institute of Occupational, Social, and Environmental Medicine, Heinrich Heine University Düsseldorf, Germany; HEI Research Committee*

Sharon Sagiv *Associate Adjunct Professor of Epidemiology, Center for Environmental Research and Children's Health, Division of Epidemiology, University of California, Berkeley School of Public Health, Berkeley, California*

Evangelia Samoli *Associate Professor of Epidemiology and Medical Statistics, Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Greece; HEI Research Committee*

Audrey Smargiassi *Associate Professor, Department of Environmental and Occupational Health, School of Public Health, University of Montreal, Quebec, Canada*

Adam Szpiro *Associate Professor of Biostatistics, Department of Biostatistics, University of Washington, Seattle*

Danielle Vienneau *Assistant Professor (Habilitation), Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Switzerland; and University of Basel, Switzerland*

Jennifer Weuve *Associate Professor, Department of Epidemiology, Boston University School of Public Health, Massachusetts*

CONSULTANTS TO THE PANEL

Julia Fussell *Senior Research Fellow, School of Public Health, Imperial College London, United Kingdom*

Frank Kelly *Humphrey Battcock Chair of Environment and Health, School of Public Health, Imperial College London, United Kingdom; HEI Review Committee*

Tim Nawrot *Professor Environmental Epidemiology, Centre for Environmental Sciences, Hasselt University, Belgium*

Gregory Wellenius *Professor of Environmental Health, Boston University School of Public Health, Massachusetts; HEI Research Committee*

Contributors continued

HEI SCIENCE STAFF

Hanna Boogaard *Project Leader, Consulting Principal Scientist*
Allison Patton *Deputy Project Leader, Senior Scientist*
Dan Crouse *Wheeze Outcomes, Senior Scientist*
Eleanne van Vliet *Term Birth Weight, Staff Scientist*
Martha Ondras *Neurological Outcomes, Research Fellow*
Eva Tanner *Peer-Review Process, Staff Scientist*
Dan Greenbaum *President*
Rashid Shaikh *Director of Science Emeritus*
Ellen Mantus *Director of Science*
Annemoon van Erp *Deputy Director of Science*

HEI EDITORIAL STAFF

Kristin Eckles *Senior Editorial Manager*
Hope Green *Editorial Project Manager*
Carol Moyer *Lead Consulting Editor*
Mary Brennan *Consulting Editor*
William Fogle *Consulting Editor*

CONTRACTOR TEAM

Meltem Kutlar Joss, Ron Kappeler, and students Lara Stucki, Zoe Roth, and Elina Wüthrich under the supervision of Professor Nino Künzli, Swiss Literature Database and Services on Health Effects of Ambient Air Pollution (LUDOK), Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, University of Basel, Switzerland, as well as students Leonie Hoffmann and Pascale Haddad under the supervision of Professor Barbara Hoffmann. We would also like to thank Alan da Silveira Fleck and Margaux Sadoine under the supervision of Dr. Audrey Smargiassi.

PEER REVIEWERS—FULL REPORT

Bert Brunekreef (chair) *Emeritus Professor of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, the Netherlands*

Haneen Khreis *Senior Research Associate, MRC Epidemiology Unit, University of Cambridge, United Kingdom*

Michael Jerrett *Professor and Chair, Department of Environmental Health Sciences, Fielding School of Public Health, University of California–Los Angeles, California; HEI Review Committee*

Susan Norris *Department of Family Medicine, Oregon Health & Science University, Portland, Oregon*

Annette Peters *Chair of Epidemiology, Director of the Institute of Epidemiology, Helmholtz Zentrum München, Germany*

Neil Pearce *Professor of Epidemiology and Biostatistics, London School of Hygiene and Tropical Medicine, United Kingdom; HEI Research Committee*

Marie Pedersen *Associate Professor, Department of Public Health, Section of Epidemiology, University of Copenhagen, Denmark*

David Savitz *Professor of Epidemiology, School of Public Health, and Professor of Obstetrics and Gynecology, Alpert Medical School, Brown University; Chair, HEI Research Committee*

Jay Turner *Vice Dean for Education and James McKelvey Professor of Engineering Education, Washington University in St. Louis, Missouri*

PEER REVIEWERS—SPECIFIC CHAPTERS

Chad R. Bailey *U.S. EPA Office of Transportation and Air Quality, Ann Arbor, Michigan*

David Carslaw *Wolfson Atmospheric Chemistry Laboratories, University of York, United Kingdom*

Flemming Cassee *Professor, Chief Science Officer, National Institute for Public Health and the Environment, the Netherlands*

David E. Foster *Phil and Jean Myers Professor Emeritus, University of Wisconsin–Madison, Wisconsin*

Mark Frampton *Professor Emeritus, Department of Medicine, Pulmonary Diseases and Critical Care, University of Rochester Medical Center, New York*

Mònica Guxens *Associate Research Professor, Barcelona Institute for Global Health, Spain*

Michael Kleeman *Professor, Department of Civil and Environmental Engineering, University of California–Davis, California*

Nick Molden *Founder and CEO Emissions Analytics, Stokenchurch, United Kingdom*

Marc Weisskopf *Cecil K. and Philip Drinker Professor of Environmental Epidemiology and Physiology, Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts*

EXECUTIVE SUMMARY

INTRODUCTION

Motor vehicles are a significant source of urban air pollution and are important contributors of anthropogenic carbon dioxide and other greenhouse gases.

Traffic-related air pollution (TRAP*) is a complex mixture of gases and particles resulting from the use of motor vehicles including heavy-duty and light-duty vehicles, buses, passenger cars, and motorcycles. Motor vehicles emit a variety of pollutants including nitrogen oxides (NO_x), elemental carbon (EC), particulate matter ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$), ultrafine particles (UFPs), heavy metals, polycyclic aromatic hydrocarbons, and volatile organic compounds. When emitted through vehicle exhaust, these pollutants are called *tailpipe emissions.* When emitted by other means, such as evaporative emissions of fuel, the resuspension of dust, the wear of brakes and tires, and the abrasion of road surfaces, they are called *nontailpipe emissions*.

Tailpipe emissions from motor vehicles and ambient concentrations of most monitored traffic-related pollutants have decreased steadily over the last several decades in most high-income countries. This trend is a result of air quality regulations and improvements in vehicular emission-control technologies and is likely to continue (Frey 2018). However, decreases in emissions from individual motor vehicles, while substantial, do not fully compensate for the rapid growth and increased vehicular congestion of the motor vehicle fleet due to population growth, urbanization, and economic activity, as well as to the continued presence of older or malfunctioning vehicles on the roads. The adoption of new technologies such as electric vehicles—while promising alleviation of some components of TRAP—has been relatively slow so far due to the slow development and cost of battery technology and infrastructure, electricity decarbonization, nontailpipe emissions mitigation, and fleet turnover (Khreis et al. 2020). However, their sale is growing rapidly as technical and infrastructural barriers are overcome, and government policies and manufacturers' pledge to boost their adoption come to fruition.

Interest in the contribution of nontailpipe emissions to air quality and health is increasing in most high-income countries as vehicle miles traveled increase and regulations continue to be targeted almost exclusively to tailpipe emissions. For the foreseeable future, a substantial number of people globally will continue to be exposed to tailpipe and nontailpipe TRAP, especially in urban settings and residences in proximity to busy roadways.

The rate at which vehicle emissions disperse into ambient air depends on multiple factors that are highly variable, including wind speed, wind direction, atmospheric stability, and terrain and land use. In addition, air pollution from other sources—such as industry, oil, coal and wood burning, and agricultural sources as well as atmospheric transport of pollutants from distant sources—contributes to the overall air quality. The results of these emissions are elevated concentrations of air pollutants through primary emissions and through the formation of secondary pollutants, such as secondary PM and ozone. People are exposed to these air pollutants when outdoors or indoors through the infiltration of outdoor air pollutants. Human exposures are also determined by various dynamic factors such as mobility patterns and distance from the source.

In 2010, HEI published Special Report 17, *Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects*. This review, developed by the HEI Panel on the Health Effects of Traffic-Related Air Pollution, summarized and synthesized research on emissions, exposure, and health effects from TRAP and drew conclusions about whether the associations between exposure and health outcomes were causal. The Panel reviewed both toxicological and epidemiological evidence. At that time, the Panel

* A list of abbreviations appears at the end of this Executive Summary. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

concluded that the evidence was sufficient to support a causal relationship between exposure to TRAP and exacerbation of asthma in children. The Panel also found suggestive evidence of a causal relationship with the onset of childhood asthma, nonasthma respiratory symptoms in adults, impaired lung function in children and adults, all-cause and cardiovascular mortality, and cardiovascular morbidity. For a number of other health outcomes, there was only limited evidence of associations, and the data were deemed to be either inadequate or insufficient to draw firmer conclusions (HEI 2010).

Since HEI published its review in 2010, many additional studies investigating the health effects of exposure to TRAP have been published, and regulations and vehicular technology have advanced significantly. In addition, there is a better appreciation that, beyond air pollution, traffic can be a source of other exposures with potential relevance to health, most notably noise. These exposures may either confound or modify the health effects of TRAP, which continues to be of public health interest and is of concern to policy makers and motor vehicle manufacturers alike. Therefore, in response to broad interest from its sponsors, HEI decided to conduct a new literature review, as described in HEI's Strategic Plan 2015–2020 (HEI 2015) and reconvened the Panel with new members to conduct the review. The new Panel consisted of 13 experts in epidemiology, exposure assessment, and statistics at institutions in North America and Europe. The resulting Special Report was subjected to detailed peer review. This review is the largest systematic effort to date that evaluates the epidemiological evidence regarding the associations between long-term exposure to TRAP and selected adverse health outcomes.

OBJECTIVE

The overall objective of this Special Report was to systematically evaluate the epidemiological evidence regarding the associations between long-term exposure to TRAP and selected adverse health outcomes. Results were quantitatively combined to evaluate the strength of the evidence, where appropriate. The Panel was charged with drawing conclusions about the confidence in the quality of the body of evidence and with assessing the level of confidence in the presence of an association. The Panel did not assess causality because they did not conduct separate, independent systematic assessments of the mechanistic, toxicological, and human clinical studies relating TRAP to human health. For these reasons, the descriptors of the overall confidence assessment still mention *association* rather than causal association, causal relationship, or effect.

The Special Report describes the methodology and findings from the systematic review of the epidemiological evidence, discusses the strengths and limitations of the evidence base and makes recommendations for future research. In addition to the systematic review of the epidemiological evidence, the Special Report features a section that addresses some important issues related to technologies and emissions from motor vehicles, including a high-level, succinct review on the mechanistic evidence of health effects of exposure to TRAP, and summarizes the health effects of short-term exposure to TRAP. This information, which is not included in this summary, is meant to provide background material and serve as complementary and supporting evidence to the systematic review on the health effects of long-term exposure to TRAP.

GENERAL METHODS

The Panel used a rigorous and systematic approach to search the literature, select studies for inclusion in the review, assess study quality, summarize results, and reach conclusions about the confidence in the body of evidence. The Panel's approach was largely based on standards set by Cochrane, the World Health Organization (WHO), and the National Institute of Environmental Health Sciences. To this end, a review protocol was published in 2019 (HEI 2019) and registered in Prospero, a registry of systematic reviews (*https://www.crd.york.ac.uk/prospero/*).

Health outcomes were selected by the Panel based on evidence of causality (causal or likely causal), according to the latest determination for general air pollution (broader than TRAP) from available authoritative integrated science assessments and other considerations such as relevance for public health and policy. Selected health outcomes were clinical (rather than preclinical) outcomes and included birth outcomes (e.g., term low birth weight), respiratory outcomes (e.g., asthma onset), cardiometabolic outcomes (e.g., ischemic heart disease [IHD] and diabetes) and all-cause and cause-specific (e.g., circulatory, respiratory) mortality.

A PECOS question (Population, Exposure, Comparator, Outcome and Study) was developed, and then inclusion and exclusion criteria were listed for each PECOS domain in relation to the selected health effects of long-term exposure to TRAP. The focus of the review was on health effects observed in the general population. Cohort, case-control, cross-sectional, and intervention studies using individual-level health outcome data were included.

An extensive search was conducted of literature published between January 1980 and July 2019. Studies were checked for eligibility by two reviewers. Data from all included studies were extracted and evaluated extensively, including key information for meta-analysis. Effect estimates from single-pollutant models were selected as the effect estimates for the meta-analysis. In this review multipollutant models were of less interest as the aim was to assess the TRAP mixture, not individual components. A random-effects meta-analysis was performed when at least three studies were available for a specific exposure–outcome pair. The Panel decided to use the pollutant concentration increments from the ESCAPE

study to reflect a realistic range of exposure contrasts in most studies (Beelen et al. 2014, 2015). Forest plots with meta-analysis estimates were produced, where appropriate. In the Special Report, the forest plots are accompanied by summary tables with important information on the studies. Risk of bias was assessed for all exposure–outcome associations that were included in the meta-analyses using a modified version of the tool developed for the risk of bias assessment in the WHO Air Quality Guidelines review (WHO 2020, 2021). Where possible, additional analyses were performed to assess consistency in subgroups of studies, for example, across geographic region, time period, risk of bias, and confounder adjustment for individual-level behavioral factors (i.e., smoking). An adapted GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment of the confidence in the quality of the body of evidence was made using the Office of Health Assessment and Translation (OHAT) method as a guide (OHAT 2019). The OHAT confidence rating was heavily geared toward the studies entering a meta-analysis. The Panel thought it was prudent to accompany the OHAT assessment with a broader approach and developed a narrative assessment to evaluate the level of confidence in the presence of an association, considering the meta-analyzed studies as well as other studies not entering the meta-analysis. The findings based on the narrative assessment and the modified OHAT assessment were combined into an overall confidence assessment, with the two approaches considered complementary.

In addition to the systematic review of the selected health outcomes described earlier, literature reviews were developed for neurodevelopmental outcomes in children and dementia-related outcomes and Parkinson disease in adults. Those literature reviews were added because the Panel thought these were important emerging areas that should be represented in the Special Report, even while a larger body of evidence develops. The literature review differs from the systematic review in some important respects: (1) no meta-analyses were conducted, (2) there was no evaluation of the confidence in the quality of the body of evidence, and (3) there was no formal risk of bias assessment on individual studies. Hence, those findings are not included in this Executive Summary.

EXPOSURE-ASSESSMENT FRAMEWORK

Exposure assessment of TRAP is challenging because it is a complex mixture of PM and gaseous pollutants and is characterized by high spatial and temporal variability. Building on the 2010 HEI Traffic Review, which identified the exposure assessment as a significant limitation in the then-current literature, the Panel developed a novel exposure framework to define transparently which studies assessed TRAP and are therefore eligible for inclusion in the current review.

The exposure-assessment framework included three strategies to determine whether a study was sufficiently traffic-specific, namely the selection of traffic-related pollutants, the exposure-assessment method, and the spatial resolution. None of the selected pollutants is fully traffic-specific and therefore the additional requirements outlined in this summary were needed.

Broadly, emissions from motorized traffic may affect air quality at the local, neighborhood, urban, and regional scale. The Panel judged, however, that epidemiological studies focusing on exposure contrasts at the local and neighborhood scale offered the greatest potential in determining exposure derived from TRAP emissions. The Panel included studies that evaluated exposure to nitrogen dioxide (NO_2), EC (which includes studies using related metrics such as black carbon, black smoke, and PM absorbance), carbon monoxide, UFPs, and other pollutants, and indirect traffic measures (distance and density), as well as $PM_{2.5}$ and PM ≤10 µm in aerodynamic diameter (PM_{10}). For studies that evaluated exposure to $PM_{2.5}$ and PM_{10}, more stringent requirements for inclusion were needed regarding exposure assessment and study setting to indicate that the exposure contrasts were likely due to variation in traffic emissions. For example, the Panel excluded studies that were solely based on monitoring data. The Panel also excluded nationwide studies on any pollutant where the primary exposure contrast was due to between-cities variations, rather than within cities.

In addition, the Panel developed a traffic specificity indicator (high or moderate) based on stricter criteria for the three elements of the general framework. For example, all $PM_{2.5}$ and PM_{10} studies were considered as having moderate (as opposed to high) traffic specificity. Furthermore, the spatial scale of the pollution surface needed to be within 1 km for high traffic specificity as opposed to only 5 km for the study to be included in the review. The majority of studies that were included based on the general exposure framework also met the stricter high traffic specificity criteria. The Panel developed two tiers of criteria because it initially thought that only one tier—based on a highly strict set of criteria—would be too restrictive, leading to fewer studies for assessment. The Panel concluded that the fact most studies satisfied the stricter criteria is reassuring and lends confidence to knowing the exposure framework successfully identified studies that are informative of the impact of TRAP on the selected health outcomes.

MAIN FINDINGS OF THE SYSTEMATIC REVIEW

The number of studies on long-term exposure to TRAP and health outcomes included in this review has more than tripled compared with the 2010 HEI Traffic Review (HEI 2010), although a direct comparison is difficult because of the difference in scope, methods, and criteria for study inclusion.

In total, 353 studies were included in the review. Respiratory effects in children (*N* = 118 studies, 33%) and birth outcomes (*N* = 86 studies, 24%) were the most common outcomes. Fewer studies investigated cardiometabolic effects (*N* = 57 studies, 16%), respiratory effects in adults (*N* = 50 studies, 14%), and mortality (*N* = 48 studies, 13%). Studies were conducted in populations residing in a wide range of countries, although the majority were done in Europe (*N* = 163 studies, 46%), and North America (*N* = 130 studies, 37%). Studies in Asia (predominantly China) emerged more recently (*N* = 41 studies, 12%). More TRAP studies in low- and middle-income countries are needed.

Most meta-analyses by outcome involved NO_2 as the most commonly studied TRAP exposure indicator, followed by EC and $PM_{2.5}$. Few studies were identified for some pollutants, in particular nontailpipe PM indicators and UFPs, and such studies were identified as a future research need.

The results of the meta-analyses of associations between long-term exposure to the most commonly studied TRAP exposure indicators (NO_2, EC, and $PM_{2.5}$) and selected health outcomes are displayed in the Executive Summary Table. We use the term *relative risk* to describe effect estimates as it is easier to communicate, even if in some of the included studies it would be technically more correct to refer to an odds ratio, or hazard ratio. The following are important considerations while reviewing the results: (1) although the results are presented by pollutant, the individual pollutants are considered indicators of the TRAP mixture; (2) effect estimates cannot be compared directly across traffic-related pollutants because selected increments do not necessarily represent the same contrast in exposure; and (3) studies included in a meta-analysis represent only about half of all studies considered for various reasons, such as when multiple studies conducted in the same population, less than three studies were available for a particular exposure–outcome pair, or definitions of indirect traffic measures varied across studies. Thus, the Panel did not pursue meta-analyses of indirect traffic measures. Despite not being included in the meta-analyses, the remaining studies added important information to the overall confidence assessment.

The Executive Summary Figure and Table provide for each health outcome the overall level of confidence in an association with long-term exposure to TRAP. This overall confidence assessment is a combination of the narrative assessment and the modified OHAT assessment. Detailed descriptors of the overall confidence assessment evidence are listed in the Executive Summary Sidebar.

The Panel found a high or moderate-to-high level of confidence in an association between long-term exposure to TRAP and the adverse health outcomes all-cause, circulatory, ischemic heart disease (IHD), and lung cancer mortality; asthma onset in both children and adults; and acute lower respiratory infections (ALRI) in children. The Panel's confidence in the evidence was considered moderate, low, or very low for the other selected outcomes. The main findings for each broad health outcome category are described in the following sections.

BIRTH OUTCOMES

The summary estimates showed that $PM_{2.5}$ exposure over the entire pregnancy is most clearly associated with measures of fetal growth restriction. The summary relative risk was 1.11 (95% confidence interval [CI]: 1.03 to 1.20) for term low birth weight and 1.09 (1.04 to 1.14) for small for gestational age, and a mean difference in term birth weight of −17.3 (−33.2 to −1.5) grams per 5-μg/m^3. The $PM_{2.5}$ associations were supported by consistent associations with PM_{10} as well. Associations for preterm birth were largely null, although a few studies of traffic-PM and indirect traffic measures (distance and density) supported an association. Associations for the other meta-analyzed traffic-related air pollutants—including NO_2, NO_x, and EC—were mostly null for all four birth outcomes, with the exception of an association of NO_x with term low birth weight. Studies that were not included in the meta-analyses broadly agreed with the summary estimates for the various pollutants.

The majority of TRAP studies and birth outcomes were conducted in North America and Europe. Most used a cohort study design and registry data and therefore lacked potentially important confounder information on lifestyle factors, such as maternal smoking during pregnancy and prepregnancy body mass index. As a result, those studies were rated high risk of bias for potential confounding, which reduced confidence in the quality of the body of evidence, particularly for term birth weight and preterm birth.

The Panel concluded that there was an overall moderate level of confidence in the evidence for an association between TRAP exposure and term low birth weight (categorical outcome) and small for gestational age, and a low level of confidence for term birth weight (continuous outcome) and preterm birth.

RESPIRATORY OUTCOMES

The summary estimates for NO_2 per 10-μg/m^3 were 1.05 (95% CI: 0.99–1.12) for asthma onset in children, 1.10 (1.01–1.21) for asthma onset in adults, and 1.09 (1.03–1.16) for ALRI in children.

For these outcomes, positive associations were also reported for other traffic-related air pollutants, either in meta-analyses or in single large studies. Most of the studies had a cohort design, were conducted in different populations, and were at a low or moderate risk of bias.

The Panel concluded that the overall level of confidence in the evidence for an association between exposure to TRAP and asthma onset in both children and adults and ALRI in children was considered moderate to high. Studies examining

Executive Summary Table. Overall Confidence Assessment and Meta-analytical Summary Estimates of Associations Between Long-Term Exposure to the Most Common Traffic-Related Air Pollutants (NO_2, EC, $PM_{2.5}$) and Health Outcomes (NOTE: the individual pollutants are considered indicators of TRAP)

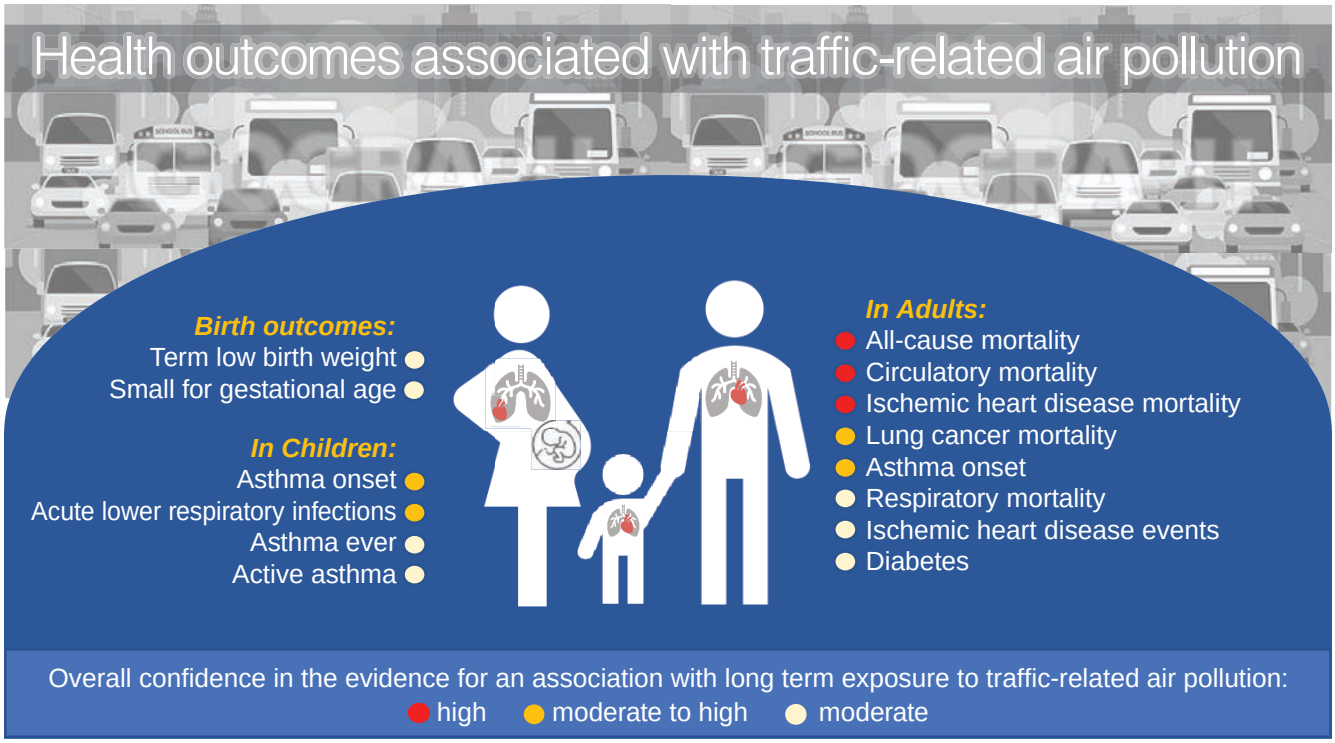
Health Outcome	Overall Confidence Assessment	NO_2 per 10-μg/m³		EC per 1-μg/m³		$PM_{2.5}$ per 5-μg/m³	
		N	Relative Risk (95% CI)	*N*	Relative Risk (95% CI)	*N*	Relative Risk (95% CI)
Birth Outcomes							
Term low birth weight	Moderate	12	1.01 (0.99–1.03)	5	1.01 (0.99–1.04)	7	1.11 (1.03–1.20)
Term birth weight	Low	8	−3.2 (−11.0 to 4.6)[a]	4	−2.6 (−6.1 to 0.9)[a]	6	−17.3 (−33.2 to −1.5)[a]
Small for gestational age	Moderate	11	1.00 (0.98–1.02)	3	1.02 (0.92–1.14)	4	1.09 (1.04–1.14)
Preterm birth	Low	14	1.00 (0.96–1.04)	5	1.02 (0.97–1.07)	4	0.99 (0.90–1.09)
Respiratory Outcomes—Children							
Asthma onset[b]	Moderate to high	12	1.05 (0.99–1.12)	5	1.11 (0.94–1.31)	5	1.33 (0.90–1.98)
Asthma ever[c]	Moderate	21	1.09 (1.01–1.18)	3	1.30 (0.56–3.04)	3	1.29 (0.58–2.87)
Active asthma[c]	Moderate	12	1.12 (1.02–1.23)	3	1.25 (0.98–1.59)	<3	NA
ALRI[b]	Moderate to high	11	1.09 (1.03–1.16)	4	1.30 (0.78–2.18)	<3	NA
Respiratory Outcomes—Adults							
Asthma onset[b]	Moderate to high	7	1.10 (1.01–1.21)	<3	NA	<3	NA
ALRI[b]	Very low to low	3	1.07 (0.71–1.61)	<3	NA	<3	NA
COPD[b]	Low	7	1.03 (0.94–1.13)	<3	NA	4	0.91 (0.62–1.36)
Cardiometabolic Outcomes							
IHD events[b]	Moderate	5	0.99 (0.94–1.05)	5	1.01 (0.99–1.03)	4	1.09 (0.86–1.39)
Coronary events[b]	Low	7	1.03 (0.95–1.11)	<3	NA	<3	NA
Stroke events[b]	Low to moderate	7	0.98 (0.92–1.05)	6	1.03 (0.98–1.09)	4	1.08 (0.89–1.32)
Diabetes[b]	Moderate	7	1.04 (0.96–1.13)	3	1.16 (0.57–2.36)	4	1.05 (0.96–1.15)
Diabetes[c]		7	1.09 (1.02–1.17)	<3	NA	3	1.08 (0.70–1.67)
Mortality							
All-cause	High	11	1.04 (1.01–1.06)	11	1.02 (1.00–1.04)	12	1.03 (1.01–1.05)
Circulatory	High	10	1.04 (1.00–1.09)	9	1.02 (1.00–1.04)	11	1.04 (1.01–1.08)
Respiratory	Moderate	8	1.05 (1.00–1.09)	8	1.01 (0.98–1.05)	7	1.03 (0.97–1.10)
Lung cancer	Moderate to high	5	1.04 (1.01–1.07)	3	1.02 (0.88–1.19)	6	1.06 (0.99–1.13)
IHD	High	6	1.05 (1.03–1.08)	6	1.05 (0.99–1.11)	7	1.07 (1.04–1.10)
Stroke	Low to moderate	6	1.01 (0.98–1.04)	<3	NA	3	1.04 (1.01–1.07)
COPD	Low	3	1.03 (1.00–1.05)	<3	NA	<3	NA

95% CI = 95% confidence interval; ALRI = acute lower respiratory infection; COPD = chronic obstructive pulmonary disease; IHD = ischemic heart disease; NA = not applicable.

[a] Mean difference in grams.

[b] Incidence.

[c] Prevalence.



Executive Summary Figure. Overall confidence in the evidence for an association between long-term exposure to TRAP and selected health outcomes. Health outcomes for which the overall confidence in the evidence was low to moderate, low, or very low are not in the figure.

exposure to NO_2 have made the greatest contribution to this evaluation. The overall level of confidence in the evidence for an association between TRAP and asthma ever and active asthma in children was moderate. Asthma ever refers to lifetime asthma prevalence and active asthma refers to prevalence of asthma in the last 12 months.

For most of the other respiratory outcomes investigated—including incidence of chronic obstructive pulmonary disease (COPD) and ALRI in adults, and wheeze outcomes as well as exacerbation of asthma and COPD in diseased adults—the confidence was very low or low for an association with TRAP, hampered in part by the small number of qualifying studies.

CARDIOMETABOLIC OUTCOMES

The summary estimates were mostly positive and were consistent with an association of PM_{10} with IHD: 1.14 (95% CI: 0.99–1.31) per 10-μg/m^3, with evidence suggesting a monotonic exposure–response function. Evidence was suggestive for EC and $PM_{2.5}$ but was less consistent overall. Associations were reported with NO_2 and diabetes prevalence with a summary estimate of 1.09 (1.02–1.17) per 10-μg/m^3, supported by consistent positive but imprecise estimates for the other pollutants. The summary estimates of EC, PM_{10}, and $PM_{2.5}$ with stroke incidence were slightly less precise, but the evidence was strengthened by several high-quality studies with a monotonic exposure–response function. Studies that were not included in meta-analyses provided additional support for an association between TRAP and IHD, diabetes, and stroke. In contrast, for coronary events the number of studies was smaller and insufficient for meta-analyses, except for NO_2, which yielded a positive but imprecise association. Because cardiometabolic outcomes are likely influenced by traffic noise, some studies investigated possible confounding or effect modification by noise with mostly similar results after adjustment for co-exposure to noise.

The Panel had overall moderate confidence in the evidence for associations between long-term exposure to TRAP and IHD and to TRAP and diabetes; low-to-moderate confidence in the evidence for an association of TRAP with stroke; and low confidence in the evidence for an association of TRAP with coronary events.

MORTALITY

The summary estimates showed that NO_2, EC, and $PM_{2.5}$ were associated with all-cause, circulatory, IHD, respiratory, and lung cancer mortality, ranging from 1.01 to 1.07. Associations of these pollutants with stroke and COPD mortality were less certain because fewer studies were available for consideration. The studies on pollutants not included in the meta-analyses and the studies with indirect traffic measures supported those associations. All studies on mortality were cohort studies, with outcome during follow-up determined by

EXECUTIVE SUMMARY SIDEBAR
OVERALL CONFIDENCE ASSESSMENT: DESCRIPTORS OF THE LEVEL OF CONFIDENCE IN THE EVIDENCE FOR AN ASSOCIATION[a]

High	Evidence is sufficient to conclude that the strength of the evidence for an association is high; that is, the exposure has been shown to be associated with health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. The determination is based on multiple high-quality studies conducted in different populations and geographical areas with consistent results for multiple exposure indicators.
	High confidence in the association between exposure and the outcome.
Moderate	Evidence is sufficient to conclude that an association is likely to exist; that is, the exposure has been shown to be associated with health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. The determination is based on some high-quality studies in different populations and geographical areas, but the results are not entirely consistent across areas and for multiple exposure indicators.
	Moderate confidence in the association between exposure and the outcome.
Low	Evidence is suggestive but limited, and chance, confounding, and other biases cannot be ruled out. Generally, the body of evidence is relatively small with few high-quality studies available; however, at least one high-quality epidemiological study shows an association with a given health outcome and/or when the body of evidence is relatively large, but the evidence from studies of varying quality and across multiple exposure indicators is generally supportive although not entirely consistent.
	Low confidence in the association between exposure and the outcome.
Very low	Evidence is inadequate to determine if an association exists with the relevant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association.
	Very low confidence in the association between exposure and the outcome.

[a] The overall confidence assessment of the association of each health outcome with long-term exposure to TRAP is a combination of the narrative assessment and the modified OHAT assessment. The descriptors are modified from the U.S. Environmental Protection Agency (2015) and the OHAT (2019).

linkage to mortality registries. Most studies were conducted in North America and Europe; some were set in Asia. The majority of studies accounted for a large number of individual and area-level covariates—including smoking, body mass index, and individual and area-level socioeconomic status—and were judged at a low or moderate risk for bias.

The overall confidence in the evidence for an association between TRAP exposure and mortality was high for all-cause, circulatory, and IHD mortality. The Panel's overall confidence was moderate to high for lung cancer, moderate for respiratory, low to moderate for stroke, and low for COPD mortality.

OVERALL CONCLUSIONS

The findings from the systematic review, meta-analyses, and evaluation of the quality of the studies and potential biases have provided an overall high or moderate-to-high level of confidence in an association between long-term exposure to TRAP and the adverse health outcomes all-cause, circulatory, IHD, and lung cancer mortality; asthma onset in both children and adults; and ALRI in children. The Panel's confidence in the evidence was considered moderate, low, or very low for the other selected outcomes.

Tailpipe emissions from motor vehicles and ambient concentrations of most monitored traffic-related pollutants have decreased steadily over the last several decades in most high-income countries. The Panel's main findings were derived from studies conducted when exposure levels were generally higher than present-day levels in high-income countries and comparable to or lower than present-day levels in low-income countries.

In light of the large number of people exposed to TRAP—both in and beyond the near-road environment—the Panel concluded that the overall high or moderate-to-high level of confidence in the evidence for an association between long-term exposure to TRAP and several adverse health outcomes

indicates that exposures to TRAP remain an important public health concern and deserve greater attention from the public and from policymakers.

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ABBREVIATIONS

ALRI	acute lower respiratory infection
CI	confidence interval
COPD	chronic obstructive pulmonary disease
EC	elemental carbon
IHD	ischemic heart disease
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
OHAT	Office of Health Assessment and Translation
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
PM_{10}	particulate matter ≤10 μm in aerodynamic diameter
TRAP	traffic-related air pollution
UFPs	ultrafine particles
WHO	World Health Organization

PART A: BACKGROUND MATERIAL

Chapter 1

Introduction

CONTENTS

CHAPTER 1

Introduction

1.1 INTRODUCTION

Motor vehicles are a significant source of urban air pollution and are important contributors of anthropogenic carbon dioxide and other greenhouse gases. In conservative global estimates, 184,000 deaths a year are attributable to traffic-related air pollution (TRAP*) (Bhalla et al. 2014). Similarly, Lelieveld and colleagues estimated that TRAP is responsible for one-fifth of deaths from air pollution in the United States, the United Kingdom, and Germany (Lelieveld et al. 2015).

TRAP is a complex mixture and refers to ambient air pollution resulting from the use of motor vehicles including heavy-duty and light-duty vehicles, buses, passenger cars, and motorcycles. TRAP is often also referred to as air pollution originating from on-road mobile sources. Motor vehicles emit a variety of pollutants including nitrogen oxides (NO_x), elemental carbon (EC), fine particulate matter ($PM_{2.5}$; PM ≤2.5 µm in aerodynamic diameter), ultrafine particles (UFPs), heavy metals, polycyclic aromatic hydrocarbons, and volatile organic compounds.

When emitted through vehicle exhaust, these pollutants are called tailpipe emissions. When emitted by other means, such as evaporative emissions of fuel, the resuspension of dust, the wear of brakes and tires, and the abrasion of road surfaces, they are called nontailpipe emissions.

Tailpipe emissions from motor vehicles and ambient concentrations of most monitored traffic-related pollutants have decreased steadily over the last several decades in most high-income countries. This trend is a result of air quality regulations and improvements in vehicular emission-control technologies and is likely to continue (Frey 2018). However, decreases in emissions from individual motor vehicles, while substantial, do not fully compensate for the rapid growth and increased vehicular congestion of the motor vehicle fleet due to population growth, urbanization, and economic activity, as well as to the continued presence of older or malfunctioning vehicles on the roads. The adoption of new technologies such as electric vehicles, while promising alleviation of some components of TRAP, has been relatively slow so far due to the slow development, and cost, of battery technology and infrastructure, electricity decarbonization, nontailpipe emissions mitigation, and fleet turnover (Khreis et al. 2020). Interest in the contribution of nontailpipe emissions to air quality and health is increasing in most high-income countries as vehicle miles traveled increase and regulations continue to be targeted almost exclusively to tailpipe emissions. For the foreseeable future, a substantial number of people globally will continue to be exposed to tailpipe and nontailpipe TRAP, especially in urban settings and residences in proximity to busy roadways.

The rate at which vehicle emissions disperse into ambient air depends on multiple factors that are highly variable, such as wind speed, wind direction, atmospheric stability, and terrain and land use. In addition, air pollution from other sources—such as industry, oil, coal and wood burning, and agricultural sources, as well as atmospheric transport of pollutants from distant sources—contributes to the overall air quality. The result of these emissions is elevated concentrations of air pollutants, through primary emissions and through the formation of secondary pollutants, such as secondary PM and ozone. People are exposed to these air pollutants in ambient air, or indoors through the infiltration of outdoor air pollutants. Human exposures are also determined by various dynamic factors such as mobility patterns and distance from the source. Human exposures to TRAP can elicit a wide range of adverse health effects. The full chain of events covering traffic activity, vehicle emissions, the dispersion of these emissions, human exposures, and their ultimate adverse health is depicted in Figure 1.1 (Khreis et al. 2020).

In 2010, HEI published Special Report 17, *Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects*. This report, developed by the HEI Panel on the Health Effects of Traffic-Related Air Pollution, summarized and synthesized research on emissions, exposure, and health effects from TRAP and drew conclusions about whether the associations between exposure and health outcomes were causal. The Panel reviewed both toxicological and epidemiological evidence. At that time, the Panel concluded that the evidence was sufficient to support a causal relationship between exposure to TRAP and exacerbation of asthma in children. The Panel also found suggestive evidence of a causal relationship with the onset of childhood asthma, nonasthma respiratory symptoms in adults, impaired lung function in children and adults, total and cardiovascular mortality, and cardiovascular morbidity. For a number of other health outcomes,

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* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

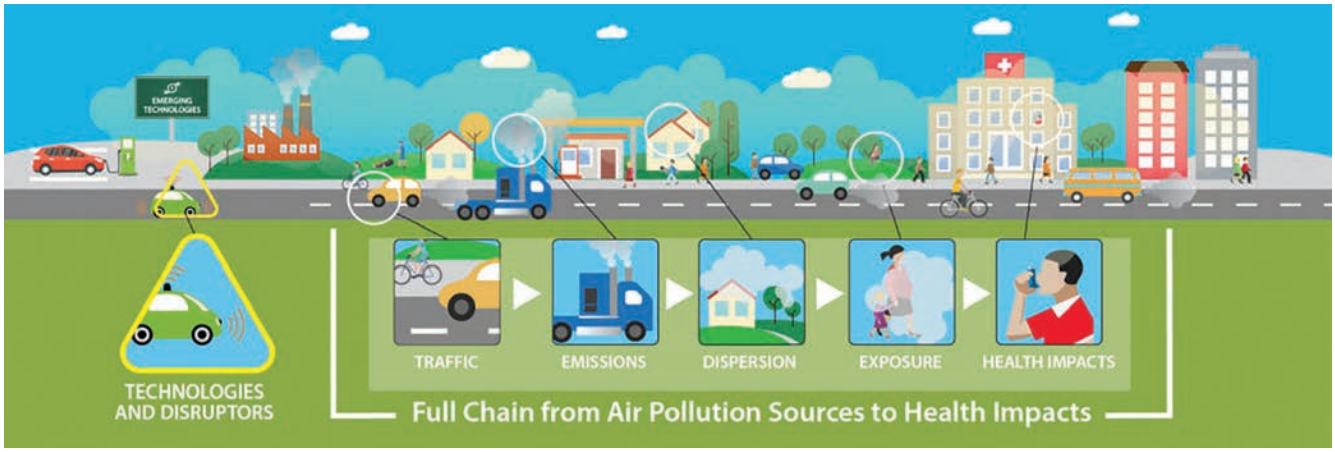

Figure 1.1. The full chain of events linking TRAP to health effects. Source: Center for Advancing Research in Transportation Emissions, Energy and Health (CARTEEH), available from https://www.carteeh.org/.

there was only limited evidence of associations, and the data were deemed to be either inadequate or insufficient to draw firmer conclusions (HEI 2010).

Since HEI published its review in 2010, many additional studies investigating the health effects of exposure to TRAP have been published, and regulations and vehicular technology have advanced significantly. In addition, there is a better appreciation that, beyond air pollution, traffic can be a source of other exposures with potential relevance to health, most notably noise. These exposures may either confound or modify the health effect of TRAP. TRAP continues to be of public health interest and is of concern to policy makers and motor vehicle manufacturers alike. Therefore, HEI in response to broad interest from its sponsors, decided to conduct a new literature review, as described in HEI's Strategic Plan 2015–2020 (HEI 2015), and formed a new panel to conduct the review. Advances in systematic review methods for environmental health (e.g., Whaley et al. 2020; Woodruff and Sutton 2014) provide a basis for more specific guidance for the conduct of this systematic review, thereby enhancing consistency and transparency. This review is the largest systematic effort to date to evaluate the epidemiological evidence regarding the associations between long-term exposure to TRAP and selected adverse health outcomes.

1.2 HEI PANEL

In 2018, the Board of Directors of HEI appointed an expert panel to review the scientific literature on traffic-related air pollution and health. The Panel consisted of scientists from a variety of disciplines and was cochaired by Francesco Forastiere, Imperial College London, and Frederick Lurmann, Sonoma Technology, Inc., Petaluma, California. During the course of the review, consultants to the Panel were added. In addition, HEI hired a contract team at the Swiss Tropical and Public Health Institute, Switzerland, to execute certain parts of the review. A draft of the Resulting Special Report was subjected to detailed peer review.

HEI is indebted to the Panel, the consultants to the Panel, and the contract team for their expertise, cooperation, and enthusiasm. HEI would also thank the peer reviewers for their thorough review of the Special Report. Please see the Contributors page for more information.

1.3 MANAGEMENT OF CONFLICTS OF INTEREST

Conflicts of interest—with or without bias—can undermine the credibility of an HEI report; hence, their appropriate management is crucial. All experts received a letter and were briefed about the types of conflicts of interest at the start of the project. In addition, they were asked to complete declaration of interest forms, which focused on relationships and affiliations that scientists often have with one or more organizations and on conflicts of interest that may be relevant to the member's work with HEI. Panel members were asked to update such information on a periodic basis. Declarations from all experts were collected and managed according to HEI's procedures, which are similar to those used by the U.S. National Academies. All experts declared that they had no conflicts of interest, and no experts had to be excluded from their respective roles.

1.4 OBJECTIVE

The overall objective of this Special Report was to systematically evaluate the epidemiological evidence regarding the associations between long-term exposure to TRAP and selected adverse health outcomes. Results were to be quantitatively combined to evaluate the strength of the evidence, where appropriate. The Panel was charged with drawing conclusions about the confidence in the quality of the body of evidence and with assessing the level of confidence in the presence of an association. The Panel did not assess causality

because there has been no separate, independent systematic assessment of the mechanistic, toxicological, and human clinical studies relating TRAP to human health.

In addition to the systematic review of the epidemiological evidence, the report includes a section that addresses some other important issues related to technologies and emissions from motor vehicles; includes a high-level, succinct review on the mechanistic evidence of health effects of exposure to TRAP; and summarizes the health effects of short-term exposure to TRAP. This information is meant to provide background information and serve as complementary and supporting evidence to the systematic review on the health effects of long-term exposure to TRAP. Moreover, literature reviews were developed for neurodevelopmental outcomes in children and for dementia-related outcomes and Parkinson disease in adults. Those literature reviews were added because the Panel thought these were important emerging areas that should be represented in the Special Report, even while a larger body of evidence develops.

1.5 SCOPE

The scope of the review encompasses epidemiological studies that reported associations of selected health outcomes to long-term exposure to TRAP. The Panel discussed the studies extensively during several meetings and also considered feasibility issues, given the vast and rapidly growing literature on the potential adverse health effects of TRAP.

The current review differs from the earlier critical review in some important aspects. The Special Report 23 review: (1) followed a systematic approach using common methods and a published protocol; (2) evaluated the epidemiological literature only; (3) evaluated only studies of long-term exposure and health; (4) used a novel exposure framework and considered exposure contrasts both in the near-roadway and neighborhood environment; (5) focused on a selected set of health outcomes chosen a priori, and (6) drew conclusions about the confidence in the body of epidemiological evidence and the presence of an association.

The target audiences for this Special Report are scientists interested in a detailed summary, synthesis, and critique of the relevant literature; those responsible for setting policy and writing regulations; and other affected stakeholders in industry and the general public.

1.6 ORGANIZATION

A schematic presentation of Special Report 23 is given in Figure 1.2. The report includes the following:

- PART A: BACKGROUND MATERIAL includes a background chapter that covers important issues related to technologies and emissions from motor vehicles (Chapter 2); a high-level succinct review on the mechanistic evidence of health effects of exposure to TRAP (Chapter 3); and summaries of the health effects of short-term exposure to TRAP (Chapter 4).

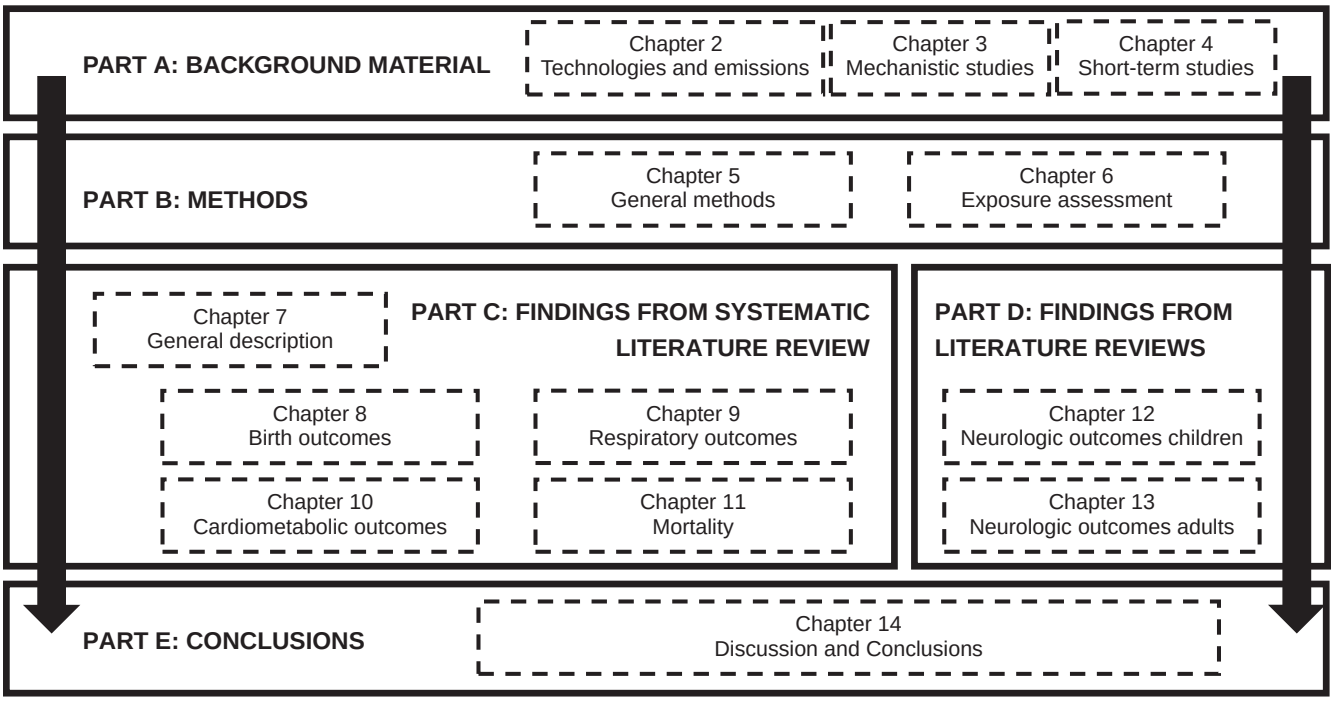

Figure 1.2. Schematic presentation of the Report's organization.

- PART B: METHODS describes the general methods (Chapter 5) and lays out in detail the exposure criteria considerations for the different exposure assessment approaches (Chapter 6).
- PART C: FINDINGS FROM SYSTEMATIC LITERATURE REVIEWS OF EPIDEMIOLOGICAL STUDIES starts with a general description of the literature search results (Chapter 7), followed by separate chapters describing the findings for each health outcome: birth outcomes (Chapter 8), respiratory outcomes (Chapter 9), cardiometabolic outcomes (Chapter 10), and mortality (Chapter 11).
- PART D: FINDINGS FROM LITERATURE REVIEWS OF EPIDEMIOLOGICAL STUDIES describes results for neurological outcomes, specifically neurodevelopmental effects in children (Chapter 12) and dementia-related outcomes and Parkinson disease in adults (Chapter 13).
- PART E: CONCLUSIONS brings together the conclusions from each of the preceding chapters to provide an integrated synthesis of the strengths and limitations of the present state of our knowledge and makes recommendations for future research (Chapter 14).

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ABBREVIATIONS

EC	elemental carbon
NO_x	nitrogen oxides
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
TRAP	traffic-related air pollution
UFPs	ultrafine particles

PART A: BACKGROUND MATERIAL

Chapter 2

Motor Vehicle Technologies and Emissions: Past, Present, and Future Trends

CONTENTS

CHAPTER 2

Motor Vehicle Technologies and Emissions: Past, Present, and Future Trends

2.1 SUMMARY

The transportation sector is a major part of industrialized societies, allowing for speedy movement of people and goods. Yet traffic-related air pollution (TRAP*) has been a major concern because of its ubiquity and proximity of the emissions to homes and businesses, and its impact on air quality. This chapter provides a high-level summary of the recent history, current trends, and the projected future of motor vehicle technologies that affect TRAP. Emissions from the road transport sector have declined substantially during the past several decades in most high-income countries, with the notable exception of carbon dioxide (CO_2). These developments are the result of impressive improvements in motor vehicle technologies and fuels as well as aggressive regulatory actions to combat TRAP emissions. Most communities benefit from the reduced emissions, improved air quality, and reduced exposures, although many challenges remain. Examples of such challenges include technological issues (e.g., emissions from cold start, older and high-emitting vehicles, ultrafine particle [UFP] emissions from vehicles equipped with gasoline direct injection engines), poor compliance (e.g., tampering), emissions cheating, nontailpipe emissions, and traffic noise. A variety of policy tools and technological developments are addressing these issues, but the problems are far from being solved.

The relatively recent requirement for automotive fuel with very low levels of sulfur has reduced particulate matter (PM) formation during combustion. It has also allowed the use of, or improved the longevity of, catalyzed after-treatment technologies, such as three-way catalytic converters, diesel particle filters, and selective catalytic reduction systems. The use of renewable fuels—notably ethanol and biodiesel—has reduced CO_2 emissions modestly but is likely to continue at today's relatively low levels.

The imperative to reduce the emissions of greenhouse gases (GHGs) from the transportation sector, which accounts for a large fraction of total GHG emissions, has spurred new regulations and technologies. The most prominent among such changes is the electrification of the vehicle fleet, which offers many benefits because of the high efficiency of such powertrains and the absence of combustion emissions at the site of use; the full benefit of electrification will be realized only as the electric grid is decarbonized. Vehicle electrification is currently available mostly for light-duty vehicles; electrification of heavier class vehicles has been developing more slowly, owing to greater technological challenges.

The convergence of new technological developments outside the transportation sphere, such as digital connectivity and artificial intelligence, and evolving mobility preferences could be poised to change the current transportation landscape. The transition to such new mobility has the potential to reduce

Highlights

- This chapter provides an overview of the recent history, current situation, and future trends in motor vehicle technologies and emissions that affect TRAP in the United States and, to a more limited extent, Europe. It is not meant to be a systematic or exhaustive review of the topic.
- TRAP emissions from the transportation sector have declined very substantially during the past several decades in most high-income countries mainly due to impressive improvements in motor vehicle technologies and fuels as well as aggressive regulatory actions to combat TRAP emissions; however, the situation in most middle- and low-income countries deserves more attention.
- Although most communities are benefiting from the significantly reduced TRAP emissions, improved air quality, and reduced exposures, many challenges remain. Examples of such challenges include technological issues (e.g., emissions from cold start, older and high-emitting vehicles, ultrafine particle emissions from vehicles equipped with gasoline direct injection engines), poor compliance (e.g., tampering), emissions cheating, nontailpipe emissions, and traffic noise.
- The importance and urgency of curbing greenhouse gas emissions from the transportation sector has spurred new regulations and technologies. The most prominent among such changes are electric vehicles, which offers many benefits. Vehicle electrification together with new developments outside the transportation sphere, evolving mobility preferences, and better urban design are likely to change the current transportation landscape.

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* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

GHG and TRAP emissions, particularly if accompanied with lasting reductions in total travel demand. Finally, planning for mobility should also include an emphasis on active transport such as walking or bicycling (which have little or no carbon footprint), better urban design (including pedestrian pathways and green spaces), and improved public transportation systems.

2.2 INTRODUCTION

Cars, sport utility vehicles (SUV), trucks, buses, motorcycles, and other forms of motorized transport are ubiquitous not only in industrialized countries and urban centers but also in rural and remote, sparsely populated areas all around the world. Globally, roughly 1.4 billion vehicles are registered today, and their numbers are increasing rapidly (U.S. Department of Energy [U.S. DOE] 2021).

Motor vehicles have played a major role in the development of modern societies, with their attendant freedom of movement of people and goods at any time of the day or night. The transportation sector—including the original manufacturers, suppliers, and parts manufacturers, as well as fuel suppliers, automobile sellers and many other subsectors—comprise an essential component of the labor market and economic productivity in the United States, Europe, and many other countries.

Such a prominent presence of the automotive sector in society, however, also has certain negative effects. Motor vehicle emissions have historically contributed to deterioration of air quality, which in turn has had adverse effects on human health (the subject of this report) and the environment. Over the past 50 years, emissions from individual vehicles and total emissions from the automotive sector have declined substantially, particularly in high-income countries, because of tightening of regulations and improvements in technology, with the notable exception of CO_2 and other GHGs. Although some countries, notably China and (increasingly) India, have made progress in controlling motor vehicle emissions, motor vehicle emissions in many other low- and middle-income countries are quite high. The great popularity of motor vehicles has also affected land use and led to congestion and urban sprawl that contribute to the loss of productive time and are a source of stress for commuters. Automobiles place a major demand on resources, leading to challenges related to extraction and shipping of raw materials, manufacturing and labor supply, and supply of fuel, which has sometimes resulted in international tensions. Some of the impacts of automobiles—for example, exposure to traffic emissions—are often experienced differently by other communities, with minority and marginalized communities shouldering a disproportionate burden. Last but not least, automobile emissions also are an important source of GHGs, contributing to the warming of the earth as well as its radiative balance.

The context in which motor vehicles have evolved has now become more complex; this complexity is driven by technological evolution and the mobility and transportation needs, both of people and goods, as well as aspirations of an increasing global population. Given concerns about exposure to TRAP, climate change, and energy security, it is imperative to find new solutions that enable mobility while overcoming these problems. This complex situation provides the impetus for improvements in existing technologies as well as rapid development and introduction of a broad range of new technologies, fuels, sources of energy, and business models, all intended to meet the needs of the modern society.

2.2.1 GOAL OF THIS CHAPTER

This chapter provides an overview of the recent history, current situation, and future trends in motor vehicle technologies that affect TRAP (Sidebar 2.1). A combination of technologies, fuels and regulations have led to significant reductions in TRAP emissions in most high-income countries. Air pollution epidemiology studies—the basis for the review of selected health effects of long-term exposure to TRAP elsewhere in this report—are by design retrospective. They provide valuable information about the past and, sometimes, more recent years but may not represent the impacts of lowered exposures from today's vehicles nor necessarily accurately predict the effects of future, expected further reductions in emissions. The information summarized in this chapter is intended to describe recent technological developments and their limitations, which have led to improvements in TRAP emissions and their impact on air quality so that future exposure assessments and health evaluations may be informed by these developments and methodologies for exposure assessment may be appropriately tailored.

Several limitations of and omissions from this chapter should be noted. First, this chapter covers a very broad subject area and is not meant to be a systematic or exhaustive review of the topic; detailed discussions and reviews are available elsewhere (see for example Frey 2018; Khreis et al. 2020). The intent of this chapter is to provide a high-level and accessible overview of this potentially unfamiliar and complex area of automotive technology and associated policies for environmental health scientists, so they can appreciate the changing nature of air pollution emissions from mobile sources. Second, this review focuses on the situation in the United States and, to a more limited extent, in Europe, where most of the studies reviewed in this report were conducted. The situation in low- and middle-income countries receives relatively brief attention. Although currently there are very important TRAP-related challenges in those countries, the technologies available and being developed in high-income countries—upon which this chapter focuses—will eventually be introduced throughout the world, as has been the case in the past. For greater details of the situation in countries outside of the United States, the reader is referred to publications by the European Union (EU), International Council for Clean Transportation, World Health Organization (WHO),

SIDEBAR 2.1 MOTOR VEHICLE PROPULSION TECHNOLOGIES

- The great majority of motor vehicles in use today deploy an internal combustion engine for propulsion. Two types of internal combustion engines currently dominate commercial production: (1) the spark-ignition gasoline engine used in cars, SUVs, and some light-duty trucks and (2) the compression-ignition diesel engines used in some cars (primarily outside of the United States), vans, and trucks. Compression-ignition diesel engines are also used for most heavy-duty applications, such as municipal, agricultural, and construction equipment. In addition to using different fuels, the principal difference between these two systems is in the way they introduce and ignite fuel in the engine combustion chamber. In spark-ignition engines, the fuel may be introduced using port fuel injection or by direct injection and ignited by a spark. Direct injection is now becoming prevalent because of its better fuel efficiency. Compression-ignition engines use higher compression ratios, which ignites the fuel spontaneously. Compression-ignition engines are more efficient and produce greater power than spark-ignition engines.
- Both spark-ignition and compression-ignition engines use petroleum-based fuels for propulsion, although biologically based additives, such as ethanol and biodiesel, have recently become quite common, generally at low-blend levels. Also, a small number of engines use compressed natural gas or liquefied petroleum gas, with either spark-ignition or compression-ignition engines.
- Electric vehicles use an electric motor for propulsion; this entirely different type of powertrain is more efficient in converting energy stored in the fuel (electricity) into propulsion. Electricity for such vehicles is obtained from a utility source (in fully electric vehicles) or from a fuel cell (which uses hydrogen). Hybrid vehicles combine the use of an internal combustion engine and an electric motor. At present, the proportion of such vehicles in the fleet is small but is increasing rapidly.

and others. Third, to manage its length and complexity, this chapter focuses on technology and emission issues and a very limited discussion of air quality issues but not on exposure issues, which are discussed in Chapter 6 of this report. Finally, this chapter focuses on on-road transportation; other aspects of transportation, namely aviation and maritime travel and shipping, as well as nonroad equipment, all of which often use similar engines and technologies but are subject to different regulatory regimes, are not presented.

2.3 TRAFFIC-RELATED AIR POLLUTION, ITS REGULATION, AND EMISSIONS TRENDS

2.3.1 TRAFFIC-RELATED AIR POLLUTION

The overall sources of air pollution from human activities include energy production (such as power plants), industrial sources, and other processes (e.g., petroleum refineries, cement kilns), building heating and cooling, cooking, agricultural burning, and transportation sources, to name some of the major sources (McDuffie et al. 2021). In some circumstances, natural sources may also contribute, such as soot from wildfires, sand dust from deserts, and salt aerosols from the sea. Additionally, air pollution may be transported over long distances and contribute to the deterioration of air quality at distant locations. Thus, air pollution in any location is a complex mix of the background, regional, and global pollution, as well as emissions from local sources, including vehicles (see Figure 6.1 in Chapter 6; HEI 2010).

The transportation sector includes light-duty cars, vans, SUVs and light trucks, heavy-duty highway trucks, and buses, as well as nonroad sources (construction and municipal equipment, marine vessels, aircraft, locomotives, agricultural equipment). This sector comprises a variety of engine types and fuels, and therefore their emissions are also quite varied (Frey 2018; U.S. Environmental Protection Agency [U.S. EPA] 2019a). Mobile sources are an important contributor to the U.S. national emissions inventories of CO_2, carbon monoxide (CO), nitrogen oxides (NO_x, mainly consisting of nitrogen dioxide [NO_2] and nitrogen oxide [NO]), PM, and numerous volatile organic compounds (VOCs) (Figure 2.1) (U.S. EPA 2019a). TRAP is of particular interest because of its significant contribution to air quality, proximity to communities, omnipresence, and the extensive dependence of modern life on motorized transportation. Thus, in the near-road environment where large numbers of people live, mobile sources are important because they greatly influence local pollutant concentrations.

PM emitted from vehicles, referred to as primary PM, are solid particles that contain thousands of chemical species. These include toxic chemicals, such as benzo- and nitropyrenes, and metallic species—adhered to a carbonaceous core. PM are found in a wide range of diameters. These include PM with aerodynamic diameter between 10 µm and 2.5 µm (PM_{10} or PM_{coarse}), PM ≤2.5 µm ($PM_{2.5}$ or fine), and PM ≤0.1 µm (UFPs); these classes have varied physicochemical characteristics. PM_{10} and $PM_{2.5}$ are generally reported as mass concentration, whereas UFPs are reported as either mass or more commonly as number concentration. The majority of the mass of $PM_{2.5}$ and

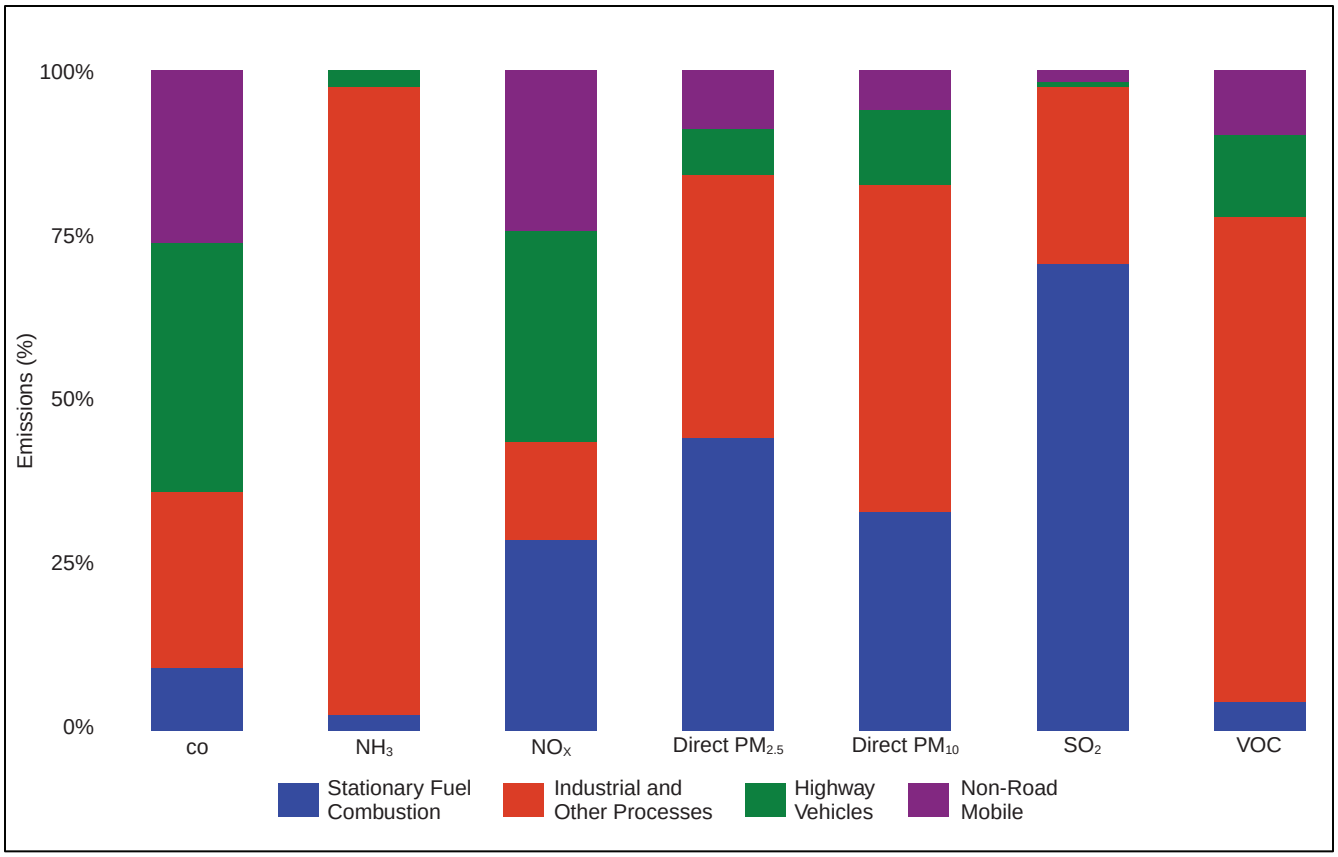

Figure 2.1. National emissions by source category in the United States (U.S. EPA 2019a). CO = carbon monoxide; NH_3 = ammonia; NO_x = nitrogen oxides; $PM_{2.5}$ = particulate matter ≤2.5 µm; PM_{10} = particulate matter ≤10 µm; SO_2 = sulfur dioxide; VOC = volatile organic compounds.

UFPs is usually carbon, which has traditionally been divided into two fractions: organic carbon and elemental carbon. Coarse particles contain a much larger fraction of noncarbonaceous material, derived from crustal material and mechanically generated (e.g., abrasion) particles.

Once airborne, the constituents of air pollution—including transportation emissions—can physically mix and chemically react with each other and form secondary air pollutants. Two of the most important of such processes is the reaction between NO_x and VOCs in the presence of sunlight and warm temperatures to form ground-level ozone. Secondly, organic compounds (e.g., VOCs and semivolatile organic compounds [SVOCs]) or inorganic gases (e.g., NO_2, sulfur dioxide, ammonia [NH_3]), can oxidize and then nucleate to form new particles or condense on existing PM; such PM is referred to as secondary PM (Seinfeld and Pankow 2003).

Additionally, many hundreds of VOCs are emitted from mobile sources; these are a subset of air toxics and are also referred to mobile source air toxics. Mobile source air toxics include benzene, formaldehyde, acetaldehyde, 1,3-butadiene, acrolein, naphthalene, and ethylbenzene. Ambient levels of select air toxics are often determined, together with criteria pollutants, to assess the contribution of TRAP to air quality and to exposure.

2.3.2 UNITED STATES REGULATIONS

Largely out of concern for ground-level ozone (smog), several laws were enacted during the 1960s and 1970s in the United States, particularly the Clean Air Act in 1970. This Act has subsequently been amended several times, most notably in 1977 and 1990, and has been supplemented by myriad regulations and standards promulgated by the U.S. EPA. Since California had, and continues to have, some of the most severe air pollution problems in the United States, the Clean Air Act also gave the California Air Resources Board (CARB) special authority to establish tougher standards. Several states in the United States and Canada often emulate California's standards for vehicular standards.

The Clean Air Act gives the U.S. EPA wide authority to control mobile source emissions using several different mechanisms. A combination of federal and state governments develop the requirements and oversee their implementation by manufacturer and refiners. New requirements have been

introduced as new issues have arisen (Frey 2018; U.S. EPA 2017), consequently the regulations have become increasingly more stringent over time. Broadly, automobile emissions are regulated via specific standards for new cars and trucks, rules for adherence to these emission limits for the useful life of the vehicle, and rules for fuels that support a reduction in emissions. The key regulations and other programs to directly address mobile source emissions in the United States include the following (U.S. EPA 2019c):

- Certification standards for light and heavy-duty and nonroad vehicles, setting limits on tailpipe emissions of NO_x, $PM_{2.5}$, CO, VOCs, along with detailed methods for vehicle testing and certification; these have been promulgated under a comprehensive system of Tier regulations of increasing stringency encompassing fuels, emissions, and other features (U.S. EPA 2018)
- Evaporative emission standards
- Fuel composition standards, including reformulated gasoline to control fuel volatility (which affects ozone formation) and sulfur content in gasoline and diesel (to reduce PM formation and prevent poisoning of after-treatment catalysts)
- Biofuel standard, stipulating biofuel content of commercial gasoline and diesel
- On-board diagnostic systems for monitoring malfunction
- Requirements for durability of pollution control equipment
- Inspection and maintenance programs to ensure ongoing in-use compliance
- Fuel economy standards and GHG (i.e., CO_2-equivalent) emission standards
- Programs targeted at heavy-duty vehicles, including the Clean School Bus program to discourage idling and funding under the Diesel Emissions Reduction Act to reduce diesel emissions exposure by vehicle retrofitting and replacement

Additional U.S. regulations, which have direct or indirect effect on vehicular emissions, are implemented by the U.S. EPA's sister agencies, particularly the National Highway Traffic Safety Administration and the Federal Highway Administration, which are both housed in the Department of Transportation. The National Highway Traffic Safety Administration has primary responsibility for vehicle fuel economy standards; although these standards originated during the 1970s when oil prices spiked, at this time the fuel economy standards are central to GHG controls. The Federal Highway Administration focuses on mobility and transportation infrastructure and provides funds to states and municipalities to maintain and build roads and public transportation systems. The Federal Highway Administration and the Federal Transit Administration also determine whether transportation plans, programs, and projects conform to state implementation plans in pollutant nonattainment and maintenance areas; the U.S. EPA writes the regulations for this transportation conformity requirement, with Federal Highway Administration and Federal Transit Administration's concurrence. The U.S. DOE has an important role for promoting alternative fuels.

2.3.3 EUROPEAN REGULATIONS

Although the United States and European countries faced similar challenges from very high levels of air pollution in 1960s and 1970s, the response in Europe took considerably longer. For example, in the EU, it was only in the early 1990s that the three-way catalyst was required for new cars and the first NO_x emission limits were established. Subsequently, standards have evolved, through the Euro series of regulations, designated by Arabic numerals for light-duty vehicles and Roman numerals for heavy-duty vehicles (Kodjak 2015). There are many differences between the U.S. and EU regulatory schemes in the ways in which the emissions are regulated and tested (Nesbit et al. 2016); two are especially pertinent for this discussion.

First, the EU responded to the oil crisis of the 1970s by imposing substantial taxes on fuel, with the aim of reducing consumption; however, diesel was taxed at a lower rate than petroleum to reduce fuel consumption, because diesel-powered vehicles give better mileage. This, among other reasons, has resulted in a high percentage of diesel cars, an issue that continues to challenge European countries to this day (Cames and Helmers 2013). In contrast, diesel cars have sparingly been sold in the United States during most of the past five decades.

The second important difference relates to EU emission standards for new cars, especially for NO_x, which had several limitations. Introduction of such standards lagged several years behind those in the United States, resulting in a large portion of the on-road fleets, especially diesel vehicles, continuing to use the earlier Euro 3/III and 4/IV technologies—with much higher NO_x emissions—for considerably longer than comparable fleets in the United States. Also, diesel vehicles in Europe, even today, have weaker standards than gasoline vehicles, as illustrated by the Euro 6 standards for NO_x: the limit value for diesel vehicles is 80 mg/km, while that for gasoline vehicles is 60 mg/km (Rodriguez et al. 2019). Moreover, the EU regulation did not have a robust method of on-road surveillance or enforcement, which resulted in real-world emissions from new vehicles exceeding certification levels many times over.

With regard to governance, the regulations in the EU are implemented by Directorate General for Internal Market, Industry, Entrepreneurship, and Small and Medium-sized Enterprises (EC 2016), with input from Directorate General Environment. The regulations mirror many of the U.S. requirements. However, the implementation and enforcement of these regulations across the 27 EU member states can vary considerably. Additionally, the control of real-world emissions (so-called real driving emissions) has only recently been actively addressed.

Many countries in the world have adopted the European regulations for both tailpipe emissions and low-sulfur fuels standard, giving EU standards great importance internationally.

2.3.4 EMISSION TRENDS

Empirical trends in tailpipe emissions of pollutants can be investigated in a number of ways, including emissions testing and monitoring, roadside, highway and tunnel measurements, remote sensing, chassis dynamometer measurements, and plume-chasing studies, to name a few. A standardized way to express tailpipe emission values is to calculate the fuel-based pollutant emission rates, which may be deduced from the ratio of the concentration of the pollutant to the emitted carbon species (CO_2, CO, and hydrocarbon) in the emission for a given vehicle and driving activity. Distance-based emission rates are also commonly reported.

Adherence to regulations has been very effective in reducing automobile emissions, as shown by a very large number of studies. For example, Propper and colleagues (2015) quantified ambient concentrations and emissions trends for several air toxics, including diesel PM. They reported that between 1990 and 2012 in California, diesel PM concentrations declined by 68% while the state's population increased by 31%, and the diesel-vehicle miles travelled and the gross state product increased by 81% and 74%, respectively (Propper et al. 2015). Using a different approach to assess long-term trends in black carbon and organic aerosol emissions, McDonald and colleagues (2015) found steep declines in black carbon and organic aerosol during 1970–2010 in southern California. McDonald and colleagues (2013) reported that automobile CO emissions in 2010 had decreased by 80% to 90% compared to their 1990 levels in Los Angeles, New York, and Houston, although fuel use was estimated to have increased by 10% to 40% during this period. Bishop and Haugen (2018) made vehicle emissions measurements in the Chicago area starting in 1989. They reported that during the following 30-year period, CO emissions were reduced by a factor of 10 and hydrocarbon emissions by a factor of 20. The authors concluded that "This nearly 30-year record illustrates the large reductions in light-duty vehicle tailpipe emissions and the remarkable improvements in emissions control durability to maintain low emissions over increasing periods of time."

Based on data from the U.S. National Emission Inventory and the U.S. EPA's MOtor Vehicle Emission Simulator (MOVES) model, Frey (2018) has summarized the past and projected trends in U.S. vehicle emission inventories. The vehicle emissions for NO_x, CO, VOC, and PM_{10} between 1970 and 2015 were estimated to decrease by approximately 75% to 90%; these estimates represent the combined effects of an increase in vehicle population and miles travelled, and reductions due to vehicle and fuel regulations.

Improvements in air quality related to reduced motor vehicle emissions are even more impressive, considering that during the same period, the U.S. economy, population, energy consumption, vehicle miles travelled, and CO_2 emissions have grown steadily. Not only have the criteria pollutant and air toxics emissions and concentrations declined, the number of days of exceedances of the U.S. National Ambient Air Quality Standards also show a downward trend, and air quality in nonattainment areas and visibility in national parks and wilderness areas have improved (U.S. EPA 2019a). A notable exception to this generally good news has been ambient ozone concentrations, which declined substantially but continue, at these lower levels, to be far more difficult to improve, particularly during the past 10–15 years, leaving several areas in the United States in ozone nonattainment. Also, despite the overall average improvements, challenges continue to be encountered at many local levels, particularly in heavily trafficked areas and in vicinity of roads and under certain meteorological conditions.

Emissions and overall air concentrations in Europe follow a similar declining trend. For example, Carslaw and colleagues measured NO_x and NO_2 emissions from vehicles in the United Kingdom using remote sensing and reported that the absolute amount of these pollutants from diesel vehicles decreased substantially from most Euro 6 vehicles since around 2007; the emissions from gasoline vehicles have been declining since the mid-1980s (Carslaw and Rhys-Tyler 2013, Carslaw et al. 2019). Mulholland and colleagues (2021) summarized national emissions data obtained from the European Environment Agency (EEA) and concluded that PM, CO, and NO_x emissions from transport sources have come down significantly, corresponding to the tightening of EU emission standards, even with a concurrent increase in transport activity (Figure 2.2) (Mulholland et al. 2021).

2.4 GASOLINE-POWERED VEHICLES

Gasoline-powered private cars, SUVs, vans, and light-duty trucks (generally referred to as light-duty vehicles) have altered the global landscape and have been a major factor in the development of modern societies, with their attendant freedom of day-and-night movement, ease of commerce, and ability to commute. Ford aspired to pricing Model T cars that his workers could afford to buy. Today, cars are relatively more expensive; the total transportation expenses for the average U.S. consumer are second only to the cost of housing (U.S. BLS 2020). Today's market is full of a variety of light-duty vehicles of different sizes, engine power, fuel efficiency, powertrain, automation, digital controls, connectivity, and myriad other conveniences. However, such omnipresence of cars has also been associated with air pollution, congestion, urban sprawl, and many other problems.

2.4.1 CONTROL TECHNOLOGIES

The engine and fuel are best thought of as a system that provides the propulsive force needed for transportation.

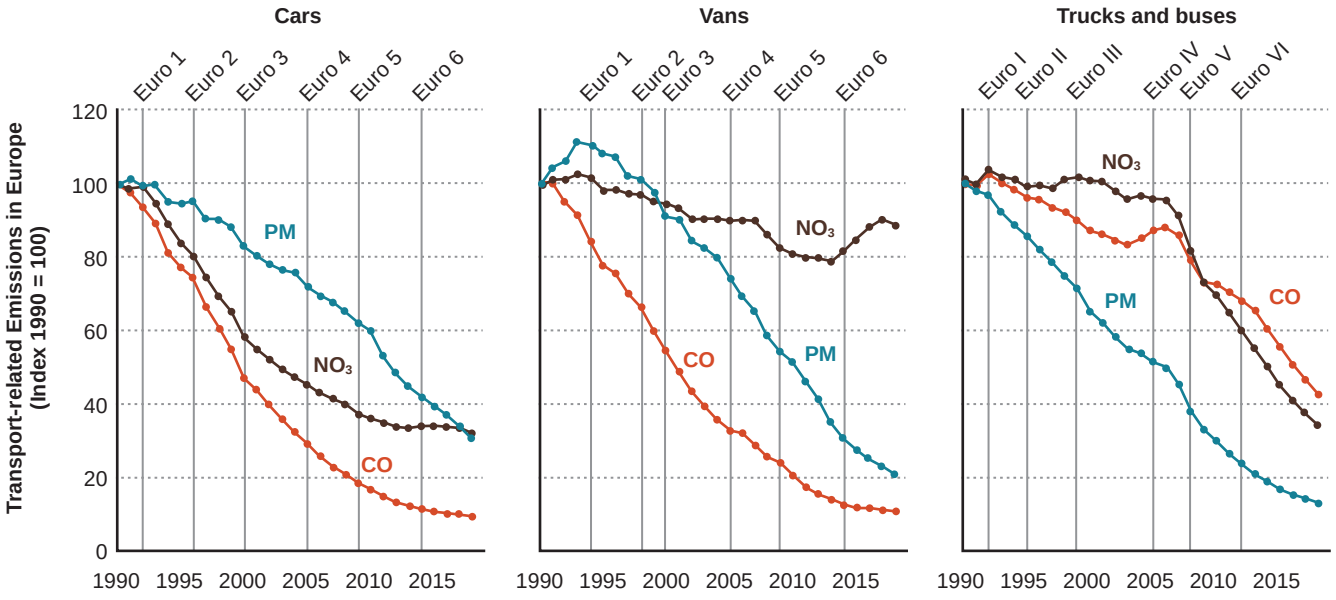

Figure 2.2. Transport-related emissions and year of implementation of Euro standards. (Mulholland et al. 2021; Creative Commons license CC BY-SA 4.0.)

Beginning in the mid-1970s, the phase-out of tetraethyl lead from gasoline—which had been added to boost octane and to reduce engine knock—along with the deployment of catalytic converters was one of the earliest approaches to reducing automotive air pollution and to meeting the U.S. EPA emission standards. Lead in gasoline not only poisoned the catalytic converter, but children's exposure to even low levels of lead had been shown to cause anemia, behavioral disorders, low intelligent quotient, reading and learning disabilities, and nerve damage (Needleman 2000). The three-way catalytic converter, whose use was made possible after removal of lead, was the most critical and revolutionary development at its time in the efforts to reduce automobile emissions (Twigg 2011) and it continues to be used in today's light-duty vehicles.

The U.S. EPA subsequently took numerous actions to control automotive air pollutants (U.S. EPA 2017, 2020a). Manufacturers have complied with these regulations by improvements in technology and the three-way catalytic converter. Today's typical three-way catalytic converters uses platinum, rhodium, palladium, and other rare metals as catalysts and, with the aid of electronic fuel injection and oxygen sensors to maintain the stoichiometric ratio of air and fuel in the combustion chambers, converts NO_x, CO, and hydrocarbon to N_2, O_2, CO_2, and H_2O. Conversion efficiency is sensitive to exhaust temperature; when working optimally (~400°C), three-way catalytic converters are 95% to 99% efficient (Mohiuddin and Nurhafez 2007) but are much less so when colder, such as during initial engine start-up. Concurrent with these regulations, the U.S. EPA has also, under the Tier regulations, put limits on the sulfur content of gasoline (at 10 ppm under the latest Tier 3 regulations) to help emission control systems work more efficiently and also to help improve fuel economy (U.S. EPA 2018).

Over the last decades, operations of both the engines and the after-treatment systems have greatly improved through the introduction of technologies such as electronic ignition systems, cylinder deactivation, variable valve timing, engine start-stop, direct injection, improved turbochargers, and regenerative braking, as well as improved tire design. Various policy actions, the use of lighter materials and better aerodynamic designs, and engine downsizing have led to added improvements in fuel efficiency and reductions in emissions from light-duty vehicles. Enforcement programs, such as in-use inspection and maintenance, have also played an important role in emissions reduction. New gasoline-powered cars sold today in the western markets have very low emissions (except for CO_2), and the U.S. EPA requires the emissions systems to comply for 120,000 or more miles (10–11 years or more).

2.4.2 REMAINING CHALLENGES

Despite these very substantial improvements, certain challenges concerning light-duty vehicle emissions remain, the major ones being high-emitting vehicles, emissions during cold-start conditions, and emissions from gasoline direct-injection engines. See Chapter 6 for discussion of another issue: specifically, air quality in urban areas, particularly in the vicinity of roads.

High-Emitting Gasoline Vehicles Total emissions of TRAP from vehicles trend toward lower levels as new cars with improved technologies enter the fleet and older vehicles

leave. However, a small percentage of light-duty vehicles on the road are improperly maintained, tampered with, or too old to be compliant with model-year specified regulations. The average age of a car on both U.S. and European roads has gradually increased, recently, to about 12 years (ACEA 2021; IHS Markit 2021; Schipper 2018; U.S. DOE 2021). As cars age, especially beyond 12–15 years, emission control systems and on-board devices deteriorate; consequently, emissions from such vehicles can increase significantly. Because newer vehicles are very clean, this creates a skewed distribution of emissions within the fleet. For example, based on studying emissions over a 30-year period in Southern California, Bishop (2019) concluded that total CO and hydrocarbon emissions from all cars decreased by a factor of 10- to 20-fold and 25-fold, respectively, resulting in about 1% of vehicles (high emitters) being responsible for more than 37% of CO and 28% of hydrocarbon emissions. More recently, an analysis of 60 million exhaust samples using remote-sensing methods found that a small proportion of older vehicles contributes disproportionately to total vehicular emissions and the contribution from the oldest vehicles increased over time, although the overall trend in fleet average emissions of pollutants showed a significant downward trend (Bernard et al. 2020). Thus, in 2010, half of the total NO mass emissions were contributed by 14% of the fleet; by 2018, this fraction had decreased to just 11% of the fleet. Policy approaches to address the problem of high-emitting vehicles have been challenged by financial constraints and economic equity issues. There is also controversy about the effectiveness of certain policy approaches, such as the U.S. government's subsidy in the late 2000s to replace old vehicles under the so called Cash for Clunkers program (Busse et al. 2012; Gayer and Parker 2013).

Cold-Start During engine start, combustion in the cylinders is facilitated by providing fuel-rich conditions, but the three-way catalytic converter does not operate optimally until it reaches a certain high temperature (~250–400 °C). Therefore, during the initial couple of minutes after start-up, emissions can be up to a few orders of magnitude higher than when the engine is hot. Cold-start emissions comprise a substantial portion of emissions across the entire certification test cycle (Drozd et al. 2016). Drozd and colleagues (2016) also calculate that one cold-start event can contribute emissions that are equal to those from 200 miles of driving. Because average commute distance in the United States is much shorter than 200 miles, the authors argue that the majority of vehicle-produced emissions are dominated by cold starts. The excessive cold-start emissions are included in various inventories and regulatory models, such as the U.S. EPA's MOVES and CARB's EMission FACtor (EMFAC) models. Some manufacturers have developed technological solutions, such as electrically preheated catalysts or the use of trapping materials, to control such emissions, but their use is not widespread and the control of cold-start emissions remains a challenge.

Gasoline Direct Injection Historically, the dominant method used to introduce gasoline in combustion chambers has been port injection, where fuel and air are mixed before their introduction into the combustion chamber. In a gasoline direct-injection engine, the fuel is injected at a higher pressure directly into the combustion chamber. Direct injection has many advantages, including improved fuel efficiency and better engine performance. Because of certain features of the combustion process, however, the particulate emissions increase, particularly in the UFP range (Raza et al. 2018). Because the removal efficiency for PM by the three-way catalytic converter is relatively low, an increase in tailpipe UFP emissions is observed. Slightly more than half of all new cars sold in 2019 in the United States were equipped with gasoline direct injection, and a great majority of cars from some manufacturers are equipped with gasoline direct injection (U.S. EPA 2021b). Many such vehicles combine gasoline direct injection with turbocharging, vehicle downsizing, and other technologies, to boost fuel efficiency.

The emission of relatively high levels of UFPs from gasoline direct-injection vehicles is an area of potential concern, and the EU and China have established particle number standards which potentially address such emissions (Williams and Minjares 2016). The use of catalyzed gasoline particulate filters can reduce UFP emissions significantly (McCaffery et al. 2020); gasoline particulate filters are now being used in new cars, although some automakers appear to be able to meet the regulatory limits for particle number without the use of gasoline particulate filters (Rodríguez et al. 2019). Additionally, there continues to be an interest in reexamining the European particle number standard because of its shortcomings (e.g., counting only solid particles with a diameter of greater than 23 nm) (Rodríguez et al. 2019).

In the absence of specific regulations to address UFP mass or particle number emissions in the United States, regulation of UFP emissions is encompassed within the broader limits on total PM emissions in the U.S. EPA's Tier 3 standards and the equivalent California LEV III regulations. Both sets of regulations began to be phased in from 2017 and will be fully implemented by the mid-2020s (U.S. EPA 2018). It is anticipated that these standards, together with ongoing technological developments, would in effect address the gasoline direct-injection UFP emissions issue in the United States as part of the overall reductions in PM emissions to 3 mg/mile (1 mg/mile in California).

Gasoline direct-injection emissions, with or without a gasoline particulate filter, are thought to potentially influence the SVOCs emissions and secondary organic aerosol formation potential (Kuittinen et al. 2021). However, a study by Zhao and colleagues (2018) examining the impact of emissions from a variety of light-duty vehicles on secondary organic aerosol formation concluded that the shift from port-fuel injection to gasoline direct-injection engines does not appear to produce a change in the secondary organic aerosol production capacity.

They also stipulate that the replacement of older vehicles with newer vehicles, which would be certified to more stringent standards, should reduce secondary organic aerosol levels.

2.5 DIESEL-POWERED VEHICLES

Diesel engines are a key part of the world's transportation and industrial infrastructure, especially in heavy-duty applications. Diesel engines are used in an extremely wide range of applications—not only in on-road uses such as buses and trucks (and cars in some markets), but also for many nonroad applications, such as small equipment and tools, construction equipment, municipal equipment, and locomotive and marine applications. The discussion in this section is limited to on-road vehicles widely used for transportation and goods movement. Compared with gasoline engines, diesel engines are more durable and efficient, and they produce a greater torque. Despite these advantages, there have long been concerns about the impact of old technology or traditional diesel engine emissions on the environment and human health because of their high emissions of PM (soot), NO_x, and hydrocarbons (including some carcinogens). Modern, new-technology diesel engines have greatly reduced such emissions with certain engine modifications and exhaust after-treatment technologies.

2.5.1 CONTROL TECHNOLOGIES

Studies published in the 1970s and 1980s provided evidence for mutagenicity and carcinogenicity of diesel exhaust, diesel soot particles, and PM (IARC 2014). Although there were earlier smoke-based emission standards, the new scientific evidence for toxicity prompted regulatory agencies to adopt measures to control diesel emissions. However, the control of diesel emissions proved technologically more challenging and lagged the control of gasoline emissions. Later health studies, both animal and epidemiological, demonstrated the carcinogenic (IARC 2014) and other health hazards of exposure to diesel emissions; subsequent regulations to control emissions grew in their stringency (Table 2.1).

Two of the earliest diesel emission control technologies were exhaust gas recirculation and the diesel oxidation catalyst; both were deployed in the mid-2000s. The exhaust gas recirculation reduces NO_x formation by reintroducing a part of the cooled engine exhaust back into the combustion chambers, thereby diluting the air-fuel mix and cooling the combustion temperature which reduces NO_x formation. Diesel oxidation catalyst oxidizes NO, CO, and hydrocarbons and other volatile compounds. Importantly, the diesel oxidation catalyst only partially oxidizes the PM because the temperature of the exhaust is not high enough, so a solution for controlling PM emissions had to be found.

During the 2000s, the emission standards of PM and NO_x for diesel engines became far more stringent (Table 2.1). The tightening of emission standards was preceded in 2006 in the United States by the lowering of the sulfur content of diesel fuel to <15 ppm; such ultra-low sulfur fuel is essential to reduce PM formation as well as to avoid poisoning of the catalysts used in after-treatment devices. In 2007, a lower standard for PM emissions, of 0.01 g/bhp-hr, went into effect, which was 10 times lower than the earlier limit. To meet this standard, engine manufacturers utilized diesel particulate filters in conjunction with diesel oxidation catalyst; together, they are extremely effective at removing diesel PM and VOCs (Khalek et al. 2011). Diesel particulate filters are typically made from a honeycomb-like ceramic structure in which alternate channels are blocked and the walls are coated with precious metal catalysts.

Because diesel engines work under high air-to-fuel ratios and high temperatures (compared with gasoline engines), the combustion process also generates substantial amounts of NO_x ($NO + NO_2$). The diesel oxidation catalyst and diesel particulate filters reduce PM levels but oxidize NO to NO_2, effectively enriching the exhaust in NO_2, which then must be reduced to N_2. Regulations beginning in 2007 in the United States saw the start of the phase-in of updated standards for lowering NO_x emissions to 0.2 g/bhp-hr, or 20 times lower than the previous standard. Therefore, the selective catalytic reduction system was introduced in which a reductant—generally

Table 2.1. U.S. Heavy-Duty Highway Diesel Engine Emissions Standards (g/bhp-hr)—Testing Under Federal Test Procedures[a]

Model Year	NMHC + NO_x (g/bhp-hr)	NO_x (g/bhp-hr)	$PM_{2.5}$ (g/bhp-hr)
1974–1978	16	—	—
1979–1984	10	—	—
1985–1987	—	10.7	—
1988–1989	—	10.7	0.6
1990	—	6.0	0.6
1991–1993	—	5.0	0.25
1994–1997	—	5.0	0.1
1998–2003	—	4.0	0.1
2004–2006	2.4	—	0.1
2007	2.4	0.2	0.01
2024–2026[b]	—	0.05	0.005
2027[b]	—	0.02	0.005

NMHC = nonmethane hydrocarbon.

[a] Simplified and adapted from U.S. EPA 2016.

[b] California standards (CARB 2020c). Changes in federal standards are under discussion.

a solution of urea—is injected into the exhaust stream. At the high temperatures in the exhaust stream, urea decomposes into NH_3, which then reduces NO_2 to N_2 on the selective catalytic reduction catalyst. To remove any remaining NH_3, an ammonia oxidation catalyst is commonly used to convert NH_3 to N_2. (However, ammonia oxidation catalyst can also lead to the formation of small quantities of nitrous oxide [N_2O], a gas with climate-warming effects.) Working in concert, these aftertreatment technologies are highly effective in greatly reducing (10- to 100-fold or greater) the emissions of CO, $PM_{2.5}$, and NO_x, as well as hundreds of toxic compounds—some of which are known animal carcinogens—that were present in old-technology diesel engine exhaust (Khalek et al. 2015).

The EU has also enacted legislation encompassing emission standards, testing and approval, and enforcement (Williams and Minjares 2016). Although the regulations have similar objectives, the differences between the timing, enforcement, and other features of the NO_x standard have made a large difference in the degree to which standards have been met in the United States versus the EU (Nesbit et al. 2016). Some of these differences, which the EU is now taking steps to overcome, are related not to technological issues but to implementation challenges in a multinational EU system. Meeting the latest EU standards to reduce diesel emissions requires the same technologies and the ultra-low sulfur fuel as required in the United States. The Euro 6/VI standards, enacted in 2009 and modified subsequently, became effective in 2013–2014 and set emission standards that are similar to 2010 U.S. standards (although there are other differences in the way the standards work), resulting in a significant decrease in emissions compared with the Euro 5/V standards. The Euro 6/VI also introduced for the first time a solid particle number standard, which the United States has not done, as discussed above. Becasue many countries around the world, including China and India, model their emission standards on the Euro standards, Williams and Minjares (2016) argue that by adopting the Euro 6/VI standards, these countries can achieve up to 99% reduction of vehicular pollutant emissions such as $PM_{2.5}$.

Diesel-powered vehicles are a diverse group that includes tractor trailers, freight and public works trucks, transit and school buses, vans, pick-ups, and in some markets cars. Many vehicles retire from use in one category only to be repurposed for another category. Nearly half of all commercial trucks in the United States, about 5.5 million class 3-8 trucks, are now equipped with the new devices that control PM and NO_x emissions (Diesel Technology Forum 2021). In addition to turn-over, this transition has been facilitated by stringent regulations in some places, for example in California and especially at California's ports. In other cases, the transition has been facilitated by programs such as the Diesel Emissions Reduction Act, which provides grants for the replacement or retrofit of old-technology diesel vehicles (including school buses) and equipment.

The very substantial reductions in heavy-duty vehicles emissions from the introduction of the new technologies has also been linked to improvements in air quality. Yu and colleagues (2021) calculated the fuel-based NO_x emissions inventories for the United States and reported that total on-road NO_x emissions have declined by about 70% nationally since 1990. More recently, NO_x emissions declined by 48% and 32% in California and the United States, respectively, since 2010, when selective catalytic reduction-equipped engines were introduced; the greater reduction in California reflects the additional steps taken in that state to accelerate enforcement of the emission standards. The 2019 air emissions inventory for the Port of Los Angeles, which has highly restrictive emissions regulations, reports that, compared with 2005, diesel PM, NO_x, and sulfur oxide emissions diminished by 87%, 62%, and 98% respectively, while the cargo volume increased by 25% (Port of Los Angeles 2020). Based on measurements during 1990–2012, Propper and colleagues (2015) concluded that diesel PM decreased by 68%, even while the vehicle-miles traveled in California increased by 81%. Haugen and colleagues (2018) collected emissions data at a weigh station near Anaheim, CA in 2017, and reported a 55% reduction in NO_x emissions compared with 2008-based emission measurements from 1,844 heavy-duty vehicles. However, they and others have also observed that as the after-treatment technologies age, their performance may deteriorate; this issue is being addressed by more recent regulatory actions by the U.S. EPA and CARB (Ruehl et al. 2021).

2.5.2 REMAINING CHALLENGES

As with the introduction of any new technology on a large scale in the marketplace, some challenges with the use of the new aftertreatment technologies have been observed.

High NO_2 Levels in the Absence of Selective Catalytic Reduction Before selective catalytic reduction was widely deployed, an additional problem of high NO_2 emissions from earlier-generation diesel engines equipped with oxidation catalysts and diesel particulate filters came to light—particularly in Europe with its high proportion of diesel vehicles—despite those vehicles meeting the Euro 4/IV (equivalent to U.S. EPA 2007) standards. For example, Font and Fuller (2016) reported that near-road concentrations of NO_2 and NO_x increased during 2005–2009, when vehicles equipped with diesel particulate filters were first coming on the roads, although road traffic was decreasing and NO_x emission standards were tightening. However, introduction of the Euro 5/V standard in 2005, with its lower NO_x emission requirement, appears to have resulted in the gradual lowering of NO_x levels during 2010–2014, a trend that has continued (Carslaw and Rhys-Tyler 2013, Carslaw et al. 2019). Still, roadside measurements in a number of European cities show NO_2 values that are above the European air quality limit values (EEA 2019a). This issue continues to be a challenge for many

European cities and has led to various actions to restrict diesel vehicles from the central city.

Inefficient Performance of Selective Catalytic Reduction Another technological challenge is that elevated NO_2 emissions are observed when the selective catalytic reduction does not operate optimally because the exhaust stream temperature is too low (that is, below 200–250˚C); such conditions are common during the cold-start, low-load, and stop-and-go driving typically encountered in urban areas (Boriboonsomsin et al. 2018; Posada et al. 2020; Rodriguez and Badshah 2021). NO_2 exposure has direct health effects, and it is also a precursor of ozone. High emissions of NO_2 are a particular challenge in areas that are not in compliance with the ozone National Ambient Air Quality Standard, such as Southern California. To address this problem, regulatory agencies in the United States and Europe are developing regulations, and engine and aftertreatment-technology manufacturers are developing new and supplemental approaches (Walker 2016), especially in view of proposals for further tightening of the emission standards.

Emissions Manipulation In 2015, Volkswagen and other manufacturers were found to have used software to disable NO_x controls when their light-duty, diesel-powered vehicles were operating under real-world conditions (i.e., when not being tested for emissions compliance) (Thompson et al. 2014). Although Volkswagen and the other manufacturers were forced to buy back, recall, or repair millions of cars in the United States and Europe, were levied very heavy fines, and faced corrective actions, it is not clear from more recent studies that the excess NO_2 emissions problems have been fully resolved, particularly in Europe (Posada et al. 2020; Tietge et al. 2019). It should be noted that, in view of the vagaries of EU laws and the multinational jurisdictions that comprise the EU, the legal response to emissions violations in Europe has been more muted than in the United States, and the European diesel fleet continues to have large numbers of high NO_2 emitting diesel vehicles.

Emissions Tampering An example of aftertreatment device tampering has come to light in the United States more recently. In November 2020, the U.S. EPA reported that its investigators had found that after-treatment devices had been tampered with in an estimated 550,000 diesel pickup trucks (15% of the national population of pickup trucks), resulting in higher emissions of regulated air pollutants (U.S. EPA 2020d). This was being achieved by installing a combination of software and hardware and by modifying the engine's calibrations, with the ostensible goal to avoid maintenance costs and to increase fuel economy. The U.S. EPA, working with state and local agencies, has taken steps to stop this illegal activity. The discovery and addressing of this sort of problem underscores the importance of in-use compliance programs.

2.5.3 REGULATORY DEVELOPMENTS

The Volkswagen defeat device episode and the ongoing challenges with the selective catalytic reduction, among others, have led to a number of regulatory developments, with the goal of tightening the overall approach to regulation of in-use emissions from diesel vehicles, including enhanced in-use compliance programs in the United States and significant improvements in the regulation of real driving emissions in the EU.

In the United States, despite recent significant reductions in NO_x emissions, heavy-duty vehicles emissions continue to be the largest source of NO_x and a contributor to the formation of ozone, which is a particular concern in ozone noncompliance areas such as the California's South Coast Air Basin. The U.S. EPA, which had earlier required in-use testing of heavy-duty vehicles (U.S. EPA 2005), is now pursuing comprehensive regulations to reduce NO_x emissions during *all* operating conditions under its Cleaner Trucks Initiative (U.S. EPA 2020a). The Agency has also issued an advanced notice of rulemaking with comprehensive goals, including the establishing of new, lower emission standards for NO_x and other pollutants, exploring opportunities to leverage modern technologies, and streamlining and improving existing requirements (U.S. EPA 2021a).

California is presently ahead of the U.S. EPA in regard to additional diesel regulations and in August 2020 the CARB approved the "Heavy-Duty Engine and Vehicle Omnibus Regulation and Associated Amendments," which will be phased in starting with model year 2024 heavy-duty vehicles (CARB 2020c). This multipronged regulation will cut the NO_x emissions standard to 0.02 g/bhp-hr (a 90% reduction from the 2010 standard) and PM emissions to 0.005 g/bhp-hr (a 50% reduction) (Table 2.1), overhaul engine testing procedures and on-board diagnostic requirements, and extend the required emissions warranty period. The Manufacturers of Emissions Control Equipment has presented evidence that these more stringent emissions reductions can be achieved without an impact on fuel efficiency (MECA 2020). Additionally, California Senate Bill 210 directs the CARB to implement a heavy-duty inspection and maintenance program that would ensure that all vehicle emissions control systems are adequately maintained throughout the vehicles' operating life. Other regulations target longevity of the after-treatment technologies; vehicle idling; and upgrade of certain fleet segments, such as buses and drayage equipment (CARB 2019). The current differences between the proposed CARB and U.S. EPA regulations are likely to be ironed out during later stages of the respective rulemaking processes.

The EU, in the wake of the Volkswagen episode, has set out and begun to implement new so-called real driving emission standards to substantially enhance vehicle certification and in-use performance requirements (EC 2019). The EU is also in the midst of deliberations, under the European Green

New Deal, to enact stricter emission standards (EC 2020a; Mulholland et al. 2021). These new standards will apply to all motor vehicles—gasoline and diesel cars, vans, trucks, and buses—and are expected to significantly improve the EU regulations for the control of TRAP emissions by imposing the use of new technologies, real-time emissions measurements, and durability of all controls.

2.6 NONTAILPIPE EMISSIONS AND TRAFFIC NOISE

2.6.1 NONTAILPIPE EMISSIONS

As new technologies and after-treatment devices have significantly decreased emissions of PM from the tailpipe, interest in nontailpipe emissions of PM, particularly from brake and tire wear, has increased. PM from such sources makes up an increasing proportion of total vehicle-related emissions; although quite variable, in some locations such emissions equal or exceed tailpipe emissions (Figure 2.3) (AQEG 2019; Baensch-Baltruschat et al. 2020; COMEAP 2020; Grigoratos and Martini 2015; OECD 2020b; Rexeis and Hausberger 2009).

Despite the heightened interest, a major challenge with gaining a good understanding of nontailpipe emissions is that the composition of brake pads and tires is highly variable and often proprietary. The composition in various products made by different manufacturers, or at different times by the same manufacturer, is not the same and depends on the intended use and the desired properties, such as physical strength, wear resistance, consumer preference, user behavior and safety requirements, to name just a few of the parameters. Because tire wear is the result of abrasion with the road surface, pavement composition and state of repair also add to the difficulties in characterizing nontailpipe emissions. Also, the need to comply with regulations or agreements can lead to changes in composition, as exemplified by the recent reduction in the amount of copper and other heavy metals in brake pads through a Memorandum of Understanding between the U.S. EPA and a number of industry groups, including brake pad manufacturers (U.S. EPA 2015).

Nontailpipe PM emissions are the result of abrasion of tires, brake pads, and pavement; these emissions are also mixed with resuspended road dust. Other vehicle materials also contribute (e.g., wheel weights and rust from chassis). These emissions comprise particles in a broad range of sizes—including the coarse, fine, and ultrafine ranges—but compared with tailpipe PM emissions, they are generally in the larger size range and have less carbonaceous material and a higher metallic content (Liati et al. 2019; Nosko et al. 2017). A number of metals can be detected in nontailpipe emissions: barium, copper, antimony, iron, and zinc are mostly derived from tires and brakes (although antimony and copper usage is being reduced), and zinc and organic compounds of the benzothiazoles class are derived from tire tread (Denier van der Gon et al. 2013; Grigoratos and Martini 2015; Pant and Harrison 2013). Silicon is generally used as a marker of crustal materials. However, none of these metal species provides a unique marker of nontailpipe emissions, making it especially challenging to characterize the emissions and attribute them to specific sources via ambient measurements. Early results indicate that such variations and the differences in brake assemblies (i.e., drum vs. disc) might affect the levels of airborne particle emissions during brake operation (e.g., Gerlofs-Nijland et al. 2019; Hagino et al. 2016), although additional tests are needed to compare brake pads of different compositions and types that are currently in use and on the market.

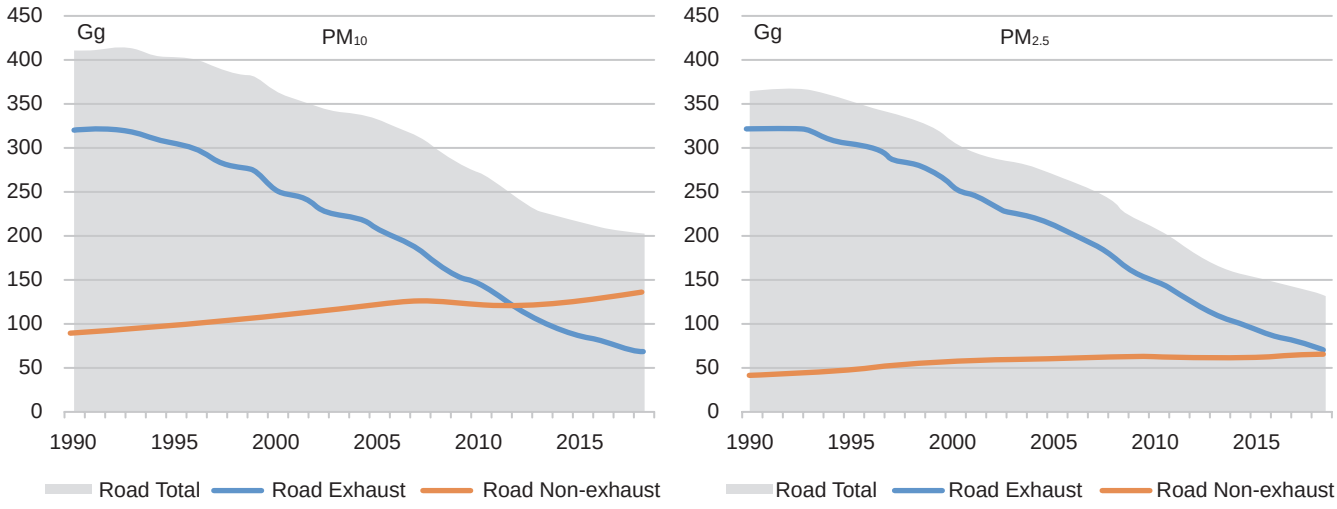

Figure 2.3. PM_{10} and $PM_{2.5}$ emissions from road transport in the EU (1990–2018) (EEA 2020b). Gg = 1,000 tonnes.

Some researchers have investigated the generation and emissions of PM from tires and brakes in laboratories, using brake or chassis dynamometers. These approaches allow the development and use of standardized methods to generate wear particles and to investigate the impact of specific variables. One of the latest examples of this approach is ongoing work by the United Nations Particle Measurement Programme focused on the development of a standardized method for measuring brake-wear particles. Particle Measurement Programme members have developed methods for measuring PM emissions of brake-wear particles (Farwick zum Hagen et al. 2019) and a real-world braking cycle (Mathissen et al. 2019). Using these approaches, a recent study confirmed changes in emissions depending on composition of the brake pad. This study also showed that emissions from brakes were highest during the middle-speed range, compared with low- and high-speed ranges, presumably because brakes are applied with only modest force in low-speed range, with more force in middle range, and infrequently in high-speed ranges (CARB 2020b). The data from dynamometer studies are often used as key input variables in regulatory models, such as MOVES and EMFAC.

Other investigators have sought to characterize nontailpipe emissions and airborne concentrations under real-world conditions, utilizing various chemical markers. To study tire wear near roads, for example, Panko and colleagues (2019) pyrolyzed their PM samples and then analyzed them by gas chromatography–mass spectrometry, focusing on certain polymers present only in the rubber used to make tires. By sampling background, urban, and rural sites, they estimated that tire wear contributed an average of 0.84% of total $PM_{2.5}$ mass. A wide range of emission factors, generally higher than those reported by Panko and colleagues (2019), have been reported in the literature (EEA 2019b), and discussion continues about the best marker and method to measure tire wear under real-world conditions.

It has been known for some time that concentrations of tailpipe emissions exhibit a distance-decay gradient near roadsides; this pattern is very steep for UFPs and EC, but less so for NO_2; it is also more pronounced on the downwind side of the road than on the upwind side (Karner et al. 2010) (see Figure 6.2 in Chapter 6). Evans and colleagues (2019) studied the decay gradients for both tailpipe and nontailpipe emissions in the vicinity of a highway in Toronto, Canada. They confirmed the decay gradients expected for tailpipe emissions but reported that within the same distance the decay gradient of nontailpipe emissions was more rapid than that of the tailpipe emissions, by an order of magnitude. This presumably reflected the larger diameter of the nontailpipe particles. Silva and colleagues (2021) built and used a mobile platform to collect high-volume samples of ambient air and road-surface PM. By studying the concentrations of a variety of elements in samples collected at different distances from roads, they concluded that the concentration of all metal species decreased significantly as a function of distance from the road, but the decay pattern of the elements typically associated with nontailpipe emissions (e.g., barium and zinc) decreased more dramatically (Huang et al. 2021).

For application in epidemiological studies, dispersion and land use regression models have been developed and applied for exposure assessments. These models have traditionally relied on concentrations of metals, such as copper, iron and zinc, as markers of brake- and tire-derived PM (de Hough et al. 2013: Ito et al. 2016). However, as noted above, the content of some of these metals is changing either because of regulatory pressures or manufacturing demands, requiring caution in their future use. An added difficulty with such modeling is that only a small number of monitors in most jurisdictions analyze PM metal concentrations, thus hindering model development and validation. Moreover, for several traffic-related variables, such as speed and congestion, it is not possible to distinguish between the effects of tailpipe versus nontailpipe emissions (Habre et al. 2020). Models developed by de Hoogh and colleagues (2013) and Ito and colleagues (2016) have found only moderately good prediction ability for nontailpipe PM metals, and the models had limited power to predict source-apportioned nonexhaust sources. There is a need to find new tracers or surrogates of nontailpipe emissions that represent the current and near-future composition of brake pads and tires, to develop readily scalable methods for estimating exposures, and to conduct studies of the potential health effects of nontailpipe PM (see future research needs in Chapter 14).

Finally, electric and hybrid vehicles use regenerative braking, which captures the kinetic energy of deceleration to recharge the electric battery, thus reducing the need for frictional braking and contributing to their higher efficiency. Although such cars might produce greater amounts of tire wear because they are generally heavier and have higher torque than internal combustion engine cars, the use of regenerative braking would likely reduce brake and tire wear emissions (i.e., because of reduced slippage between the tire–road interface). However, the estimates of such emissions and experimental data vary widely, potentially because of differences in the methods used (Beddows and Harrison 2021; OECD 2020b; Timmers and Achten 2016). Because the number of vehicles in the fleet that employ regenerative braking is rapidly increasing, there is a need to improve our understanding of brake and tire wear emissions from such vehicles.

2.6.2 TRAFFIC NOISE

Ambient noise—unwanted and unpleasant sounds—ranks high among important environmental health risk factors (Hanninen et al. 2014). In a recent report, the EEA estimated at least 20% of the EU population lives in areas where traffic noise levels are harmful to health (EEA 2020a). In the United States, it has been estimated that in 2013 at least 146 million people (~46% of the population) were at potential risk of

hypertension, one of the possible health outcomes due to noise, although the U.S. data on noise exposure are dated and inadequate (Hammer et al. 2014). Not surprisingly, the levels of road noise are closely correlated with the concentrations of certain components of TRAP, making isolating the health effects of noise exposure from TRAP difficult.

For the United States, a nationwide transportation noise map is available from the U.S. Department of Transportation for recent years (U.S. DOT 2021). Unlike air quality regulations, the responsibility of ambient noise regulations and enforcement lies primarily with state and local governments in the United States. The U.S. EPA is not active in this area; most of the responsibility for traffic noise issues resides within the Federal Highway Administration, which enforces its regulations of vehicle noise standards and abatement requirements through the highway financial aid program (Vehicle Noise Emission Standards 40 CFR 205.52; U.S. FHWA 2017). Additionally, many states and cities also have rules and ordinances for noise control.

Historically, noise has received a higher priority in Europe than in the United States. Since the 1970s, successive Europe-wide directives have laid down specific noise emission guidelines for transportation and community noise. EU Directive 2002/49/EC harmonized noise assessment and mandated EU member states to produce strategic noise maps in large cities, near the main transportation infrastructures and industrial sites (EC 2020b). Most recently in 2018, the European office of the WHO issued comprehensive environmental noise guidelines, supported by a series of systematic reviews, which includes noise originating from mobile sources (WHO 2018).

The general approach to managing automotive noise focuses on controls at the source (i.e., the vehicle), interfering with the propagation path along which noise travels, and noise-proofing the dwellings where people work and live (Brown and van Kamp 2017). Control of noise is an important factor in automotive design; indeed, a whole field of engineering—noise, vibration, and harshness engineering—is devoted to it. Noise arises from various processes within the powertrain, such as air intake, fuel delivery, combustion chamber, crankshaft and transmission, brakes, exhaust, and muffler. Other characteristics, such as vehicle weight, engine type, presence of turbocharger, chassis design, air conditioning use, vehicle speed and aerodynamics, tire tread and pavement surface, and miscellaneous vibrations also play important roles. Various sources of noise in modern vehicles are controlled by improvement in engine and vehicle design, vibration isolation and damping, acoustic insulation, and road-surface and tire-design improvements, among many other approaches.

Abatement of noise along the path it travels can be achieved, generally only partially, by constructing physical noise barriers or planting vegetation and, most effectively, appropriate traffic management, land use, and urban design; the Federal Highway Administration requires noise abatement as a part of its aid programs (U.S. FHWA 2017). Road traffic noise continues to be a challenge, especially in heavily trafficked areas and for disadvantaged communities often living in proximity to roadways (Casey et al. 2017; EEA 2020a).

Finally, another approach to prevent traffic noise penetration into buildings is by the use of materials that absorb, reflect, or diffuse the noise. These materials may be applied as retrofits or used during new construction. Many local jurisdictions and the U.S. Department of Housing and Development for the projects it finances stipulate that interior sound levels in buildings be about 45 dB (U.S. HUD 2009).

Noise from the power train, a key component of automotive noise, is greatly reduced in hybrid and particularly electric vehicles traveling at low to moderate speeds, so much so that rules are emerging to add sound at low vehicle speeds to warn pedestrians and bystanders. Although the reduced powertrain noise is likely to provide some respite for busy neighborhoods, the noise from tires traversing roads at high speeds becomes louder, appearing to overtake the advantage of reduced power train noise (Iverson et al. 2015).

2.7 ALTERNATIVE FUELS

Most of the fuel used for powering motor vehicles around the world is currently obtained from distillation of crude oil; the transportation sector consumed 26% of all the oil used in the United States in 2020 (U.S. EIA 2020b). Ethanol and biodiesel—both blended at low levels with gasoline or diesel—are the most prominent alternative fuels in today's market. The development and use of other, renewable, biomass-derived fuels and low-carbon synthetic fuels is a very active field with new developments announced frequently.

The use of low molecular weight alcohols, such as ethanol and to a lesser extent methanol and butanol, have a long history of use in light-duty vehicles (Kovarik 1998). Fuel shortages during World War II led the U.S. Army to significantly increase the use of ethanol, made mostly from corn. Later, to address CO- and ozone-related air quality issues arising from vehicular emissions, the Clean Air Act Amendments in 1990 mandated the addition of oxygenates to gasoline. Although methyl-tert-butyl ether was initially used for this purpose, its use was soon discontinued because of ground water contamination incidents; ethanol became the oxygenate of choice for light-duty vehicles.

For the heavy-duty vehicles sector, the use of plant-based fuels for powering compression-ignition engines also has a long history; indeed, Rudolf Diesel powered his first engine with vegetable oil. A transesterification process was later developed that, after removal of byproducts, yields fatty acid alkyl esters (or biodiesel) from vegetable oils to serve as a

transportation fuel, especially when blended with petroleum diesel (Balasubramanian and Steward 2019; Bušić et al. 2018). Today, biodiesel is manufactured from animal fats and waste grease from cooking but most commonly from vegetable oils derived mostly from soybean in the United States and rapeseed (canola) in Europe. Biodiesel, which is a mix of fatty acid methyl esters, is used as low-level blends (B2 and up to B20), without the need for engine or fuel infrastructure modifications. Finally, renewable diesel can be manufactured from the hydrolysis of cooking oil or tallow. The product comprises hydrocarbons that can be used directly as fuels, without the need for blending. The availability of renewable diesel is currently small, but it is increasing in response to the requirements for low-carbon fuels in California and some other states.

Despite the earlier regulatory and market pressures, it was The Energy Policy Act (42 USC §13201 et seq. [2005]) and the Energy Independence and Security Act (42 USC § 152 [2007]) that finally put ethanol, as well as biodiesel and other renewable fuels, on a firm footing by mandating renewable fuel blending by oil refiners. The rationale for these actions was a combination of improvements to fuel efficiency, performance, energy security, and reductions in GHG and TRAP emissions. The laws created a rather complex (and, by now, highly contentious [Loyola 2019]) mechanism—the Renewable Fuels Standard—which gradually increases the proportion of ethanol, biodiesel, and other so-called advanced biofuels in the nation's fuel supply through 2022 (U.S. EPA 2019d). At the present, the United States is considerably behind the year-wise mandates for alternative fuels blending for a variety of complex reasons, including the lack of advanced biofuel availability (Loyola 2019; U.S. EPA 2020c). Currently, most gasoline sold in the United States contains 10% ethanol, which is obtained mostly from corn. The diesel fuel in the U.S. market is generally a 5% biodiesel blend, derived from soybeans and other sources. The increase in the use of such fuel blends can be attributed to economic factors including the availability of various government incentives, subsidies, and requirements to grow the crops and to produce, sell, and use alternative fuels to meet the requirements of the Renewable Fuel Standards. Although vehicles are available that can operate on very high blend levels (such as 85% ethanol [E85]), they are not in wide use, and their numbers are likely to remain small in the future.

In Europe, the use of biofuels is a part of the Renewable Energy Directive for the period 2021–2030 (RED II), which specifies increasing levels of renewable fuels in the transportation sector (ICCT 2018). The directive gives leeway to member countries to tailor their policies to meet or exceed targets. There has been a controversy in Europe about biodiesel, owing to its dependence, until recently, on the import of palm oil from Indonesia and Malaysia that provided incentives in those countries for the clearing of tropical forests (Keating 2019); such imports have now been banned in Europe.

The influence of biofuel blending on tailpipe emissions has been studied by many investigators. The findings of available studies are greatly influenced by testing parameters such as fuel composition and properties (for example, blend levels and source of the biofuel, how the blends were prepared, amounts of fuel constituents such as benzene and other aromatic compounds, and various physical attributes), as well as engine characteristics, emissions certification, and operating conditions. Given such complexities, as well as the attendant expense of testing, relatively few studies have been performed that systematically parse the effects of the myriad factors in detail (U.S. EPA 2019b). Consequently, the results of emissions testing with biofuel blends have shown a lot of variability. Importantly, it should also be noted that few studies have been performed with late-model Tier 3 or LEV III vehicles.

In January 2021, the U.S. EPA published a report that examined whether the mandated volumes of renewable biofuels required by the law would adversely impact air quality because of changes in vehicle and engine emissions and whether any regulatory action would be necessary to mitigate such impacts (U.S. EPA 2021c). Based on the modeling that was developed for this report, the U.S. EPA concluded that, on its own, marketing of biofuel blends (10% ethanol and 5% biodiesel) in compliance with the Renewable Fuel Standard requirements would have led to increases in several air pollutants. However, the Tier 3 motor vehicle emissions and fuel standards, phased in between 2017 and 2025, are more stringent than earlier standards. Consequently, the U.S. EPA determined that any increases in emissions due to biofuel blending would have been mostly offset with Tier 3 vehicles in 2018 and fully offset by 2030. Although this was the case for PM, NO_2, and air toxics, the U.S. EPA found some increases in the emissions of acetaldehyde in some geographic areas. Acetaldehyde is a primary byproduct of ethanol combustion; no fuel controls would address this pollutant except reducing the use of ethanol, which would run contrary to provisions of the Renewable Fuel Standard. In summary, the U.S. EPA concluded that "no additional fuel control measures are necessary . . . to mitigate adverse air quality impacts of required renewable fuel volumes."

With respect to the overall impact of the alternative fuels on CO_2 emissions, there has long been a question about the balance between the lower CO_2 emissions during vehicular use versus CO_2 generated in the upstream production of the fuels. Additionally, there have also been concerns about potential other impacts of biofuel production (such as deforestation, diversion of agricultural land and resources such as water to biofuel production). Consequently, the changes and the shifts in the location and quantities of emissions along the entire fuel cycle requires that a life-cycle analysis of the fuel-vehicle system be conducted so that the net environmental effect on the entire system can be evaluated in a comprehensive and consistent fashion. However, life-cycle analyses are highly

susceptible to initial assumptions—some based on data and others on conjecture—so such complex evaluations and their conclusions have been debated in the literature (e.g., see Malça and Freire 2011). Some earlier assessments raised doubts about the overall climate advantages of corn ethanol. However, more recent assessments point out that improvements in corn production and ethanol refinery technologies, along with a lack of land-use changes assumed in earlier analyses, have led to an overall GHG benefit (Lewandrowski et al. 2020, 2021). Nevertheless, the matter is far from settled and the debate continues.

Although ethanol and biodiesel arguably lower the life-cycle CO_2 emissions, they represent about 5% of the energy consumed by the U.S. transportation sector in 2020 (U.S. EIA 2020b); thus, their use would need to increase greatly to produce a substantial impact on total U.S. GHG emissions. In a recent study, Bieker (2021) probed the impact of current biofuel policies and future blend levels on the reduction of life cycle GHG emissions from gasoline and diesel vehicles; the author concluded that the reduction will be negligible to 9% (Bieker 2021).

The use of biofuels for on-road transportation is forecast to stay at about today's blend levels and is expected to grow only modestly over the coming years in the United States and Europe. However, their use may increase in developing countries (OECD/FAO 2020a; U.S. EIA 2020a). Biofuel use will depend on policy implementation and economic factors, including oil prices, tax incentives, agricultural policy, export markets, breakthroughs in nontraditional sources of biofuels, and the results of efforts to promote electrification of the fleet. If internal combustion engines are indeed phased out over the next 25 to 30 years, it is possible that the demand for biofuels will decline. At the same time, because electrification is currently not an option for aviation and maritime travel and shipping, it is quite possible that low-carbon renewable fuels will find a place in such applications.

In conclusion, in terms of tailpipe emissions of TRAP from late model vehicles, it appears that the use of low blends of ethanol or biodiesel is not likely to lead to significant increases compared with their base petroleum fuels; the many caveats to this conclusion are discussed above. As the fleet turns over and more recent models comprise a greater portion of the vehicles on the road, it is likely that any impacts of biofuel blending on air quality would be reduced further by new emission-control technologies.

2.8 CLIMATE CHANGE MOTIVATED REDUCTIONS

Climate change, caused by the anthropogenic emission of CO_2 and other climate-forcing gases, is the most urgent problem of our times. There have been many activities, debates, publications, and controversies about meeting the goals of programs and strategies—generally under the auspices of the United Nations and through a series of international conferences—to reduce GHG emissions. Most nations are now committed to a variety of goals and strategies, although thus far concrete actions for GHG emission reductions have been insufficient and fall short of the earlier voluntary commitments. There is general scientific agreement that to limit global warming to 1.5°C the world needs to reach net zero GHG emissions by 2050 (Masson-Delmotte et al. 2021). President Biden has laid out ambitious plans for the United States to reach the goal of economy-wide net-zero (that is the sum of all emissions and removals of GHG gases) by 2050 (U.S. The White House 2021). Many, but not all, major economies in the world have also pledged similar reductions by 2050.

Beginning in 2017, cars and trucks in the United States were responsible for more CO_2 emissions than any other economic sector, including power plants (U.S. EIA 2017). Furthermore, CO_2 emissions from power plants have been decreasing, while emissions from the transportation sector have been increasing (U.S. EIA 2017). The transportation sector, relying very heavily on combustion of fossil fuels, contributes about 30% of total GHG emissions in both the United States and Europe; the global proportion of GHG emitted from the transportation sector is about 15% (U.S. EPA 2021d). The main GHG emissions of concern from the transportation sector are CO_2 (80% for United States), along with smaller amounts of methane (10%), N_2O (7%), and hydrofluorocarbons (3%). It is important to note that many solutions for reducing GHG from transportation (e.g., improved fuel economy, electrification) often go hand in hand with reducing TRAP emissions.

Spurred by the 1970s oil embargo and concerns about future fuel scarcity, cost, and national security, the U.S. government put pressure on the automobile industry to improve fuel efficiency; this was well before the climate change phenomenon was widely appreciated. During the late 1980s and subsequent years, as gasoline prices stabilized at relatively affordable levels, even if with periodic fluctuations, governments and industry paid less attention to fuel economy, which consequently stagnated. Since about 2005, fuel economy has increased again (Figure 2.4). Over this time frame, however, vehicle miles traveled have increased and consumer preferences have shifted to larger, heavier, and therefore less fuel-efficient vehicles, such as SUVs and small and medium-size trucks; these preferences have partly counteracted the gains in fuel economy. Today, half or more of light-duty vehicles sales fall in these categories in the United States (U.S. EPA 2021b). In Europe, SUV sales also make up a significant and rising part of total new auto sales (ICCT 2020).

Awareness about climate change and the realization of its serious consequences accelerated in the new century. There were also significant legal developments in the United States (Massachusetts vs. Environmental Protection Agency,

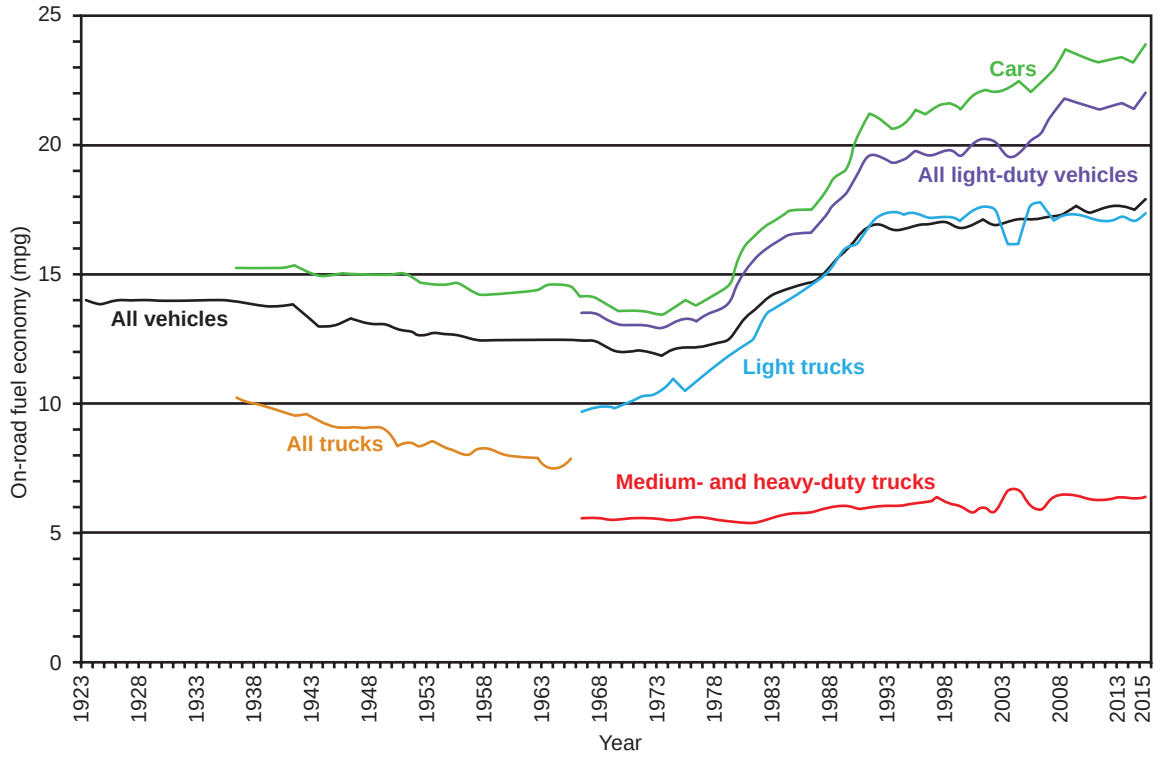

Figure 2.4. On-road fuel economy of vehicles from 1923 to 2015 (Sivak and Schoettle 2017).

549 U.S. 497 [2007]) which forced the U.S. EPA to develop policies to curb GHG emissions (U.S. EPA 2020e). For the transportation sector, the policies designed to increase fuel efficiency are now central to GHG controls. Also, the regulatory actions are now focused on electrification of the powertrain (as exemplified by hybrid and electric vehicles, discussed later), alternative fuels with lower carbon intensity (such as renewable or biologically based fuels, discussed earlier), reduction in travel demand by improved public transportation and other policies, and, to much lesser degree given the lack of political support for such measures in the United States, pursuing programs that put a tax on carbon emissions. In view of the climate impact of GHG emissions, the long-term goal of these programs is to reduce the use of fossil fuels for transportation and, instead, rely on renewable energy derived from wind, solar, and other sources to power electric vehicles.

2.9 ELECTRIC-POWERED VEHICLES

Although electric vehicles perform better than traditional internal combustion engine vehicles in many respects, the major impetus for their development is their lower GHG emissions profile. Such vehicles are far more efficient than their internal combustion engine counterparts in converting fuel energy into propulsion. However, because of high battery cost and limited range, their market share has been modest until recently. With more than 20 years of experience and technical developments, with increased awareness and urgency regarding climate change and with supportive government policies, battery technology has improved and costs have begun to come down. As a result, the development and projected market for electric vehicles is on a steep climb, which bodes well for reduction in both TRAP and GHG emissions. The electricity used to power such vehicles is derived either from a utility source or a hydrogen-based fuel cell; the vehicle uses the electricity either as the primary source of energy or uses it in tandem with an internal combustion engine to improve the overall vehicle efficiency. Such vehicles come in several configurations, from hybrid and plug-in hybrid vehicles to battery or fuel-cell electric vehicles.

Hybridization involves the introduction of an electric propulsion system to work synchronously with, or in assistance to, the internal combustion engine. Such vehicles are powered by both a petroleum-based internal combustion engine and an electric motor that uses energy stored in a battery. The battery is recharged through regenerative braking and by the internal combustion engine (i.e., without an external electricity sources). Plug-in hybrid vehicles are also propelled by an internal combustion engine and electric motor, but their batteries can be recharged by plugging into an external electric

power source. Both hybrid and plug-in hybrid vehicles have a short range of operation on electricity alone, but the gasoline engine extends the overall driving range.

Electric vehicles are powered by an electric motor alone, using energy from a battery that is recharged by plugging into a source of power or by an on-board hydrogen fuel cell. Historically, battery electric vehicles were among the first automotive designs (Matulka 2014). Because of the high battery cost, weight, and low energy density compared with hydrocarbon fuels, combustion engines became and remain the dominant vehicle propulsion system. Because they rely entirely on power from the electric grid or hydrogen fuel cells, electric vehicles do not produce local tailpipe emissions. Although the initial purchase price of all electric vehicles is currently higher than internal combustion engine vehicles, with lower maintenance costs, an expanding market, and improved technology, their costs are expected to head toward parity with traditional vehicles (Penney 2021).

Electrification is now also being applied to heavier vehicle classes. Today many SUVs and light trucks are available in hybrid, and more recently as fully electric, models (Smith et al. 2019). The recent introduction of bi-directional charging—whereby the charged-vehicle battery can be used as a source of electricity, for example, for powering a home or light equipment—opens up new avenues for usefulness of electric vehicles. Electric urban buses and delivery vehicles are also now available, but the most challenging application for electrification is long-haul heavy-duty trucks whose power demands are high and for which a (fast) recharging infrastructure is necessary. The technology solutions to these problems will probably be available but may take some time.

The disadvantages of the battery in electric vehicles—their size, weight, recharging time, and the generally limited range—are overcome in hydrogen fuel-cell vehicles. These use hydrogen to produce electricity, which powers the motor. Hydrogen produces no emissions except water. Currently, these vehicles have a range of 250–350 miles or more, and the onboard hydrogen tank can be refilled in minutes (U.S. DOE n.d.). Similar to battery electric vehicles, these vehicles are more efficient, their efficiency is boosted by the replacement of a large and heavy battery with a light and small fuel cell. However, development of the fuel-cell powered vehicles has lagged behind that of other electric vehicles. Additionally, there is as yet little hydrogen infrastructure in the United States or Europe. Developing one will be expensive although government support is now being mobilized (e.g., California Energy Commission, n.d.). Finally, the overall climate benefit of fuel-cell vehicles depends on the carbon footprint of the hydrogen. Fuel-cell vehicles is an active area of research and development; a limited number of models are now being marketed for sale in restricted regions of the United States.

2.9.1 LOOKING AHEAD

In addition to technological developments, electrification of vehicles in the United States is being driven by a host of emerging and evolving regulatory changes. The state of California has led the way, through a number of programs to reduce GHG emissions from all sectors of its economy (CalEPA n.d.). Transportation emissions, which account for 41% of the state's current GHG emissions (CARB 2020a), are being targeted by aggressive actions through programs such as the Clean Fuels Program, Clean Cars 4 All, adoption of electric vehicles and building of charging infrastructure, reduction of GHG and pollution from freight and port activities, and by committing the state to transition away from gas-powered vehicles by 2035 (Lashoff and Saha 2020). In late 2021, the U.S. Congress passed and the President signed the Infrastructure Investment and Jobs Act, which includes a substantial increase in electric charging facilities (U.S. The White House 2021). Other proposals and bills are also being considered by the U.S. Congress to further promote electrification and other climate-friendly solutions. Washington has set a goal of 50% of all vehicle sales to be electric by 2030 (Kerry 2021).

The EU is already ahead of the United States in electrification of the fleet, and sales of electric vehicles increased very sharply during 2020 and 2021 (Wappelhorst 2021). The European Green Deal, aimed at making the EU carbon-neutral by 2050, stipulates about 1 million public charging stations for 13 million zero- and low-emission vehicles by 2025, which would be a very steep increase. The Chinese government also has ambitious plans. For a variety of mixed motivations, including the aspiration to move ahead of the rest of world in a cutting-edge technology area, the Chinese government has put a premium on developing electric vehicles and battery technologies, offering myriad supportive policies and generous subsidies to its industry. China's target is an approximately 20% share for new energy vehicles in new vehicle sales by 2025 in China, which is the largest global market for automobiles.

Thus, it seems highly probable that the proportion of internal combustion engines vehicles in the world fleet will decline and that of electric powered vehicles will rise rapidly. In addition to technology developments and government actions, a number of automobile manufacturers have indicated plans to phase out petroleum cars while making huge investments in electric car manufacturing.

Despite this momentum, it is important to note that the electric vehicle market still has several barriers to overcome (Requia et al. 2018). The overall environmental benefit of electric vehicles is closely tied to the degree of decarbonization of the electric grid: the more renewable or clean the source of energy, the smaller climate footprint of electric vehicles. Although there are substantial regional and temporal variations within the United States, the national average

electricity generation mix is roughly 41% from natural gas, 19% from coal, 20% from nuclear, and 20% from renewables (including hydropower) (U.S. EIA 2021b). Of all the sources of power, coal is by far the least expensive but also the most polluting. In comparison, natural gas—although also a fossil fuel—burns more cleanly and is a preferred fuel for the short run.

Another issue with all electric powertrain vehicles concerns the battery: its use and disposal. Electric vehicle batteries use metals such as nickel, lithium, manganese, and cobalt. There are concerns about potential harm to the environment and for occupational and community exposures during metal mining and refining, during battery manufacturing, disposal, and recycling, as well as from accidental exposures (such as from car crashes and fires). Despite their cost, current battery design does not allow for ready recycling (Morse 2021). Additionally, the location of mines for such metals in certain countries may also be a source of international tensions in the future (LeVine 2021).

A robust recharging infrastructure is essential for greater adoption of electric vehicles; similarly, a hydrogen-refueling infrastructure is needed if fuel-cell vehicles are to become more common. The location of recharging stations, whether on outstretched highways, in congested cities or outside multifamily dwellings, is an important consideration. Also, the recharging time for battery-powered vehicles is a factor for the consumer and long-haul truck drivers, although fast-charging technologies are being developed rapidly. Many of the policies currently under consideration propose to build recharging infrastructure, and private groups are also making investments, but fully implementing these plans will take time.

Additionally, it is important to note that vehicle fleets turn over at a slow rate, which is also a challenge in meeting the goals of reduction in GHG emissions. There are also numerous other forces at play, including the market impact of reduced petroleum demand, fuel prices, refineries substituting other petroleum products for liquid fuels, loss of revenues from gasoline and diesel taxes, and other policy changes—such as direct subsidy of fossil fuel extraction and use—that would influence such a transition. In light of such uncertainties, some organizations are circumspect in their projections. For example, the U.S. Energy Information Administration, in its most recent Energy Outlook (U.S. EIA 2021a), estimates that electric and hybrid vehicles will make up only about 20% of light-duty sales in the United States by 2050; this also means that internal combustion engine vehicles will continue to be a part of the fleet for some decades to come (see also Plumer et al. 2021).

Finally, the progress in light-duty vehicles, and in some heavier-duty urban vehicles, is likely to be substantial in the coming years; however, development and deployment of electric technologies for heavy-duty long-haul trucks is more challenging. It is possible that alternative fuels such as hydrogen may fill some of that need, but much technology development is needed to reach that goal.

Notwithstanding these many challenges, if the world community is to achieve the deep decarbonization needed to meet 2030–2050 climate goals, the transportation sector must make deep cuts in its GHG emissions, and the only immediately viable path for doing this for the great majority of on-road vehicles is to electrify the powertrain and decarbonize the power grid (or the source of hydrogen). Given all the benefits and challenges listed above, what is likely to be the overall impact of electric vehicles compared with gasoline or diesel vehicles? This issue has been addressed using life-cycle analysis, which compares the footprint of vehicles—from both the power train and fuel—and includes not only tailpipe emissions but also those from fuel production and vehicle manufacturing. Although there have been many life-cycle analyses, in a comprehensive recent study, Bieker (2021) investigated the GHG emissions of current and future passenger cars in China, Europe, India, and the United States; he looked at internal combustion vehicles and hybrid, plug-in, fully electric, and fuel-cell electric vehicles. Bieker concluded that deep decarbonization can be achieved only with battery and fuel-cell electric vehicles, as their expected lifetime emissions are as much as two thirds lower than those of gasoline cars. As the power grid continues to decarbonize, these figures would get even better. The best climate benefit of fuel-cell electric vehicles is achieved using so-called green hydrogen (produced from fully renewable sources); the benefit would be less with grey hydrogen (generally produced chemically from natural gas, a fossil fuel).

In conclusion, achieving zero emission from vehicles is a high priority for worldwide regulators and manufacturers, as well as for civil society groups. In view of the increasingly evident effects of climate change, the pressure for accelerated and urgent action is mounting. At this time, it seems safe to conclude that, given recent policy initiatives, technological developments, and societal aspirations, the market share for electric vehicles may in fact grow faster than some projections. At the same time, the overall climate benefits of electrification will be realized only by concomitant decarbonization of the electric grid. Also, management of the travel demand, societal travel budget, and alternate mobility options will be a necessary component to meet the challenges of the requisite deep reductions in GHG emissions (Alarfaj et al. 2020).

In the absence of any onsite combustion, the on-road TRAP emissions from electric vehicles are zero. Hybrid vehicles, of course, generate emissions, but less than their nonhybrid counterparts because of their greater efficiency. Besides addressing climate change, the absence of emissions is indeed one of the reasons for their adoption in many jurisdictions, especially in those with difficult air pollution challenges,

such as Southern California. With no tailpipe emissions, the only on-road emissions are nontailpipe emissions (see Section 2.6.1 Nontailpipe Emissions).

2.10 NEW MOBILITY

Since the advent of automobiles, Western societies have mostly relied on private vehicle ownership, which has been supplemented in some places, particularly outside the United States, with public transportation. However, this private vehicle ownership model of mobility is now becoming more complex for several reasons (Sperling 2018; Sumantran et al. 2017). The ubiquity of cars and trucks—with all their attendant benefits—has also produced many challenges, not only those related to emissions, both TRAP and GHGs, but also those from accelerated urbanization and urban sprawl, utilization of space needed for housing, recreation, walking, and bicycling. These challenges are often accompanied with crippling traffic congestion and noise. In the past, a private vehicle was one of the fastest modes of getting from one place to another (at least within short and medium distances), but this assumption is weakening in the face of such interconnected problems. Thus, private automobiles in the increasingly urbanized world are not always an asset, and this is reflected, in turn, in attitudes about private car ownership (McDonald NC 2015; Thigpen and Handy 2018). There is also an increased acceptance of and emphasis on changing urban traffic infrastructure and personal behaviors to reduce GHG and TRAP emissions. Finally, in modern societies, a certain fraction of workers does not need to travel to a centralized workplace (at least not every day), reducing the demand for commuting-related transportation; this trend has become more pronounced since the spring of 2020, when Covid-19-related lockdowns began.

Along with existing vehicular technologies, a combination of new and emerging technologies, such as electrification and autonomous vehicles, digital connectivity and artificial intelligence, are laying the foundation for changes in the movement of people and goods. The term *new mobility* is often used to describe this situation, and it may be understood simply as the evolving and interconnected ways, comprising both existing and new technologies, organizational systems, and ownership, in which we may envision meeting our needs for mobility (Slowick and Kamakaté 2017).

Rapid improvements in digital connectivity, even without powertrain electrification, has been a major factor in these developments. Connectivity in its various forms, most especially with the smartphone, provides opportunities for personalization and minute-to-minute information sharing, along with a myriad of other conveniences. Using mountains of data and powerful analytics, the growing connectivity opens the path to an improved and more efficient experience of movement, helping people with planning the journey, finding and renting transport, and paying for the trip, all along keeping them connected with information on their location through geographic information systems, and personal communications via voice or text. Additionally, connectivity has the potential to ease travel by conveniently coordinating and facilitating different modes of travel, whether walking, bicycling, or taking public transportation, and resolving the first and last mile problem, among others. The new mobility model re-envisions a transition of mobility from an *asset* to a *service*.

Such connectivity has led to numerous additional developments. Ridesharing, through transportation network companies such as Uber and Lyft in the United States allows door-to-door mobility made possible using smartphone applications, allowing for alternatives to personal vehicle ownership. Short-term car, bicycle, and scooter rentals are other uses that depend on digital connectivity. Vehicle-to-vehicle connectivity allows for accident avoidance and soon other benefits, such as vehicle-to-urban infrastructure communication (High Mobility 2018). On a larger scale, connectivity allows for intelligent transportation management, including such functionalities as congestion management on urban roads and highways, traffic and pedestrian routing applications, and truck platooning (linked driving in a convoy), just to name a few (U.S. DOT, n.d.). Interestingly, some of these features are already becoming common in today's internal combustion engine vehicles; as fleetwide electrification spreads, their role is likely to intensify. Autonomous vehicles, if and when they become common, will add to this multifaceted new mobility environment.

As presented above, these potential benefits of a new mobility approach to transportation are arguably too optimistic. More likely, given all the uncertainties, any predictions about the future mobility scenario, energy use, or pollutant reduction is at best speculative. On the one hand, if the promises of new mobility are realized, they may deliver many benefits, including more efficient driving and fuel savings, increased speed, congestion mitigation, reduced vehicle ownership, and higher occupancy, along with the accompanying improvements in efficiencies for individual drivers and the transportation system as a whole. This will result in reductions in TRAP and GHG emissions, particularly as vehicle electrification spreads; it is also likely that some of these benefits will go beyond the transportation sector to other parts of modern societies.

On the other hand, technology penetration is never straightforward and is impossible to predict. There is the potential danger that these developments may be accompanied by increased travel demand and delivery services, with a reduction in the use of public transport. This would lead to more travel and traffic congestion and, therefore, increased emissions and associated adverse health effects. Indeed, Sperling and colleagues (2018) have argued that, in addition

to electrification and automation, unless we abandon reliance on single-occupancy vehicles and adopt pooling and sharing of automobiles, our current problems will continue or worsen and "we risk creating a nightmare." Although the potential for the mobility enhancements may be high in dense urban centers, the question of what role they may play in lower density urban, suburban, and rural areas is still very much open. Finally, the transition to new mobility also demands high levels of investment in infrastructure; while governments are currently investing in and providing incentives for early phases of such developments, their commitment would have to endure over the long run. Ultimately, vigilance on the part of policy makers as well as all citizens will be necessary to ensure that the advantages of the new mobility far outweigh the disadvantages.

Finally, there are also good arguments for avoiding too heavy a reliance on technology, whether old or new, to solve all transportation-related challenges (e.g., Glazener et al. 2021, Glazener and Khreis 2019). Active transport such as walking or cycling are some of the modes of transportation for short distances with little or no carbon footprint. As a part of the new mobility mix, they can make important contributions toward solving transportation challenges. To reduce congestion and TRAP, many cities, particularly in Europe, have banned cars from city centers, and others have established low-emission zones. Cities are also redesigning pedestrian and bicycling infrastructure to encourage active transport. Green spaces not only add to the esthetic of urban living, but they also help with heat island effects, encourage physical activity, and can be integrated with pathways for active transportation. New settlements can also be designed so that the need for transportation is minimized; for example, by building communities where most amenities are available within a walkable or bikeable distance (the so-called 15-minute city). In addition, active transport also helps to overcome a sedentary lifestyle, a growing trend in most high-income countries that is associated with several adverse health outcomes.

2.11 CONCLUSIONS

This chapter has summarized the trends in motor vehicle technologies and their likely future trends, with a particular focus on their impact on TRAP emissions, and with some references to GHG emissions. The focus has mostly been on the situation in the United States and, to a more limited extent, Europe. It has presented evidence for the very significant reductions in TRAP emissions from technological and regulatory developments but also discussed topics that deserve continuing attention and investigation. The overall goal of this chapter was to present contextualized information within which the current epidemiological assessment may be considered, and also to emphasize the need for fine-tuned or newly developed exposure assessment methodologies that would capture the future of evolving emissions scenarios and population behavior. The following are the main conclusions of this chapter:

- TRAP emissions from the transportation sector have declined very substantially during the past several decades. The emissions from well-maintained, late-model gasoline- and diesel-powered vehicles are the lowest they have ever been. This has contributed to improvements in air quality; the important exception being GHG emissions, which have only recently begun to be specifically addressed. Reductions in TRAP emissions are the result of notable improvements in after-treatment technologies, chiefly: the three-way catalyst for gasoline-powered vehicles and a combination of diesel oxidation catalyst, diesel particulate filter and selective catalytic reduction system for diesel-powered vehicles.
- Although most communities are benefiting from significantly reduced TRAP emissions, improved air quality, and reduced exposures, many challenges remain. Examples of such challenges include technological issues (e.g., emissions from cold start and UFP emissions from vehicles equipped with gasoline direct injection engines); the need for improved compliance (e.g., from vehicle aging as well as from tampering and cheating); nontailpipe emissions; older and high-emitting vehicles; and traffic noise. Additionally, NO_x emissions—from selective catalytic reduction-equipped diesel vehicles operating under low-power demand—and the related issue of ozone formation are a continuing challenge in many locations. A variety of policy tools and technological developments are addressing these issues, but the problems are far from solved, and continued progress toward addressing these challenges is needed.
- With respect to fuels, the requirement for very low levels of sulfur has reduced PM formation during combustion and has also allowed the use of, or improved the longevity of, catalyzed after-treatment technologies for use in gasoline- and diesel-powered vehicles. Most gasoline sold in the United States today is a 10% blend of ethanol, and most diesel is a 5% blend of biodiesel. The use of these renewable fuels is likely to continue at today's relatively low levels for road transport. Current evidence does not suggest a large impact on TRAP emissions at low blend levels of biofuels when used in late-model vehicles. The overall impact of biofuels on GHG emissions is controversial. These topics also deserve further research.
- An area of vehicular emissions that is currently receiving greater attention is nontailpipe PM emissions, arising from abrasion of brakes, tires, and road surfaces; in some places, such emissions surpass tailpipe combustion emissions. The presence of some metal species

with well-known toxicological properties is a cause of concern for human health. The composition of tire and brake materials are proprietary; they vary by the use and manufacturer. Consequently, such emissions remain insufficiently characterized.

- The importance and urgency of curbing GHG emissions from the transportation sector has spurred new regulations and technologies. The most prominent among such changes is the electrification of the vehicle fleet, which offers many benefits because of the high efficiency of such powertrains and the absence of combustion emissions at the site of use; the full benefit of electrification will be realized only as the electric grid is decarbonized. Vehicle electrification is currently available mostly for light-duty vehicles; electrification of heavy-duty vehicles is developing more slowly because of many technological challenges.
- The convergence of new technological developments outside the transportation sphere, such as digital connectivity and artificial intelligence, and evolving mobility preferences could be poised to change the current transportation landscape. The transition to such new mobility has the potential to reduce GHG and TRAP emissions, particularly if accompanied with lasting reductions in total travel demand. Finally, planning for mobility should also include an emphasis on active transport, such as walking or bicycling, which have little or no carbon footprint, better urban design that includes pedestrian pathways and green spaces, and improved public transportation systems.
- Thus, despite the noteworthy improvements in air quality related to reduced motor vehicle emissions concerns about TRAP and their impact on human health, even at reduced levels, are likely to continue in the near and medium-term. The overall impact of transportation, or more broadly mobility, on air quality and human exposure is a highly dynamic and rapidly changing area; its consideration should be a part of any future research planning.

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ABBREVIATIONS

CARB	California Air Resources Board
CO	carbon monoxide
CO_2	carbon dioxide
EEA	European Environment Agency
EMFAC	EMission FACtor
EU	European Union
GHG	greenhouse gas
MOVES	MOtor Vehicle Emission Simulator
N_2O	nitrous oxide
NH_3	ammonia
NO	nitrogen oxide
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
PM	particulate matter
PM_{coarse}	particulate matter between 2.5 and 10 µm in aerodynamic diameter
$PM_{2.5}$	particulate matter ≤2.5 µm in aerodynamic diameter
PM_{10}	particulate matter ≤10 µm in aerodynamic diameter
SUV	sport utility vehicle
SVOC	semivolatile organic compound
TRAP	traffic-related air pollution
UFPs	ultrafine particles
U.S. DOE	U.S. Department of Energy
U.S. DOT	U.S. Department of Transportation
U.S. EIA	U.S. Energy Information Administration
U.S. EPA	U.S. Environmental Protection Agency
VOCs	volatile organic compounds
WHO	World Health Organization

PART A: BACKGROUND MATERIAL

Chapter 3

Mechanistic Evidence Underlying the Health Effects of Traffic-Related Air Pollution

CONTENTS

CHAPTER 3

Mechanistic Evidence Underlying the Health Effects of Traffic-Related Air Pollution

3.1 INTRODUCTION

3.1.1 BACKGROUND AND APPROACH

The mechanistic pathways by which traffic-related air pollution (TRAP*) damages human health are undoubtedly multiple, complex and inter-related. It is likely that associations with acute and chronic health effects are the result of multiple components of traffic emissions acting through different physiological mechanisms. The objective of the current chapter of this Special Report is not to provide an exhaustive evaluation of the mechanistic literature, but rather to present an overview of the biological mechanisms through which TRAP is believed to elicit the health outcomes included in the epidemiological systematic reviews and meta-analyses. To broaden this narrative, readers are referred to other comprehensive reports that provide critical perspectives on the toxicity of pollutants such as ultrafine particles and nitrogen dioxide (NO_2) that are significant contributors to the overall mix of air pollutants emitted from vehicles (HEI 2013; U.S. EPA 2016). A highly detailed appraisal of the evidence of the carcinogenicity of diesel and gasoline engine exhausts from animal data and in vitro genotoxicity studies can be found in Volume 105 of the International Agency for Research on Cancer Monographs (IARC 2014). It should be noted that many of the studies investigating mechanisms underlying cardiorespiratory disease have used exhaust or particles collected from traditional older technology diesel engines and generators; the concentrations and nature of particulate matter (PM) and pollutant gases from diesel engines equipped with current after-treatment devices are very significantly reduced and produce few exposure-related biological effects in laboratory rodents. An overview of this work that studied the presence of tumors and an array of endpoints (hematological, serum chemistry, lung lavage, pulmonary function, genotoxic) using new technology diesel engines is presented in the Advanced Collaborative Emissions Study (HEI 2015).

The disease endpoints addressed in this chapter reflect those included in the evaluation of epidemiological evidence

Highlights

- The objective of this chapter is not to provide an exhaustive evaluation of the mechanistic literature, but to present an overview of the biological mechanisms through which TRAP is believed to contribute toward respiratory disorders, cardio-metabolic disease, and birth outcomes (i.e., health outcomes included in the epidemiological systematic reviews and meta-analyses of this report).
- Experimental studies on particles in vehicle exhaust, and especially diesel exhaust, heavily dominate the literature base. In contrast, mechanistic research underlying the effects of traffic-related pollutant gases and other volatile components has received much less attention.
- Mechanisms linking TRAP to the development and exacerbation of asthma include eosinophilic and neutrophilic inflammation, interplay with environmental antigens, interactions with sensory nerves in the lung, and epigenetic changes.
- The limited mechanistic research on how TRAP contributes to the airway pathophysiology of COPD has focused on airway remodeling, inflammation, neutrophil function, and mitochondrial dysfunction.
- TRAP may impair pulmonary clearance of bacterial infections, reduce capacity of alveolar macrophages to internalize bacteria, and increase susceptibility and response to viral respiratory infections.
- Studies have shown that TRAP can be linked to cardiovascular endpoints through vascular dysfunction, an acceleration of atherosclerosis, increased propensity for thrombosis, and imbalance of the autonomic nervous system.
- Studies provide evidence that exposure to TRAP may be a risk factor in the development of diabetes, particularly in those who have existing insulin resistance, and that maternal exposure may persistently influence glucose homeostasis.
- TRAP may elicit adverse birth outcomes by negatively affecting placental growth and function, disturbing umbilical cord structure, inducing inflammation and oxidative/nitrosative stress, and modifying epigenetic mechanisms.

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* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

(Chapters 8, 9, and 10), that is, asthma, chronic obstructive pulmonary disease (COPD), acute lower respiratory infection, cardiometabolic outcomes (including several cardiovascular events plus diabetes) and birth outcomes. With the exception of reports of deaths among farm animals and pets during air pollution episodes (Nemery et al. 2001), few studies have investigated the effects of air pollution on animal mortality in an epidemiological context. To this end, experimental studies into effects of TRAP on all-cause and cause-specific mortality have not been addressed.

In this chapter selected data generated from epidemiological studies that have simultaneously looked at markers of a mechanistic process, controlled human exposure studies and research employing healthy and diseased/susceptible animal models, isolated organs and in vitro systems are examined. Although each of these types of investigation has their own strengths and weaknesses, together they offer complementary approaches (Sidebar 3.1).

Studies discussed in this chapter have investigated the effects of exposure environments that are enriched in traffic pollutants, proxies for TRAP such as residential distance to nearest roadway, plus inhalation exposures to specific components of traffic emissions. These components include PM collected from traffic-dominated urban air, whole vehicle exhaust, and primary gaseous emissions including nitrogen oxides. Examples of traffic-related PM include elemental carbon or black carbon, road dust, tire wear, and brake wear. Studies focused on particles in vehicle exhaust, and especially DE, heavily dominate the literature base. This substantial research interest stems from the high numbers of ultrafine particles in these emissions. Smaller particles may have a greater potential for harm due an ability to penetrate deeper into the lung and a larger reactive surface area that may heighten their toxicity. In contrast, mechanistic research underlying the effects of gaseous emissions, such as NO_2, has received much less attention.

A challenge facing toxicologists is designing studies to investigate the relatively small excess health effects detected in epidemiological studies. This is often addressed by using exposure concentrations considerably higher than real-world ambient concentrations, which in turn may instigate

SIDEBAR 3.1 APPROACHES TO EVALUATE MECHANISTIC PROCESSES

- Mechanistic data generated from epidemiology studies describe effects on the population of concern, under real-life conditions at pollutant concentrations within relevant ranges, thereby eliminating the need for cross species and high to low dose extrapolation. Limitations include exposure measurement error, the presence of confounding factors and other potential biases, all of which may influence findings.
- Controlled exposure studies in human volunteers involve the most relevant species and can remove confounding by design. Participants are usually selected using specified criteria and characterized thoroughly. Exposures in a controlled environment provide the opportunity to study specific pollutants in isolation or together (but in doing so may not be representative of a real-world pollution mix). For example, studies have investigated acute (1 or 2 hr) exposures to 100–300 μg PM/m^3 of diesel exhaust (DE) to broadly model concentrations found in close proximity to emissions in heavy traffic and are representative of total PM concentrations reached in some megacities. On the other hand, controlled exposure studies are restricted by small sample size, an inability to study the potentially most susceptible subgroups that may be at most risk of adverse events (e.g., children and adults with severe asthma) and the use of acute exposures with relatively short follow-up that precludes studying effects of chronic exposure. Also, some controlled exposure studies have used diesel generators and older engine technologies that do not represent current vehicles fleets.
- Animal inhalation exposure experiments have the strengths of well-characterized exposures, the capacity for invasive procedures and the availability of genetically engineered and manipulated models to explore the role of specific genes that affect individual susceptibility. Despite these advantages, they are generally limited to short-term exposures, assessing acute or subacute effects because of practical challenges. Other restrictions include uncertain relevance of animal to human exposure and frequent necessity of extrapolating from the higher exposure levels to lower—more relevant—ambient concentrations. For example, dosimetry is affected by body size, airway structure, and metabolic pathways and pollutant responses might be affected by differences in organism physiology, diurnal cycles, diet, body temperature, stress responses, and disease susceptibility.
- In vitro studies provide mechanistic insights within specific cell types and tissues. However, the advantage of being able to isolate certain parameters and specifically examine them is also a disadvantage. Isolated and cultivated cells that lack interactions with other cell types usually differ strongly from the corresponding cell type in an organism. Other challenges include extrapolation from in vitro concentrations to in vivo doses, simulating the consequences of long-term exposures and extrapolating from perturbed pathways or biomarkers in vitro to adverse effects in vivo. New approaches such as lung-on-a-chip that provide an opportunity to study various cell types in interaction with one another are now becoming available for pharmaceutical research but have not been used much in environmental research as of yet.

different underlying mechanisms as well as accentuated health outcomes. Other approaches are to study populations or animal models that have increased susceptibility (e.g., rats with hypertension) and measure more subtle effects using molecular markers that are predictive for adverse health outcomes. This chapter has focused on research using relevant pollution exposure methods (i.e., nose-only or whole-body inhalation) and concentrations generally within two orders of magnitude of western world air quality standards. This range in relevant exposure concentrations accounts for differences in dosimetry, toxicokinetics and biological sensitivity of different species/strains and potentially at-risk populations (U.S. EPA 2016). It should also be emphasized here that a typical controlled exposure of human subjects of 300 µg PM/m^3 for 2 hours equates to a realistic one when extrapolated to a daily dose (25 µg PM/m^3 over 24 hr). Animal studies using inhalation concentrations higher than two orders of magnitude of western world air quality standards or different exposure methods (e.g., intranasal instillation, intratracheal instillation) are considered only if they provide information relevant to understanding mechanisms or at-risk human populations.

Despite the focus on long-term exposures to TRAP within the epidemiological evaluations, the studies discussed in this chapter include short-term (e.g., hours), subacute (e.g., 28 days), subchronic (e.g., 90 days) and chronic (e.g., 12 plus months) exposures. This is not solely owing to the relative scarcity of long-term mechanistic studies in the literature, but also because of a relevance of shorter exposures. Specifically, short-term exposure to TRAP may demonstrate an incremental capacity to adversely affect health, sensitizing populations to subsequent challenges. In this way, repeated periods of short-term exposures, which may occur during rush hour traffic, are potentially capable of promoting chronic disease.

This chapter begins with a discussion of causal pathways by which air pollution is believed to exert harmful effects on various organ systems. The sections that follow give an overview of the biological mechanisms through which TRAP may contribute toward respiratory disorders, cardio-metabolic disease, and adverse birth outcomes. The sheer volume of literature prohibits a comprehensive review of all relevant studies and a detailed critical analysis of individual assays, study designs, and inconsistences. Instead, studies selected for discussion and/or tabulation (Appendix Tables 3A to 3F, available on the HEI website) are those primarily from peer-reviewed journals that have been instrumental in forming our understanding of the mechanisms underlying the health outcomes. This does not exclude negative studies.

3.1.2 PATHWAYS LINKING THE INHALATION OF AIR POLLUTANTS TO DISEASE ETIOLOGY, PROGRESSION, AND DEVELOPMENT

There is an increasing scientific consensus that a chain of events involving pollutant-induced oxidative stress and inflammation, mediated via redox-sensitive signaling pathways and transcription factors, constitutes a primary pathway leading to observed health effects in exposed populations (Brook et al. 2010; Ward 2010). An excessive oxidative challenge (as opposed to one which is [1] essential for normal physiological redox signaling and [2] effectively removed by protective adaptions) is a serious imbalance between the generation of reactive oxygen species (ROS) and antioxidant protection in favor of the former, causing oxidative damage (Mudway et al. 2020). ROS is the collective term for oxygen free radicals (molecules with one or more unpaired electrons) and other nonradical derivatives of oxygen that can easily generate free radicals and/or cause oxidative damage. Reactive nitrogen species also exist and when overproduced or under-eliminated can create damage via nitrosative stress.

Major cell components, including DNA, proteins, and lipids, are attacked and oxidized by ROS/reactive nitrogen species, giving rise to DNA mutations, protein oxidations, and lipid peroxidation. This can lead to appreciable impairment of cellular function and—in the worst case—to cell death, organ dysfunction, and eventually severe disease phenotypes. Mechanistic evidence for oxidative stress includes measurement of biomarkers (e.g., oxidized proteins and lipids, urinary isoprostanes, and oxidative DNA adducts), identification of the presence of free radicals, exploration of genetic polymorphisms conferring altered susceptibility to oxidative stress, as well as prevention/reversal of ill effects with antioxidant compounds.

Various individual pollutants that make up the TRAP mix are free radicals (e.g., NO_2) or have the ability to drive oxidative reactions (e.g., PM and ozone). Once inhaled, NO_2 instantaneously reacts with proteins and lipids present in lung lining fluid to produce secondary oxidant species. If these pollutants overcome the rich supply of endogenous antioxidants they can initiate a signaling cascade that attracts inflammatory cells into the lung (Kelly and Tetley 1997). The latter induces a second wave of ROS production and reinforces the oxidative stress within the tissue.

More complicated and inter-related pathways, which may well operate simultaneously, exist by which inhaled traffic-related PM could elicit adverse outcomes in the lung and other organ systems (Figure 3.1). The classical hypothesis describes the (1) ability of the particle surface per se to elicit oxidative stress and/or (2) introduction into the body of oxidizing species such as redox active transition metals or polycyclic aromatic hydrocarbons present on the particle surface (Kelly and Mudway 2006). If, as described above, protective mechanisms are overwhelmed, the response transitions to a more damaging inflammatory stage, inducing a secondary source of ROS and an overspill of inflammatory mediators into the circulation. In support of this, markers of systemic inflammation (e.g., tumor necrosis factor-α [TNFα] and interleukin-6 [IL-6]) and oxidative stress (e.g., the antioxidants copper/zinc superoxide dismutase and glutathione) have been identified in the blood of humans and animals after exposure to PM (Brook

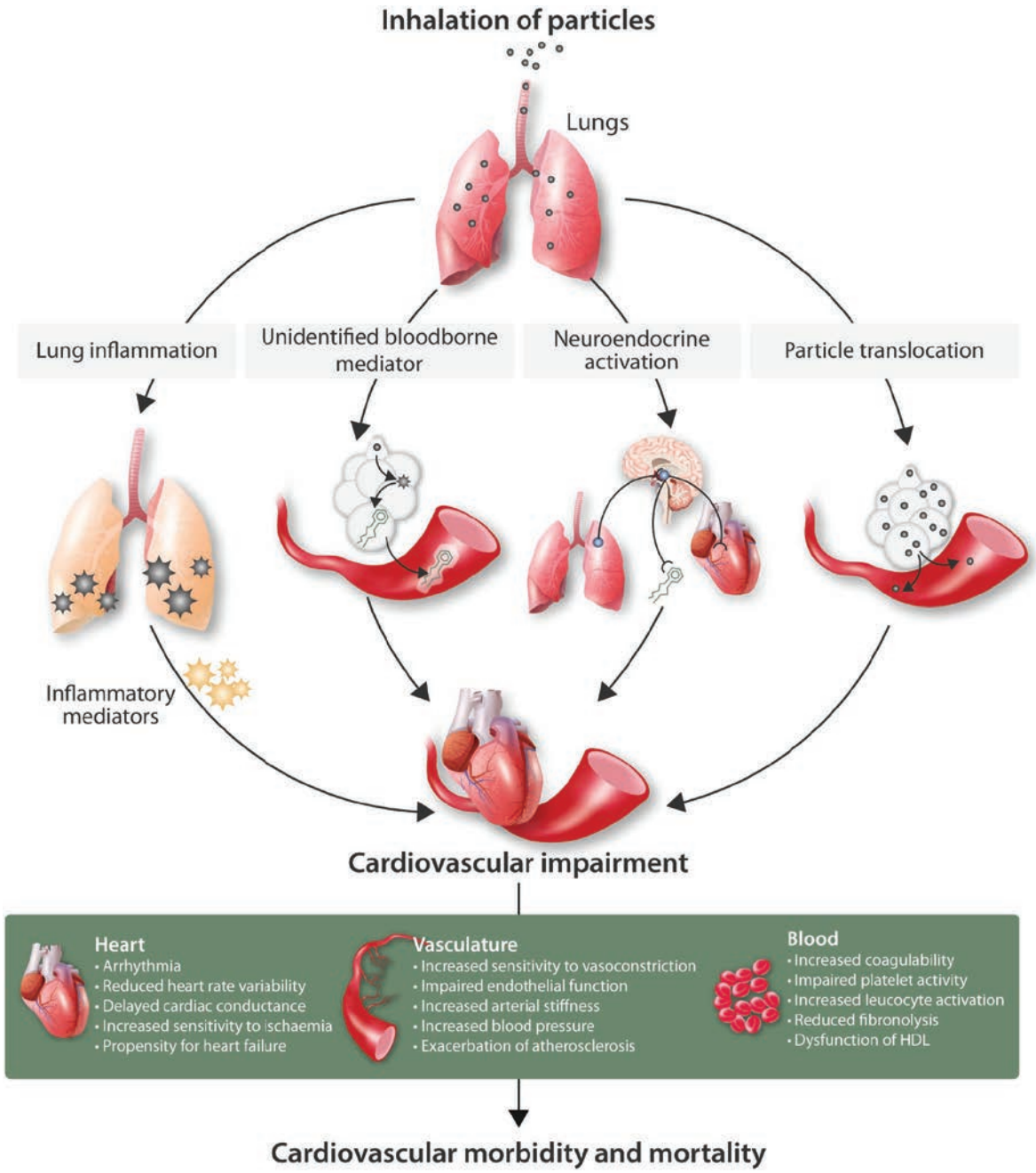

Figure 3.1. Biological mechanisms linking inhaled particles to adverse outcomes in the lung and other organ systems. (Miller and Newby 2020; Creative Commons license CC BY-NC 4.0)

et al. 2010). There are, however, alternative pathways through which components of inhaled particles can trigger inflammation, as exemplified by the induction by organic components of Th17 signaling through activation of the aryl hydrocarbon receptor (O'Driscoll et al. 2019). Particles may also trigger the formation of alternative biological intermediates (other than inflammatory ones) to mediate systemic effects. An example of this is an increased formation of oxidized phospholipids in the lung that mediate a systemic cellular inflammatory response through toll-like receptor/nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-dependent mechanisms (Kampfrath et al. 2011).

Inhaled particulates and/or gaseous pollutants can also activate lung-specific afferent sensory nerves to elicit respiratory symptoms and alter cardiorespiratory function via changes in autonomic balance (Perez et al. 2015; Robinson et al. 2018).

Animal studies have shown that pharmacological inhibition of alveolar sensory receptors or beta-adrenergic receptors lessens the cardiac effects of diesel exhaust particles (DEP) (Perez et al. 2015; Robertson et al. 2014). Also, polycyclic aromatic hydrocarbons that are present in DEP activate airway afferents through the aryl hydrocarbon receptor and subsequent mitochondrial ROS production (Robinson et al. 2018).

A very small fraction of ultrafine PM or leachable components may translocate across the lung into the blood where they can directly harm the vasculature and/or other organs of the body. The percentage of those particles is of the order of 1% (Kreyling et al. 2002) or substantially less (Miller et al. 2017a,b). Evidence also suggests that a small proportion of very small particles that are inhaled enter the brain via the olfactory nerves leading from the nasal passages to the olfactory bulbs (Oberdörster et al. 2002); reach the gut via mucociliary clearance from the lungs (Möller et al. 2004); are ingested via food and water sources (De Brouwere et al. 2012); are removed from the lung surface and retained in the interstitium (Semmler-Behnke et al. 2007); and are further translocated into the lymphatics (Leak 1980). Initial studies in animals provided evidence that nanoparticles are able to translocate to extra-pulmonary sites. More recent studies in humans have detected nanoparticles in the blood (Miller et al. 2017a,b), heart (Calderón-Garcidueñas et al. 2019), brain (Maher et al. 2016), and placenta (Bové et al. 2019; Liu 2021). It is not yet known, however, whether translocation is sufficient to induce ill health.

3.2 RESPIRATORY OUTCOMES

3.2.1 ASTHMA

Asthma is a chronic disease of the conducting airways, characterized by a reversible airway obstruction, chronic airway inflammation, airway hyperresponsiveness, and airway remodeling that lead to shortness of breath, coughing, wheezing, and chest tightness. Asthma can be subdivided in a number of phenotypes based on age at onset and inflammatory cell profile (Wenzel 2012). The best-characterized phenotype is (early onset) allergic asthma, defined by the presence of allergen-specific immunoglobulin E in serum and/or a positive skin-prick test to common allergens in association with type 2-mediated immune responses (i.e., elevated levels of eosinophils and helper T cell (Th2) cytokines [IL-4, IL-5, IL-13]). Other phenotypes are type 2–mediated late-onset nonallergic eosinophilic asthma and nontype 2 asthma in which Th1 and Th17 responses appear to be important.

As summarized below, TRAP can induce airway inflammation and airway hyper-responsiveness (Brown 2015; Dales et al. 2008). In addition, oxidative stress (a feature of severe asthma) has been associated with pollutant exposures (Liu et al. 2009; Patel et al. 2013). Associations between exposure and exacerbations and possibly even the onset of asthma are therefore feasible. A framework for how outdoor air pollution may contribute to the development and exacerbation of asthma identifies four key mechanisms: oxidative stress and damage, airway remodeling, inflammatory pathways and immunological responses, and enhancement of respiratory sensitization to aeroallergens (Gowers et al. 2012; Thurston et al. 2020) (Figure 3.2).

Although attempts can sometimes be made to distinguish whether a particular mechanistic finding supports a causative effect for disease onset versus one that exacerbates pre-existing disease, this is rarely done with much certainty, most likely because findings can invariably support either endpoint. Indeed, the induction of pulmonary oxidative stress and inflammation are both involved in the onset and/or exacerbation of respiratory diseases. Furthermore, variation in genes regulating these mechanisms could confer increased susceptibility to either pollutant-induced development of new-onset asthma or exacerbations of existing disease.

The underlying pathways by which pollutants induce features of asthma are likely to be complex and the product of interactions between other environmental exposures as well as individual genetic susceptibility. The most frequently described mechanisms linking air pollution to the development and exacerbation of asthma are eosinophilic and neutrophilic inflammation, driven by stimulation of airway epithelium and oxidative injury to the airways. Indeed, the airway epithelium represents a unique interface with the environment and is thought to be a key player in the way that air pollutants can initiate or contribute to the pathological features of asthma (Figure 3.3) (Bontinck et al. 2020; Muñoz et al. 2019). The literature also supports an interaction of pollutants with environmental antigens to enhance their activity, a noninflammatory pathway involving a direct interaction between pollutants and sensory nerves in the lung (Robinson et al. 2018)

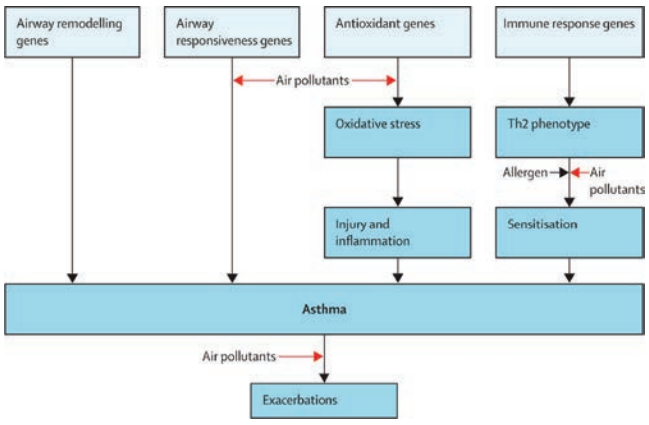

Figure 3.2. Mechanistic framework for the effects of air pollution on asthma. (Reprinted from Guarnieri and Balmes 2014 with permission from Elsevier)

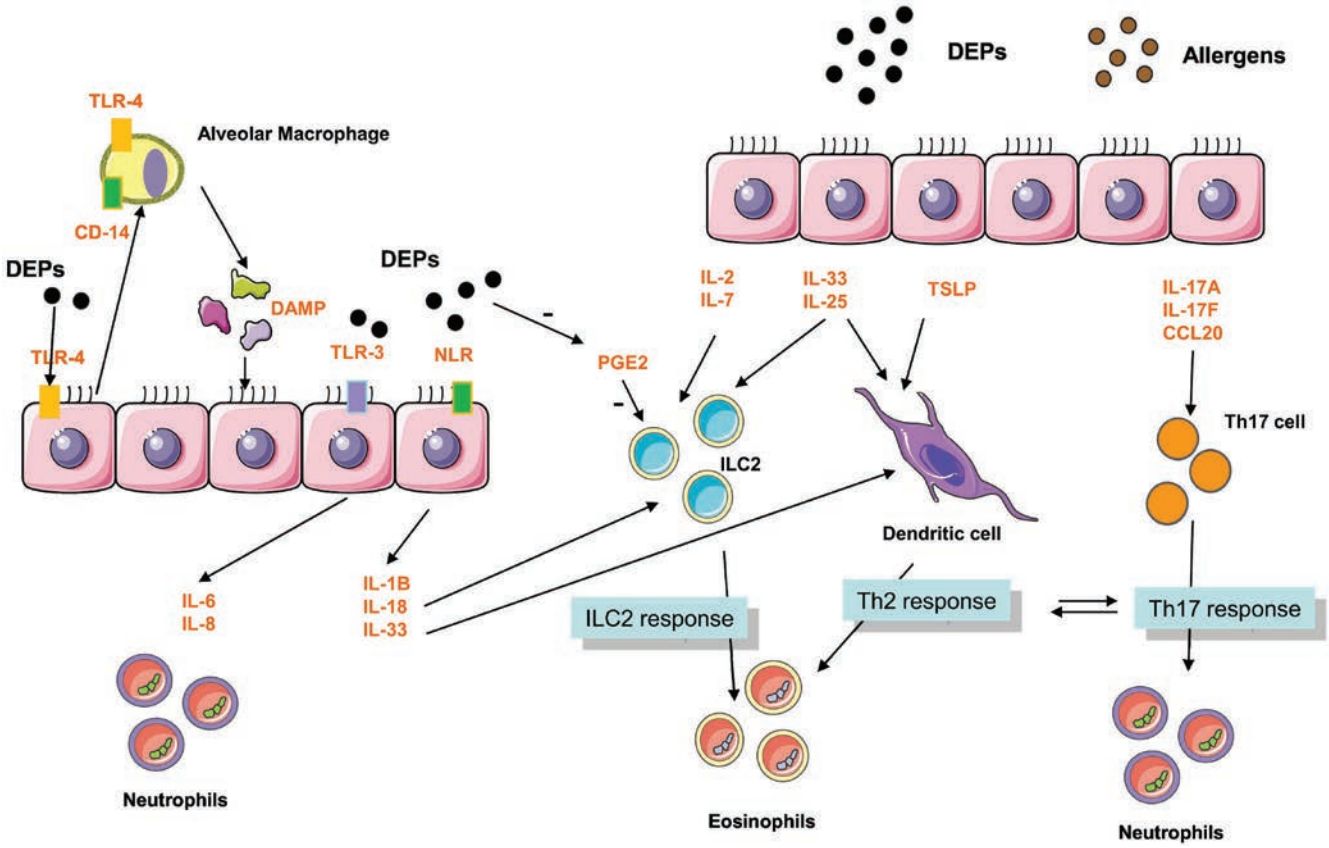

Figure 3.3. Diesel exhaust particles and immunological mechanisms that orchestrate the asthmatic response. (Reprinted from Muñoz et al. 2019 with permission from Elsevier)

and epigenetic changes (reviewed by Ji et al. 2016). Details of all references cited below, plus some additional studies that have not been selected for this broad discussion, for the sake of brevity are presented in Appendix Table 3A (available on the HEI website).

3.2.1.1 Inflammatory Effects on Airway Epithelium and Immune Cells

A series of studies investigating the acute effects of whole DE (particulates and associated gas phase; PM ≤10 µm in aerodynamic diameter [PM_{10}]: ≈ 100–300 µg/m^3 for 1–2 hr) from an idling engine (Volvo TD45, 4.5L, four cylinders, 680 rpm, model 1991) on a comprehensive series of markers of neutrophilic and allergic inflammation have been instrumental in uncovering a systemic and pulmonary inflammatory response attributed, in part, to the oxidative properties of exhaust PM (Behndig 2006; Mudway et al. 2004; Nordenhäll et al. 2001; Pourazar et al. 2004, 2005; Salvi et al. 1999). In healthy participants, DE exposure resulted in an acute inflammatory response characterized by influx of neutrophils, lymphocytes, and mast cells into the airways in association with enhanced expression of IL-6, IL-8, and IL-13 in the bronchial epithelium. In asthmatic subjects exposed to DE, a significant increase in the degree of airway hyperresponsiveness has been observed (Nordenhäll et al. 2001), but not enhanced airway inflammation (Behndig et al. 2011; Stenfors et al. 2004). If, therefore, an increased sensitivity to DE in participants with asthma exists, it may not necessarily be associated with classical acute inflammation or aggravation of standard cellular indicators of allergic asthmatic inflammation. Real-world exposure scenarios have also shown upper airway inflammation, persistent lung function decrements, and increased myeloperoxidase concentrations in adults with mild-to-moderate asthma who are walking along a road carrying only diesel-powered vehicles (as opposed to in a nearby park) (McCreanor et al. 2007). Potential mechanisms behind this action of TRAP to acutely decrease lung function include the pro-inflammatory effect of pollutants increasing airway mucosal inflammation and mucus production and a direct effect of pollutants to stimulate neural respiratory reflexes (Robinson et al. 2018).

The 2016 U.S. EPA Integrated Science Assessment (ISA) for Oxides of Nitrogen examined experimental evidence for a relationship between short-term effects of NO_2 on asthma exacerbation as well as long-term exposure and asthma development (U.S. EPA 2016). Conclusions of short-term

effects in controlled human exposure studies included an increase in nonspecific airway hyperresponsiveness (382–573 μg/m^3 NO_2 for 30 min or 191 μg/m^3 for 60 min) in adults with asthma and enhanced allergic inflammation (repeated exposures of 1,146 μg/m^3 NO_2 for 30 min) in adults with asthma and allergy. However, most studies (382–7,640 μg/m^3 NO_2 for 30 min to 6 hr) did not report effects on lung function in adults with asthma or provide strong evidence for NO_2-induced increases in respiratory symptoms in adults or adolescents with asthma.

Toxicological and controlled human exposure studies provide biological plausibility for a relationship between long-term NO_2 exposure and asthma development. These include long-term-exposure animal toxicology data demonstrating enhanced airway hyperresponsiveness (e.g., 1,910–7,640 μg/m^3 NO_2 for 6 or 12 wk [Kobayashi and Miura 1995]) and development of allergic responses (e.g., 5,730 μg/m^3 for 2 wk [Kobayashi and Miura 1995]) in guinea pigs and increases in pulmonary inflammation and oxidative stress (e.g., 5,730 μg/m^3 for 1 wk [Sevanian et al. 1982]) in rats. The controlled exposure studies in healthy adults reported upregulation of Th2 cytokines in the bronchial epithelium, suggesting the potential of NO_2 to elicit a "pro-allergic" effect (e.g., 3,820 μg/m^3 for 6 hr over 4 consecutive days [Pathmanathan et al. 2003]) and pulmonary oxidative stress (e.g., 7,640 μg/m^3 for 3 hr [Mohsenin 1991]).

3.2.1.2 Interaction of Pollutants with Environmental Antigens

A potential enhancing effect of TRAP exposure on responses to inhaled allergens has been studied in humans, with evidence for such an effect on lung function and nasal/pulmonary inflammatory responses to NO_2 and DEP. Exposure to inhaled DE (6.0 kW generator with Yanmar engine, PM with aerodynamic diameter ≤2.5 μm [$PM_{2.5}$]: 300 μg/m^3 for 1 hr) preceding segmental allergen challenge augmented allergic inflammation in the lower airways relative to allergen alone (Carlsten et al. 2016). Effects were more pronounced in genetically "at-risk" individuals, who were glutathione-S-transferase (GST) T1 null. The same group of researchers have demonstrated that inhaled DE plus allergen co-exposure can enhance the abundance of secreted proteins in human lungs, some of which are (e.g., cystatin-SA) inflammatory mediators associated with uncontrolled asthma (Mookherjee et al. 2018). Several mechanisms through which air pollutants could enhance sensitization to aeroallergens have been proposed and include increased deposition of allergen in the airways due to carriage by particles, increased epithelial permeability due to oxidative injury, and increased antigenicity of proteins following chemical modification.

Wooding and colleagues recently investigated whether particle depletion remediates the enhancing effects of DE on responses to allergen. Individuals with or without pre-existing bronchial hyperresponsiveness were exposed to DE (6.0 kW generator with Yanmar engine; $PM_{2.5:}$ 290 μg/m^3) or particle-depleted DE ($PM_{2.5}$: 20 μg/m^3) for 2 hours (Wooding et al. 2019). Not only did DE plus allergen and particle-depleted DE plus allergen each increase airway hyperresponsiveness in normally responsive participants, but particle-depleted DE plus allergen co-exposure impaired lung function more than DE plus allergen. This suggests that certain diesel particulate–filtering technologies may not protect against the harmful effects of DE, particularly in the context of allergen co-exposure. Of the measured gaseous components of DE, the only differences between DE and particle-depleted DE were that particle-depleted DE contained lower total volatile organic compounds and higher NO_2 (287 versus 101 μg/m^3) concentrations in the emissions, pointing to NO_2 as a potentially important player in these responses. This aligns with the overall conclusion of a meta-analysis (Brown 2015) that in turn informed the U.S. EPA ISA conclusion of increased airway hyperresponsiveness in a significant fraction of individuals with asthma exposed at rest to NO_2 (382–573 μg/m^3 for 30 min or 191 μg/m^3 for 60 min) (U.S. EPA 2016).

3.2.1.3 Cellular and Molecular Mechanisms

Mechanistic studies in humans, animals, and in vitro suggest that effects of TRAP (alone or concomitant with or after sensitization to a variety of allergens) on airway hyperresponsiveness and enhanced neutrophilic/eosinophilic airway inflammation are associated with a switch to Th2/Th17 asthma phenotypes (De Grove et al. 2018; Han et al. 2017; Ji et al. 2015; Martin et al. 2013; Pathmanathan et al. 2003). Findings from studies with DEP are particularly well characterized describing the modulation of epithelial function and multiple inflammatory cytokines through the activation of Toll-like receptors, NOD (nucleotide-binding and oligomerization domain)-like receptors, epithelial growth factor receptor, and the induction of oxidative stress (reviewed by De Grove et al. 2018 and Huff et al. 2019). These cytokines include IL-1β, IL-6, and IL-8, which are linked with typical innate responses by macrophages and neutrophils; IL-25, IL-33, and thymic stromal lymphopoietin, which initiate type two responses by activation of dendritic cells and IL-17, which is implicated in many aspects of pathogenesis of severe asthma including neutrophilic inflammation, airway hyperresponsiveness, steroid insensitivity, and airway remodeling (Figure 3.3).

Findings of particular interest include data supporting the hypothesis of early programming in the susceptibility of developing asthma (Manners et al. 2014) and the potential mechanisms by which DEP contributes to asthma risk and exacerbations (Brandt et al. 2013, 2015). Offspring of pregnant mice exposed to DEP (SRM 2975; 50 μg intranasally on gestational days 3, 6, 9, 12, 15, and 18) developed substantial postnatal manifestations of allergic asthma (airway hyperresponsiveness, increased serum levels of ovalbumin-specific immunoglobulin E and increased pulmonary and systemic levels of Th2 and Th17 cytokines) after allergen sensitization (Manners et al. 2014). Among 235 children enrolled in the

Greater Cincinnati Pediatric Clinic Repository, high ambient DEP (defined as >0.46 µg/m^3; derived from estimates of elemental carbon attributable to traffic using a land use regression model) exposed children with allergic asthma had increased serum IL-17A levels (implicated, as previously mentioned, in severe forms of asthma) and more frequent symptoms compared with low DEP-exposed children (Brandt et al. 2013).

Furthermore, a parallel study that used a murine model of allergic airway inflammation also showed that combined exposure to DEP (4-cylinder Deutz engine; 150 µg intratracheally; 3×/wk over 3 wk) and house-dust-mite antigen induced a mixed Th2/Th17 response. The same investigators went on to demonstrate that the same DEP exposure protocol exacerbated house-dust-mite–induced allergic airway responses in neonatal and adult mice, resulting in increased effector/memory T-cell accumulation in the lungs and potentiating house-dust-mite recall responses in vitro and in vivo (Brandt et al. 2015). In 578 allergen-exposed and -sensitized children in the Cincinnati Childhood Allergy and Air Pollution study, co-exposure to high levels of elemental carbon attributable to traffic in the first year of life was associated with earlier allergen sensitization and increased prevalence of asthma (Brandt et al. 2015). Collectively, the authors took these data to suggest that exposure to DEP and elemental carbon attributable to traffic results in early sensitization and accumulation of allergen-specific Th2/Th17 memory/effector cells in the lungs, thereby potentiating secondary allergen recall responses and the development of allergic asthma.

3.2.1.4 Sensory Nerve Activation

Despite the large number of studies on the inflammatory effects of DEP on airway epithelium and immune cells, it is only recently that we have gleaned knowledge on how TRAP can elicit respiratory reflexes by directly activating airway sensory nerves and, in doing so, initiate exacerbating symptoms such as cough or bronchospasm. Using in vitro (human and animal vagal tissue; DEP: 1 µg/mL) and in vivo electrophysiological techniques (anesthetized guinea pigs, DEP: 10 µg/mL intratracheally), Robinson and colleagues demonstrated a direct interaction between DEP (SRM 2975) and airway chemo-sensitive C-fiber afferents mediated through activation of the transient receptor potential Ankyrin-1 (TRPA1) ion channel (Robinson et al. 2018) (Figure 3.4). The organic extract of DEP (DEP-OE SRM 1975), but not the cleaned particulate core, activated the vagus nerve, and this was shown to occur through activation of the aryl hydrocarbon receptor and subsequent mitochondrial ROS production. TRPA1 is activated by a number of toxic environmental irritants and has been shown to cause cough in both human participants and guinea pigs (Birrell et al. 2009). TRPA1 is also thought to be a key channel involved in the late asthmatic response in a rat model of allergic inflammation (Raemdonck et al. 2012) and TRPA1

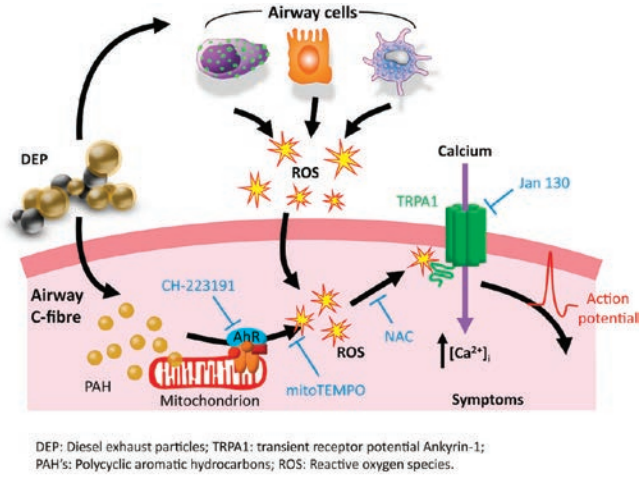

Figure 3.4. Mechanistic link between diesel exhaust particles and respiratory reflexes. (Robinson et al. 2018; Creative Commons license CC BY 4.0)

gene polymorphisms have been associated with childhood asthma (Gallo et al. 2017).

3.2.1.5 Epigenetic Modifications

Research is shedding new light on the epigenetic mechanisms (that control the level of gene expression without changing the DNA sequence) by which exposure to TRAP may contribute to the development and persistence of asthma, as reviewed by Ji and colleagues (2016). For example, there is evidence that DNA methylation, the most studied and best understood epigenetic modification, is involved in the development of asthma (Davidson and Yang 2018), with epigenetic marks regulating many processes of relevant immune cells, particularly T lymphocytes (Bégin and Nadeau 2014). DNA methylation levels at specific loci also have potential to be used as biomarkers for asthma severity and exposure-related asthma exacerbations (Fu et al. 2012).

Among 141 nonasthmatic participants from the Normative Aging Study, Sofer and colleagues identified an association between the methylation of genes in the asthma pathway and 30-day average exposure to black carbon, primarily from DE (Sofer et al. 2013). Methylated genes included those related to the Th2/B cell signaling pathway, eosinophils, and airway inflammation. This finding provides a potential mechanism for the reported association of traffic pollution—particularly DE, and especially the particles—and the exacerbation of asthma.

The epigenetic effects of TRAP can potentially begin in utero, supporting a mechanism by which maternal exposure enhances postnatal development of asthma. In a cohort of 56 children, *ACSL3* methylation in cord blood cells was found to be significantly associated with maternal airborne polycyclic aromatic hydrocarbon exposure, determined by personal air monitoring, and with a higher risk of developing asthma

prior to age 5 (Perera et al. 2009). Epigenetic modifications of regulatory genes crucial to the development of asthma-related pathophysiology may therefore form the mechanistic basis of this disease. Research has also uncovered the association of methylation of saliva *FOXP3* (a gene that plays a key role in maintaining tolerance to common antigens in asthma and allergy) with DE exposure (calculated by estimating exposure to elemental carbon attributable to traffic), during the first year of life and persistent wheezing and asthma diagnosis at age 7 in a subset of 92 children from the Cincinnati Childhood Allergy and Air Pollution study (Brunst et al. 2013), again implicating the epigenome as a mediator of the impact of early life TRAP exposure on developing persistent wheezing and asthma.

3.2.1.6 Summary

A substantive and well-established literature base of experimental studies exists that describes characteristic features of asthma (i.e., airway inflammation, airway hyperresponsiveness, and oxidative stress) following exposures to TRAP.

The most frequently described mechanisms linking TRAP to the development and exacerbation of asthma are eosinophilic and neutrophilic inflammation, driven by stimulation of airway epithelium and oxidative injury to the airways.

The literature base supports an interaction of (1) DE with environmental antigens to enhance activity and (2) gaseous and particulate traffic pollutants with the epigenome in contributing to the development and persistence of disease, and particularly an impact of early life TRAP exposure on developing persistent wheezing and asthma.

Findings that DEP can directly interact with airway C-fiber afferents to elicit respiratory reflexes provide another mechanistic insight as to how exposure to urban air pollution could initiate exacerbating symptoms.

3.2.2 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is characterized by progressive and largely irreversible airflow obstruction that involves structural changes in the lung, including emphysema and small airway remodeling. The destruction of lung tissue is caused by an imbalance between protease (enzymes that degrade proteins) and antiprotease activity, where the excess of proteolytic enzymes, such as matrix metalloproteinases (MMPs), is insufficiently counterbalanced by a rise in antiproteolytic molecules, such as tissue inhibitors of MMP (Barnes et al. 2003). Oxidative stress, inflammation, reduced ciliary action in the airways, amplification of viral infections, increases in bronchial reactivity, and compromised pulmonary function are not only known effects of exposures to TRAP but also represent features relevant in the development and/or course of COPD. Details of all references cited below are presented in Appendix Table 3B (available on the HEI website).

A study assessing the effects of acute DE exposure (6.0 kW generator with Yanmar engine; $PM_{2.5}$: 300 µg/m^3; NO_2: 218 µg/m^3; nitrogen oxides [NO_x]: 6,590 µg/m^3 for 2 hr) on neutrophil function (the most abundant inflammatory cells present in the bronchial wall and lumen of patients with COPD), in never-smokers, ex-smokers, and patients with mild-to-moderate COPD suggests that COPD patients may be more prone to an activated inflammatory state following exposure, and that the release of neutrophil extracellular traps may be a mechanism to explain how TRAP contributes to airway pathophysiology and thus contributes to the development of COPD (Wooding et al. 2020). The DE concentration used was chosen to represent exposure levels documented in polluted megacities and occupational exposures. Researchers observed a reduction in circulating band cells (a marker of bone marrow stimulation and release of neutrophils into the circulation), but an increase in neutrophil activation; these responses were exaggerated in COPD patients. In all participants, DE exposure increased the release of neutrophil extracellular trap. Neutrophil extracellular trap consist of neutrophil-derived DNA, released in chromatin filaments, which form web-like structures coated with granular histone proteins (Brinkmann 2004). They are known to be related to COPD severity (Dicker et al. 2018) and worsening of lung function (Grabcanovic-Musija et al. 2015). In addition, proteolytic neutrophil proteins within neutrophil extracellular traps can damage the endothelium and epithelium, (Fuchs et al. 2007; Saffarzadeh et al. 2012) and exposed histones can increase inflammation (Allam et al. 2014).

Few animal studies have focused on the role played by TRAP in the development of COPD as most animal models replicate only a few COPD features, and such experiments are expensive, technologically challenging, and time-consuming (Huang et al. 2017; Jones et al. 2017). Furthermore, certain studies have not employed environmentally relevant models (Amara et al. 2007; Chang et al. 2011). To better understand the biological consequences that occur during the onset of COPD and the pathogenesis of the disease, He and colleagues exposed 6-8 week old rats to motorcycle exhaust (1.8 kW 1-cylinder Wuyang WY48QT-2 engine, particulate matter ≤1 µm in aerodynamic diameter [PM_1]: 1,450 µg/m^3; carbon monoxide: 78.52 µg/m^3; NO_x: 956.25 µg/m^3; 2×2 hr/day, 5 day/wk for 1, 3, 5, or 7 mo). Observations included pronounced COPD, characterized by lung function reduction, mucus metaplasia, lung and systemic inflammation, emphysema and small airway remodeling (He et al. 2017). These changes are consistent with those that occur in COPD patients. Almost all the multiple cytokines tested in serum were at their highest levels after 1 month of exposure to motorcycle exhaust, and this was consistent with when the highest degree of pulmonary inflammation was observed in the exposed rats.

To further identify molecular alterations underlying air pollution–induced pulmonary injury, another study performed lung function and histological examinations along with quantitative proteomics analysis and functional validation after

exposing 6 month old rats for 3 and 6 months to TRAP (PM_1: 16.3 µg/m³; NO_x: 62.8 µg/m³; ozone: 29.7 ppb) in an urban region near a major highway and expressway in New Taipei City, or high-efficiency particulate air–filtered gaseous pollutants in the same urban area (Jheng et al. 2021). Rats in the 6-month unfiltered TRAP–exposed group exhibited a significant decline in lung function compared with the gaseous pollutants group. The latter did, however, exhibit decreased forced expiratory flow at 25% and 75% of forced vital capacity compared with the control group. Histological analysis revealed lung damage, as evidenced by increased congestion and macrophage infiltration in 3-month unfiltered TRAP–exposed rat lungs but not in the gaseous pollutants-exposed lungs. These results suggested that the presence of PM caused lung damage and lung function decline. The lung tissue proteomics analysis identified 2,673 proteins that highlighted the differential dysregulation of proteins involved in oxidative stress, cellular metabolism, calcium signaling, inflammatory responses, and actin dynamics under exposures to PM_1 and gaseous pollutants. The presence of PM_1 specifically enhanced oxidative stress and inflammatory reactions at 3 months and suppressed glucose metabolism and actin cytoskeleton signaling at 6 months.

In vitro studies have focused on defining the molecular mechanisms by which DEP regulate MMP in human respiratory epithelial cells (Amara et al. 2007; Li et al. 2009, 2011b). Of interest, a regulatory effect of DEP (produced by a 30 kW 4-cylinder Deutz engine) on the MMP-1 gene has been shown to critically involve the –1607GG MMP-1 promoter polymorphism (Li et al. 2009). Because this polymorphism is present in 25% of Caucasians homozygously and 50% heterozygously, with similar frequencies in Asian and African-American populations (Fujimoto et al. 2002), for most humans, breathing DEP-polluted air may trigger increased MMP-1 activation in airway epithelia, increasing their vulnerability to chronic pulmonary injury.

3.2.2.1 Summary

Oxidative stress, inflammation, reduced ciliary action in the airways, amplification of viral infections, increases in bronchial reactivity, and compromised pulmonary function are not only known effects of exposures to TRAP but also represent features relevant in the development and/or course of COPD.

A controlled human DE exposure study showed that COPD patients demonstrated an enhanced activated inflammatory state compared with lower-risk populations. The study also identified a potential new inflammatory biomarker, neutrophil extracellular traps, the release of which represents a possible mechanism to explain how TRAP contributes to the airway pathophysiology of COPD.

Animal studies utilizing real-world traffic exposures for varying periods up to 7 months have observed changes in the airways of rats consistent with those of COPD patients, in association with the release of multiple cytokines from airway cells. Results suggest a greater role for the PM fraction compared to gaseous components in causing lung damage and lung function decline as well as distinct molecular mechanisms of pulmonary injury by traffic-related PM versus gaseous pollutants.

3.2.3 ACUTE LOWER RESPIRATORY INFECTION

Experimental studies summarized below have uncovered several mechanisms by which TRAP could increase susceptibility to both bacterial and viral pathogens. Toxic particles and gases may singly or in combination have a multitude of effects. These include reducing mucociliary clearance (an important mechanism in the clearance of foreign particles and pathogens from the lungs) and suppressing phagocytic activity of alveolar macrophages (cells that play a critical role in removing pathogens from the airways). Pollutants may also enhance the susceptibility of cells to viral infection, heightening viral multiplication as well as having broader systemic immunotoxicity via effects on both the myeloid and lymphatic systems. The mechanisms underlying any adverse effects that exposure to TRAP may have on the transmission and/or lethality of severe acute respiratory syndrome coronavirus 2 is outside of the scope of this review and as such, have not been evaluated. Details of all references cited below, plus some additional studies that have not been selected for this broad discussion for the sake of brevity, are presented in Appendix Table 3C (available on the HEI website).

3.2.3.1 Impaired Bacterial Recognition and Killing

The small body of studies in experimental animals investigating the effects of long-term NO_2 exposure on respiratory infections were reviewed in the 2016 U.S. EPA ISA for Oxides of Nitrogen (U.S. EPA 2016). A single study by Henry and colleagues (1970) looked at increased susceptibility. In that study, squirrel monkeys were exposed to 9,550 µg/m³ NO_2 for 2 months and then subsequently exposed to *K. pneumoniae* or influenza. The monkeys exhibited increased markers of infection, white blood cell counts, and erythrocyte sedimentation rate (Henry et al. 1970). Studies also demonstrated that NO_2 exposures (e.g., a base of 955 to 7,640 µg/m³ with or without twice-daily 2,865 to 9,550 µg/m³ spikes) for 6 weeks or longer can modulate lung host defense in the form of altered alveolar macrophage numbers in the airways (Chang et al. 1986; Gregory et al. 1983), impaired alveolar macrophage function (Greene and Schneider 1978), and changes in the response of lung mast cells (Fujimaki and Nohara 1994). More recent contributions to this evidence base have not been identified.

Exposure of rodents to high concentrations of DEP (SRM 1650 or 2975) 5,000 µg intratracheally (Castranova et al. 2001; Yang et al. 2001) or 20,000–100,000 µg/m³ by nose-only inhalation for 4 hr for 1 or 5 days (Yin et al. 2002, 2003, 2004b) has been shown to impair clearance of gram-negative and -positive bacteria as a consequence of reduced phagocytosis

(Castranova et al. 2001; Yang et al. 2001; Yin 2004b; Yin et al. 2002, 2003). Studies that have compared DEP and carbon black suggest that this suppressive effect on phagocytosis is at least partially caused by adsorbed organic chemicals rather than the carbonaceous core of the particle (Castranova et al. 2001; Yang et al. 2001). These animal studies (Castranova et al. 2001; Yang et al. 2001; Yin 2004b; Yin et al. 2002) plus in vitro mechanistic studies utilizing DEP or their organic extract (10, 50, or 100 μg/mL for 1 to 24 hr) (Jaguin et al. 2015; Yin 2004a; Yin et al. 2007) observed a reduced capacity of alveolar macrophages to internalize bacteria and produce antimicrobial oxidants, inhibitory effects on the secretion of proinflammatory cytokines, and an increased production of immunosuppressive mediators. Consistent with the notion that exposure to diesel exhaust emissions (year 2000 heavy-duty Cummins engine, PM: 30–1,000 μg/m^3; 6 hr/day for 1 wk) can exacerbate lung disease during a pulmonary bacterial infection, Harrod and colleagues reported increased inflammation and decreases in ciliated and nonciliated airway epithelial cell numbers (in a concentration-dependent manner) subsequent to reducing the clearance of *P. aeruginosa* (Harrod et al. 2005).

One of the few studies to explore the potential toxicity of nonexhaust traffic particles used the U937 monocyte-derived macrophage cell line to perform side-by-side characterizations of the effects of brake abrasion dust (a richly metallic, nontailpipe-derived wear particle) and DEP (SRM 2975; 4–25 μg/mL for 24 hr) (Selley et al. 2020). Although brake abrasion dust contained considerably more metals/metalloids than DEP, both particles elicited a similar and significant reduced ability of U937 cells to ingest *S. aureus*, even at particle concentrations as low as 4 μg/mL. The phagocytic deficit recovered when challenged cells were incubated for a further 24 hr in particle-free media and the initial responses were abrogated by metal chelation, suggesting that the impaired ability of immune cells to ingest respiratory pathogens occurs in a transient and metal-dependent manner.

3.2.3.2 Adverse Viral Responses

Although controlled human experiments to define the mechanisms of an air pollution–induced risk for respiratory viral infections are difficult to design, Noah and colleagues, using a live attenuated influenza vaccine, reported that prior exposure to DE (100 μg/m^3 average particle concentration for 2 hr) leads to increased and prolonged eosinophil activation and increased virus quantity after inoculation in participants with allergic rhinitis but not in healthy individuals (Noah et al. 2012).

Exposure to high concentrations of DEP (500 or 2,000 μg/m^3 4 hr/day for 5 day/wk for 6 mo or 2,000 μg/m^3 7 hr/day, 5 day/wk, for 6 mo) or DE (PM 500–1,000 μg/m^3 with NO_2: 8,977–33,616 μg/m^3 and NO_x: 82,130 μg/m^3, 4–6 hr/day 5–7 days) has also been shown to increase susceptibility and response to viral respiratory infections in rodent models (Castranova et al. 2001; Ciencewicki et al. 2007; Harrod et al. 2003). These effects are accompanied by oxidative stress and a reduction in expression and production of antimicrobial surfactant proteins (Castranova et al. 2001; Ciencewicki et al. 2007; Gowdy et al. 2008, 2010). Differences in engine load (at the same PM mass concentration of 2,500 μg/m^3, 6 hr/day for 7 days) are important determinants of the type and magnitude of responses, with high-load DE (Cummins year 2000 heavy-duty engine) causing more pulmonary inflammation and greater susceptibility to viral infection than partial-load DE (McDonald et al. 2011). The high-load operating mode produced exhaust with less carbon monoxide and less organic material than did the partial-load mode, which was dominated by organic carbon in both the gas and particle phases.

In vitro studies in which differentiated human nasal and bronchial epithelial cells and a respiratory epithelial cell line were exposed to an aqueous-trapped solution of DE (Caterpillar engine, model 3304; 22 or 44 μg/cm^3 for 2 hr and 6–25 μg/cm^3 for 2 hr, respectively) also suggested a role for oxidative stress in mediating the increased susceptibility to influenza infection (Jaspers et al. 2005). Studies also suggested that DEP (30 kW 4-cylinder Deutz BF4M1008 engine; 10 μg/mL for 18 hr) reduced the ability of natural killer cells, which have a crucial role in fighting viral infections, to kill virus-infected host cells (Müller et al. 2013). With a focus on the increased susceptibility of individuals with respiratory inflammation to TRAP-induced respiratory infections, murine lung epithelial cells have been treated with a cytokine mixture (Cytomix: TNFα, IL-1β, and interferon gamma [IFN-γ]) to induce a generic inflammatory state before exposure to DEP (generated in 1999 by a diesel-powered automobile; 25 μg/m^3 for 2 hr) (Manzo et al. 2012). Due to interactions of cytokine-induced nitric oxide (NO) and DEP-induced superoxide anion radical, the Cytomix plus DEP exposure was associated with nitrosative stress in surface epithelial cells and resident lung phagocytes.

3.2.3.3 Summary

The literature base of experimental studies investigating mechanisms by which TRAP could increase susceptibility to bacterial and viral pathogens is noticeably old and studies have invariably employed high exposure concentrations of NO_2, DE, or DEPs.

Findings include impaired pulmonary clearance of bacterial infections, reduced capacity of alveolar macrophages to internalize bacteria, and increased susceptibility and response to viral respiratory infections.

Animal and in vitro studies suggest that mechanisms underlying these effects include a reduced capacity of the host to produce antimicrobial oxidants, inhibitory effects on the secretion of proinflammatory cytokines and antimicrobial surfactant proteins, an increased production of immunosuppressive mediators, and a reduced cytotoxic potential of natural killer cells.

Work investigating the comparative toxicity of brake abrasion dust and DEP demonstrated a broadly equivalent impairment of bacterial phagocytosis and that metals are key drivers in this toxicity. These findings emphasize the requirement to consider contributions of abrasion particles to traffic-related clinical health effects.

3.3 CARDIOMETABOLIC OUTCOMES

Evidence suggests that adverse TRAP-associated cardiovascular endpoints are manifested through several, likely overlapping, "effector" pathways including endothelial dysfunction/vascular tone, atherosclerosis, procoagulant changes, alterations in autonomic nervous system balance, and increased blood pressure (Figure 3.5). For example, atherosclerosis of the coronary vasculature is the basis for ischemic heart disease as well as most cases of cardiac arrest. Occlusion of major coronary arteries can lead to (1) prolonged ischemia, resulting in death of the downstream myocardial cells and myocardial infarction and (2) fibrosis or death of regions of the heart leading to loss of cardiac function and obstruction to cardiac electrical conductance. Atherosclerosis, increased thrombogenicity, alterations in autonomic nervous system balance, and loss of vascular flexibility are also plausible pathways by which TRAP could induce ischemic and hemorrhagic stroke, respectively.

Although somewhat artificial, it can be useful to separate the pathways based on time courses of exposure and the timing of biological responses. Pathways that have relevance to short-term exposures on the triggering of acute effects include autonomic nervous system imbalance, elicitation of acute inflammatory reactions, and increases in blood pressure. Other pathways are expected to play a more long-term role. For example, abnormal endothelial function is one of the major pathways leading to pathological changes in the cardiovascular system as a consequence of what can be the gradual development of an array of perturbations including fibrinolytic imbalance, aggregation of platelets, and subsequent thrombogenesis and atheroma formation. In fact, endothelial dysfunction is one of earliest events in the formation of an atheroma and the magnitude of endothelial dysfunction correlates with the extent of atherosclerosis (Anderson et al. 1995).

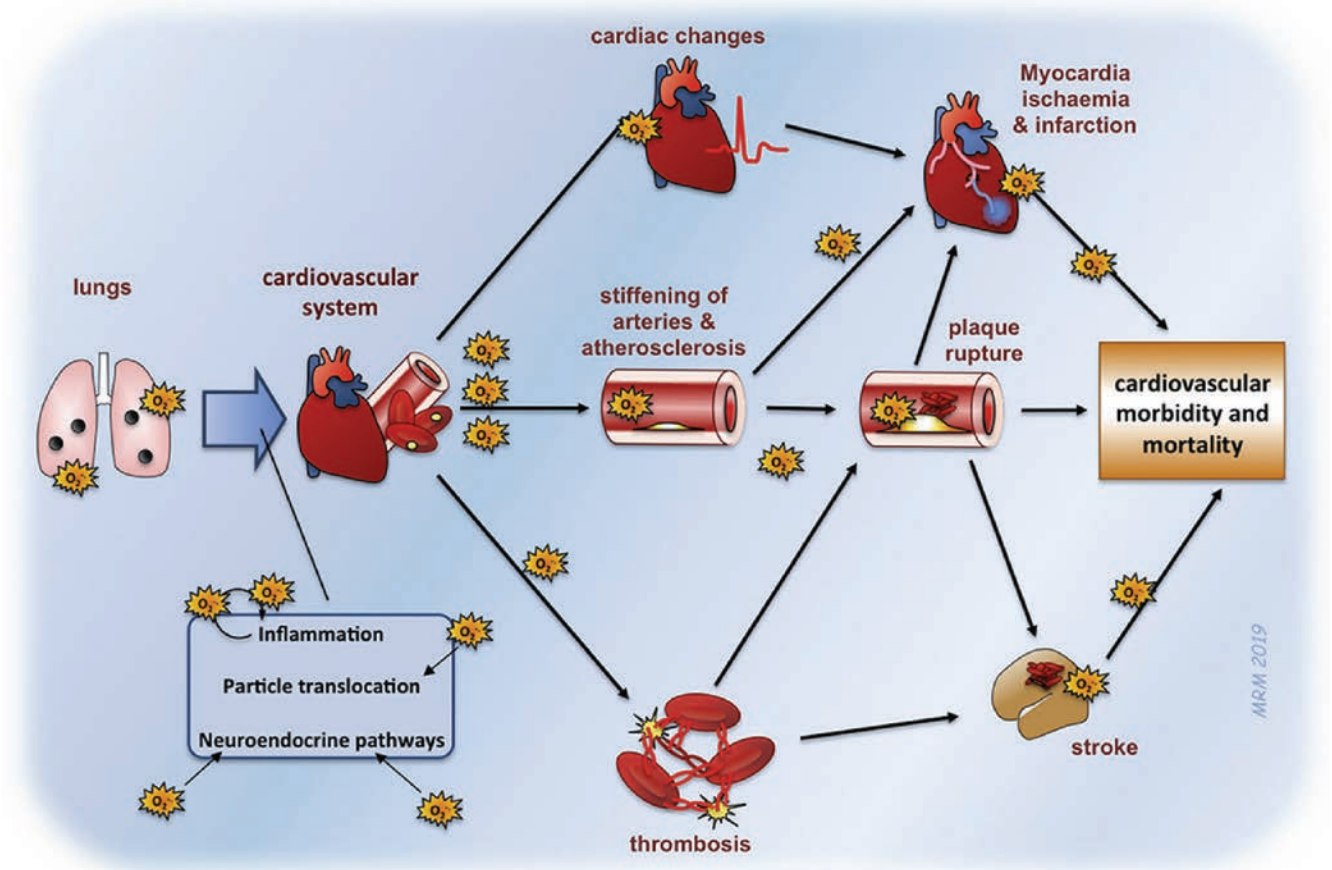

Figure 3.5. Mechanistic effects of air pollution on cardiovascular morbidity and mortality. (Miller 2020; Creative Commons license CC BY 4.0)

Risk factors for cardiovascular disease are intricately linked to those of Type 2 diabetes, with pathophysiology of vascular beds commonly developing as diabetes progresses. Endothelial dysfunction often precedes insulin resistance (a key player in the development of diabetes), and the dual vascular and inflammatory effects of air pollutants on glucose homoeostasis (Rajagopalan and Brook 2012) and cardiovascular function (Brook et al. 2010) likely contribute to comorbidity. Indeed, animal studies show synergism between air pollution and hypercholesterolemia, promoting insulin resistance, adiposity, and visceral inflammation (Sun et al. 2009) in addition to endothelial dysfunction and atherosclerosis (Maresh et al. 2011).

3.3.1 CARDIOVASCULAR DISEASE

The mechanistic studies described below are structured by different facets of the cardiovascular system (Figure 3.5). The literature base is large but heavily dominated by research focused on the effects of DE and DEP, whereas the potential effects of copollutant gases, such as NO_2, have received much less attention. Details of all references cited, plus additional studies of mechanisms underlying cardiovascular effects following exposure to TRAP that have not been selected for this broad discussion for the sake of brevity, are presented in Appendix Table 3D (available on the HEI website).

3.3.1.1 Endothelial Function/Vascular Tone and Blood Pressure

The endothelium is a single layer of cells lining the inner surface of blood vessels, forming an interface between the vascular wall and systemic circulation. By ensuring a quiescent vascular blockade to inflammation, cellular proliferation, and thrombosis, as well as through the synthesis and release of active mediators, the endothelium regulates vasomotor function, that is, the ability of blood vessels to dilate and contract and thereby regulate central blood pressure as well as blood flow in the downstream vascular bed. One of the most important biological mediators is NO owing to its many protective functions. These functions include relaxation of underlying vascular smooth muscle to control blood flow through arteries and blood pressure, inhibition of smooth muscle proliferation and remodeling, regulation of blood clotting, and inhibition of circulating inflammatory cells. In contrast, endothelin (ET-1), the actions of which are mediated by ET_A and ET_B receptors, has potent and long-lasting vasoconstrictor effects, a capacity to induce vascular remodeling, fibrosis, cell proliferation and apoptosis, and is linked to oxidative stress. Nitric oxide and ET-1 are thus natural counterparts in vascular function, and an imbalance between them is a characteristic of endothelial dysfunction and important in the progression of vascular disease. Endothelial dysfunction in association with oxidative stress can stem from the production of the superoxide anion radical via activation of NADPH oxidases, which are widely distributed within the heart. The superoxide anion radical scavenges NO, thus compromising its protective functions. Studies have shown that exposure to components of TRAP is associated with impaired vascular responses as well as implicating oxidative stress as a potential mechanism.

For example, a panel study of 93 elderly nonsmoking adults repeatedly measured endothelial-mediated vasodilation and exposures to size-fractionated PM from regional air-monitoring stations (including chemical composition and oxidative potential) for 6 weeks each during the warm season and cool season (Zhang et al. 2016). Decreased microvascular function of arterioles was inversely associated with the oxidative potential in accumulation ($PM_{0.18–2.5}$) and ultrafine ($PM_{0.18}$) PM, and transition metals. These smaller arteries play a significant role in blood pressure regulation, with high blood pressure being a prominent risk factor of cardiovascular disease. Although it is likely that several mechanisms contribute to the hypertensive effect of air pollution, a role for oxidative stress stems from the ability of superoxide to scavenge NO, a key mediator that controls vasodilatation of blood vessels, as discussed above. Diminished reactive hyperemia responses (a measure of endothelial-mediated vasodilation) and decreased resting plasma nitrite (a meaningful reflection of endothelial NO) in an older population was also observed following a 1.5-hour drive in a passenger vehicle in rush-hour traffic on a busy roadway (Pettit et al. 2015). The absence of an effect of cabin particle filtration may suggest that gaseous pollutants were responsible for the observed effects. Studies have not found associations between TRAP and blood pressure to be modified by gene variants related to antioxidant defense (Levinsson et al. 2014; Mordukhovich et al. 2009).

A comprehensive program of work led by Newby and Mills has utilized well-characterized DE exposures (Volvo TD45, 4.5 L, 4 cylinders, 680 rpm; 250–300 µg PM/m^3 for 1–2 hr) in healthy volunteers to demonstrate prominent effects on the vasculature, including an impaired ability of blood vessels to relax in response to infusions of vasodilator agents (Barath et al. 2010; Langrish et al. 2009; Mills et al. 2005, 2011b; Törnqvist et al. 2007). These findings strongly support a role for oxidative stress mediated through endothelial-dependent and NO pathways. Studies indicate that particles drive these effects in that no impact on vascular function was observed in volunteers exposed to NO_2 (7,640 µg/m^3 for 1 hr) (Langrish et al. 2010). In addition, studies have demonstrated that a retrofit "particle trap" on the engine exhaust and filtering of particles from DE—as in modern diesel engines—prevents the vascular impairment observed with whole exhaust (Lucking et al. 2011; Mills et al. 2011b). Particle composition also appears to be important because exposure to pure carbon nanoparticulates (inhalation of $4{,}000 \times 10^3$ particles/cm^3 for 2 hr) was not associated with cardiovascular effects (Mills et al. 2011b).

Experimental work has shown that inhalation of DE (Yanmar diesel generator; 300 µg PM/m^3 for 5 hr) led to impaired endothelium-dependent relaxation and increased

superoxide production in coronary arteries of rats (Cherng et al. 2011). Following weekly episodic exposure of rats to DEP (30 kW Deutz engine; 2,100 μg/m^3 5 hr/day, 1 day/wk for 16 wk), increased mRNA biomarkers of oxidative stress and altered vascular contractility (ET-1, ET receptors, and NO synthase) occurred in the aorta, but not the heart (Kodavanti et al. 2011). A role for NADPH oxidase has also been implicated in vascular impairment and elevated blood pressure induced by DEP (SRM 2975; 800 μg 3×/wk for 4 wk) and of note, in spontaneously hypertensive (but not normal) rats, suggesting a possible synergism between DEP-induced oxidative stress and classical risk factors (Labranche et al. 2012). Similarly to in vivo studies, isolated blood vessels directly treated with DEP (SRM 2975; 0–100 μg/mL) exhibit impaired endothelial-dependent and NO-mediated vasodilation (Labranche et al. 2012; Miller et al. 2009). These effects are reversed in the presence of the antioxidant superoxide dismutase, supporting the view that if particles reach the systemic circulation they could directly impair vascular function through oxidative stress without the need for prior interaction with the lung or inflammatory cells.

In addition to the large number of DE and DEP studies, NO_2 exposures in rodents have also demonstrated the presence of markers indicative of endothelial dysfunction, oxidative stress, and inflammation (Li et al. 2011a). Following NO_2 exposure (5,000, 10,000, and 20,000 μg/m^3 6 hr/day, for 16 days), Li and colleagues reported mild pathology in the heart of rats, accompanied by reduction/induction of antioxidant activity, elevated levels of malondialdehyde and protein carbonyls, and increased transcription and/or expression of ET-1, NO synthase, TNFα, and IL-1β (Li et al. 2011a). More recently, Karoui and colleagues tested the hypothesis that NO_2 may alter coronary microvascular reactivity through mitochondrial dysfunction/ROS production (Karoui et al. 2020). Repeated exposures to NO_2 in rats (9,550 μg/m^3 3 hr/day, 5 day/wk for 3 wk) led to cardiac dysfunction, mitochondrial dysfunction, and an increase in mitochondrial ROS production. Moreover, repeated NO_2 exposures promoted endothelial dysfunction of the coronary arteries due, at least partially, to a superoxide-dependent decrease of NO bioavailability.

3.3.1.2 Atherosclerosis

Endothelial dysfunction is an early initiating event in the development of atherosclerosis. Loss of endothelial function and increased expression of adhesion molecules (intercellular adhesion molecule 1 [ICAM-1] and vascular cell adhesion molecule 1 [VCAM-1]) attracts and tethers circulating inflammatory cells to the vascular wall. Loss of NO and changes to endothelial cell phenotype also encourage the oxidation of circulating lipids (e.g., low density lipoprotein [LDL] to oxidized LDL [oxLDL]) that are preferentially retained by inflammatory cells, promoting the formation of lipid-laden foam cells—the landmark in the development of atherosclerosis. These cells penetrate the damaged endothelium, inducing the formation of fatty plaques in major arteries that reduce blood flow. Erosion or rupture of advanced plaques is the trigger for thrombosis (a blood clot) that may occlude arteries, leading to onset of myocardial infarction or stroke. Whereas high circulating levels of LDL decreases NO bioavailability either by reducing the concentration and/or activation of NO synthase or by enhancing NO degradation, the athero-protective properties of high density lipoproteins (HDLs) include suppression of vascular-LDL accumulation, inflammation, oxidation, endothelial damage, and thrombosis (Badimon and Vilahur 2012).

As an example of multiple studies using preclinical markers, the potential impact of antioxidant gene polymorphisms on the relationship between black carbon and serum concentrations of (soluble) sICAM-1 and sVCAM-1 has been examined in a cohort of 809 participants in the Normative Aging Study. Exposure to BC (2 days prior to blood sampling) was significantly associated with increased sVCAM-1 (but not sICAM-1) with larger effects seen in participants with a glutathione S-transferase M1 (GSTM1) deletion (Madrigano et al. 2010). Studies focusing on circulating lipids have shown that occupational exposure (n = 50 bus drivers; n = 20 garage men) to vehicle emissions led to greater levels of several markers of systemic oxidative stress in comparison with comparative controls but there was no striking relationship with blood LDL or HDL (Bagryantseva et al. 2010). A similar study found greater levels of oxLDL and decreased concentrations of antioxidants in the blood of taxi drivers (n = 39) compared to nonoccupationally exposed persons (n = 21) (Brucker et al. 2013), and among 371 people in Shanghai, living close to a major road was associated with elevated levels of LDL and decreased antioxidant capacity (Jiang et al. 2016). These effects were accompanied by increased blood pressure, indicators of insulin resistance, and decreased antioxidant capacity.

Reviews of the epidemiological literature have shown that individuals with greater exposure to TRAP exhibit greater degrees of atherosclerosis as assessed by a number of different methods such as coronary artery calcification, aortic calcification, and carotid intima media thickness (Künzli et al. 2011; Tian et al. 2021). More recently, associations between outdoor residential NO_2 and total plaque area, a stronger predictor of cardiovascular disease risk than the aforementioned endpoints (Inaba et al. 2012) and more mechanistically related to the pathobiological process driving cardiovascular disease events (Brook et al. 2006; Spence 2015), have been examined. For example, in a cross-sectional study of 2227 patients (62.9 ± 13.8 yr) at the Stroke Prevention and Atherosclerosis Research Centre in London, Ontario, low levels of TRAP (mean NO_2: 30.1 μg/m^3) were significantly associated with higher carotid plaque burden and exhibited a linear dose response (Johnson et al. 2020). Positive associations with triglycerides, total cholesterol, and the ratio of LDL to HDL cholesterol were also observed, suggesting that air pollution–mediated atherosclerosis may be related to metabolic changes including dyslipidemia and hypertriglyceridemia. In contrast, a previous

study, the Multicultural Community Health Assessment Trial in Vancouver, observed no significant associations between NO_2 and total plaque area in a younger (median age 46 years) and smaller-sized (n = 509) population (Gan et al. 2014).

Although the acute nature of controlled exposure studies in human participants does not lend itself to studying the chronic development of atherosclerosis, studies have unveiled effects that may promote the eventual development of such vascular disease. Exposure of healthy participants to DE (Cummins engine; 100 µg PM/m^3 for 2 hr) increased plasma-soluble lectin-like oxidized low density lipoprotein receptor (sLOX-1; the main oxLDL receptor of endothelial cells) levels, which would be expected to mediate, at least in part, the accumulation of lipids within the vascular wall (Lund et al. 2011).

Due to the long-term development of atherosclerosis in humans and limited means to noninvasively measure atherosclerosis clinically, studies using rodent models of atherosclerosis have been particularly informative. The atherosclerosis prone apolipoprotein-E knockout mice and LDL receptor knockout mice have been especially useful, as advanced atherosclerotic plaques can develop in these mice in a few weeks if they are fed a high-cholesterol diet. Inhalation studies have now shown that exposure to traffic-dominated urban air, whole diesel/gasoline exhaust, or exhaust particles accelerate the development of atherosclerosis in these mice (reviewed in Miller et al. 2012 and Møller et al. 2011) and support a range of operative mechanisms including oxidative stress (Bai et al. 2011; Li et al. 2013; Lund et al. 2009, 2011; Soares et al. 2009; Yin et al. 2013), dysfunctional HDL (Li et al. 2013; Yin et al. 2013), signaling through LOX-1 pathways (Kodavanti et al. 2011; Lund et al. 2009), expression of MMP-9 and ET-1, and monocyte/macrophage infiltration (Lund et al. 2009, 2011) all of which, as discussed above, are associated with progression of atherosclerosis. The exposure concentrations used in these studies were generally representative of high ambient concentrations and exposure durations ranged from 7 days to 4 months (see Appendix Table 3D for full details; available on the HEI website). Miller and colleagues (2013), employing a DEP instillation study (SRM 2975; 35 µg intratracheally 2×/wk for 4 wk), reported not only an increased size, but also complexity of atherosclerotic plaques in ApoE–/–mice. The more complex phenotype was described as being analogous to more advanced plaques and, as such, to lesions potentially more susceptible to rupture.

In vitro, exposure of THP-1 derived human macrophages to carbon black nanoparticles (2.5 µg/mL) increased cellular lipid load (indicative of foam cell formation) but not cell adhesion (Cao et al. 2014). This occurred at concentrations lower than those required to trigger increased intracellular oxidant production and whereas the presence of the glutathione inhibitor buthionine sulphoximine increased the carbon black–induced ROS production, it showed no effect on particle-induced lipid accumulation. DEP (SRM 2975; 10 µg/mL) has also been demonstrated to induce lipid droplet formation in macrophages but, again, at concentrations that were not associated with increased generation of oxidants (Cao et al. 2015).

Atherogenic effects of NO_2 were initially demonstrated following a long-term exposure (306 µg/m^3 for 32 wk) to obese rats that led to elevated levels of triglycerides and decreased HDL and HDL/total cholesterol levels (Takano et al. 2004). HDL levels were also decreased after 1,520 µg/m^3 NO_2 in nonobese rats, as well as in the obese strain of rats. These results prompted the authors to suggest that obese animals were at greater risk of dyslipidemia following NO_2 exposure. In another study, Channell and colleagues showed that blood plasma from healthy human volunteers exposed for 2 hours with intermittent exercise to 955 µg/m^3 NO_2 or to DE (Cummins engine, 106 µg/m^3 particles, 1,528 µg/m^3 NO_2; 2.8 ppm carbon monoxide; 2.4 ppm hydrocarbons) resulted in an upregulation of ICAM-1 and VCAM-1 and the release of IL-8 from cultured coronary endothelial cells immediately and/or 24 hours post exposure (Channell et al. 2012). In addition, an increased amount of sLOX-1 was found in plasma obtained from subjects 24 hours post exposure. Owing to the temporal relationship between sLOX-1 and endothelial cell activation, this was conjectured to be representative of an activated pathway rather than a mediator of toxicity.

3.3.1.3 Thrombosis—Procoagulant Changes

If an atherosclerotic plaque becomes physically disrupted, the procoagulant material within its core is exposed to coagulation proteins in the circulating blood and this triggers thrombosis that can block an artery. Thrombotic occlusion of arteries, at sites of atherosclerotic plaque rupture or erosion or through lodging of emboli, is the predominant cause of heart attacks and strokes. As reviewed by Robertson and Miller, a number of pathways could mediate the prothrombotic effects, including inflammation and oxidative stress, tissue factor, fibrinogen binding, impaired fibrinolysis, and platelets (Robertson and Miller 2018). Blood markers of prothrombotic pathways include fibrinogen, tissue factor, von Willebrand factor (vWF), soluble platelet selectin and plasminogen activator inhibitor-1. Tissue plasminogen activator is a biomarker of the fibrinolytic pathways that mediate clot breakdown (Figure 3.6).

In a panel of elderly participants with coronary artery disease, short-term exposure to traffic-related air pollutants (elemental carbon, primary organic carbon, black carbon, NO_x, carbon monoxide) was associated with increased systemic inflammation, soluble platelet selectin, and decreases in antioxidant levels in red blood cells (Delfino et al. 2009). The composition of PM from five locations in the Netherlands, including a continuous and a stop-and-go traffic location, has been explored in relation to thrombotic biomarkers (Strak et al. 2013). Although OC, nitrate, and sulfate did have an influence on the biomarker levels, an association with other components of the air pollution mixture, including particle number concentration between 0.007 µm and 3 µm,

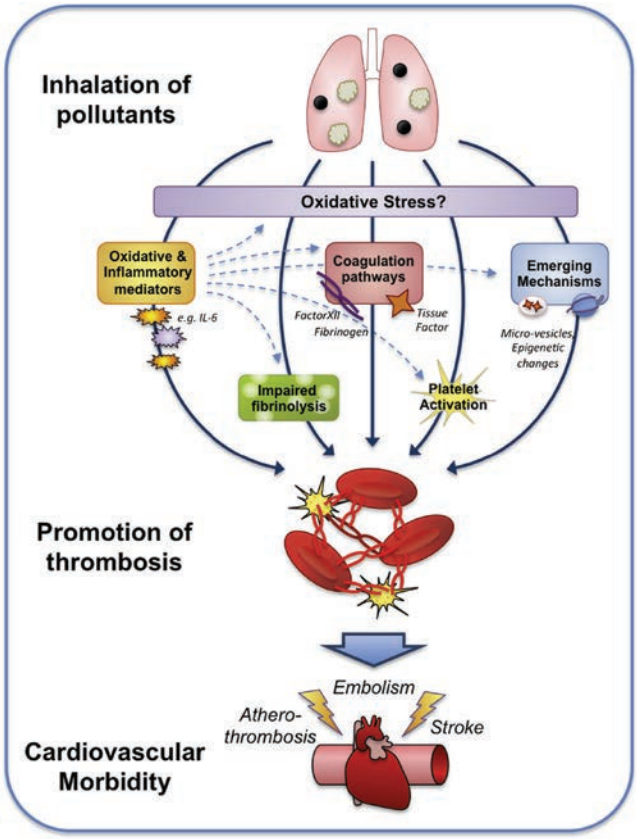

Figure 3.6. Pathways by which inhalation of pollutants can promote thrombosis. (Miller 2020; Creative Commons license CC BY 4.0)

elemental carbon, trace metals and NO_2, was not associated with the biomarkers after adjusting for other pollutants. Wu and colleagues enrolled a panel of healthy students to evaluate the relationship between short-term exposures to various chemical constituents of traffic-related $PM_{2.5}$ and coagulative biomarkers (Wu et al. 2012). They found a robust relationship between fibrinogen and Mg, Fe, Ti, Co, and Cd; plasminogen activator inhibitor-1 and Ti, Co, and Mg; tissue plasminogen activator and Cd and Se; and vWF and Al concentrations.

An ex vivo model of thrombosis using human blood flowing over a damaged blood vessel has been used to demonstrate that acute exposure to DE (Volvo TD40 GJE, 4.0 L, 4 cylinders; 300 µg PM/m^3 or type F3M2011, 2.2 L, 500 rpm Deutz engine; 350 µg PM/m^3 for 1 hr) promotes blood clotting, the mechanisms of which included activation of platelets (Lucking et al. 2008, 2011) and reduced release of tissue plasminogen activator from the vascular endothelium (Mills et al. 2005). Exposure to DE (Volvo TD45, 4.5 L, 4 cylinders, 680 rpm; 300 µg/m^3 for 1 hr) also inhibits fibrinolytic capacity in men with stable coronary heart disease (Mills et al. 2007).

In normal and aged spontaneously hypertensive rats, exposure to DEP (30 kW Dutz engine; 2,100 µg/m^3; 5 hr/day, 1 day/wk; 16 wk) and ultrafine carbon particles (180 µg/m^3; 24 hr) has also been shown to upregulate vWF tissue factor, plasminogen activator inhibitor-1 and tissue plasminogen activator (Kodavanti et al. 2011; Upadhyay et al. 2014). Pulmonary instillation of DEP (SRM 2975; 500 µg intratracheally or 500 µg/kg intravenously) potentiates thrombotic occlusion of the carotid artery following arterial injury through increased platelet activation and impaired fibrinolysis (Tabor et al. 2015), complementing the findings of the clinical exposures to DE (Lucking et al. 2008; Mills et al. 2005). It is noteworthy that the Advanced Collaborative Emissions Study found only a few effects on inflammatory and thrombotic pathway endpoints measured in plasma of rats following more than 24 months of exposure to DE (NO_2: 0.1–4.2 ppm; PM: 2.5–8.0 µg/m^3 for 16 hr/day, 5 days/wk for 24 mo) from a 2007–compliant engine (McDonald et al. 2015).

In vitro, direct addition of DEP (National Institute of Standards and Technology, Gaithersburg, MD, USA; 1 µg/m^3) to whole blood increases blood coagulation, which could be prevented with the antioxidant/anti-inflammatory agent emodin (Nemmar et al. 2015). Use of cultured human umbilical vein endothelial cells have also demonstrated alterations in endogenous fibrinolysis; however, there was a pattern for lower thrombin-induced release of tissue plasminogen activator after exposure to DEP (SRM 2975; 10–150 µg/mL), but this did not achieve significance (Tabor et al. 2015).

3.3.1.4 Arrhythmia and Heart Rate Variability

An arrhythmia is an abnormal heart rhythm caused by problems in the conduction system that sends out electrical impulses, making a heartbeat too slowly, too quickly, or in an irregular way. Some arrhythmias produce a life-threatening condition that leads to cardiac arrest. On the other hand, intermittent atrial fibrillation, while in itself not life threatening, is a major cause for thromboembolic stroke.

The majority of the mechanistic epidemiology studies in this area have made use of noninvasive techniques to measure heart rate variability (HRV). The latter constitutes a set of parameters indicative of the modulation of the electrical activity of the heart and, particularly, its regulation by the autonomic nervous system. For most HRV parameters, a reduction confers a greater risk of developing conditions such as arrhythmia and mortality in people with heart disease. A Normative Aging Study analysis, evaluating pollutant exposures up to 10 hours before the study visit reported associations between the heart-rate–corrected QT interval (QTc; a marker of ventricular repolarization and risk factor for ventricular arrhythmias and sudden cardiac death) and BC (but not $PM_{2.5}$ as a whole) (Baja et al. 2010). This association was stronger for participants who had a high number of unfavorable genotypes related to oxidative stress, as well those who were obese or diabetic. Increased QTc for interquartile range changes in NO_2 were not statistically significant. A personal monitoring study of young healthy taxi drivers during a 12-hour shift before, during,

and after the Beijing 2008 Olympic Games also revealed an association between traffic-related $PM_{2.5}$ exposure and altered cardiac autonomic function (Wu et al. 2010).

Experimental human studies also indicate that exposure to real-life concentrations of PM from urban street air impairs HRV. Within the Atlanta Commuters Exposures Study, a group of 42 adults (21 with and 21 without asthma) experienced elevations of markers indicative of pulmonary and systemic inflammation and oxidative stress and decreases in HRV parameters indicative of autonomic dysfunction within 3 hours after conducting a 2-hour highway commute during morning rush hour (Sarnat et al. 2014). No significant difference in strength of response by asthma/nonasthma health status was observed. In a cross-over study of 60 overweight middle-aged and elderly adults with 5 hours of chamber exposure to ambient ($PM_{2.5}$: 24 μg/m^3) or filtered ($PM_{2.5}$: 3 μg/m^3) air from a busy Copenhagen street again resulted in significant decreases in HRV measurements (Hemmingsen et al. 2015). Interventions to reduce exposure to TRAP have also been investigated. Reducing personal exposure to Beijing PM (that had substantial capacity to generate superoxide free radicals) by using a facemask beneficially altered selected HRV parameters in 98 patients with ischemic heart disease walking alongside city-center roads (Langrish et al. 2012). Among 32 healthy volunteers and 20 well-treated patients with stable coronary heart disease, no significant arrhythmias or changes in HRV occurred during or following brief exposure to DE (Volvo TD45, 4.5 L, 4 cylinders, 680 rpm; particle concentration 300 μg/m^3; 1 hr) (Mills et al. 2011a).

Exposure to whole ($PM_{2.5}$ 150–500 μg/m^3 for 4 hr) and filtered DE (Yanmar generator) increases the sensitivity of the hearts of spontaneously hypertensive rats to arrhythmias, suggesting that the gaseous components play a role in the proarrhythmic response (Hazari et al. 2011). Another study reported that in rats instilled with DEP (SRM 2975; 500 μg) before performing ischemia/reperfusion under anesthesia, the heart is rendered significantly more vulnerable to subsequent ischemic arrhythmia and to reperfusion-associated injury (Robertson et al. 2014). Outcomes from pharmacological intervention within the same study support a role for pulmonary sensory TRPV1 receptors and also β1 adrenoreceptors in mediating these effects.

3.3.2 METABOLIC DISORDERS

Studies, summarized below, that have explored the mechanisms linking TRAP and metabolic disorders have explored effects on (diet-induced) increased susceptibility to weight gain, energy homeostasis, insulin resistance and lipid metabolism by evaluating mechanisms involving inflammation and fatty acid/amino acid metabolism. Because effects of environmental exposures may be greatest during critical windows of development, prenatal and early life exposures have been explored. Details of all references cited below, plus additional studies of mechanisms underlying effects of TRAP exposure on metabolic dysfunction that have not been selected for this broad discussion for the sake of brevity, are presented in Appendix Table 3E (available on the HEI website).

3.3.2.1 Insulin Resistance—Glucose Homeostasis

The effects of urban, traffic-related PM_{10} or $PM_{2.5}$ (250 μg PM intratracheally 1×/wk for 3 wk) on insulin resistance (evaluated by homeostatic model assessment of insulin resistance) was evaluated in rats fed a high-fat diet or normal chow diet for 6 weeks (Yan et al. 2011). Compared with animals on a normal chow diet, body weight and insulin resistance of rats on a high-fat diet increased and these effects were enhanced further after repeated exposure. The central role that energy metabolism plays in the pathogenesis of obesity and type 2 diabetes has prompted an evaluation of long-term effects of prenatal and postnatal DEP (SRM 2975) exposure in mice (20 μg intratracheally 3 times/wk from when mouse dams were 5 wk of age until offspring were weaned) on metabolic programming in offspring (Chen et al. 2017). To determine the window of developmental programming, offspring were switched between vehicle- and DEP-exposed dams once born. Prenatal maternal exposure to DEP did not impact the birth weight of offspring but did significantly decrease their body weight from postnatal week 2. This coincided with decreased food intake, no alteration in brown adipose tissue morphology and, paradoxically, an increased mass of epididymal adipose tissue (metabolically active abdominal fat). In contrast, postnatal mothering by DEP-exposed dams increased offspring body weight during lactation and adulthood and this was associated with markedly increased body fat but not an alteration in food intake. The same investigators, adopting an identical protocol, showed that postnatal (but not prenatal) mothering by DEP-exposed dams caused glucose intolerance in adult male offspring, accompanied by a marked decrease in glucose-induced insulin secretion (but not insulin resistance), decreases in the insulin content of pancreas, and the sizes but not numbers of pancreatic islets and β cells (Chen et al. 2018). It is notable that exposure approaches to investigate the effects of TRAP on insulin resistance or energy metabolism are limited to intratracheal instillation and although this has long been used in toxicity testing as an alternative to inhalation exposure due to its simplicity and cost saving, outcomes can be different between the two approaches (Costa et al. 2006).

3.3.2.2 Inflammation

Type 2 diabetes is preceded by increased circulating concentrations of pro-inflammatory immune mediators (Herder et al. 2011), as well as an upregulation of anti-inflammatory cytokines that possibly represent a counter-regulatory effect (Herder et al. 2013). Such evidence has promoted studies to evaluate whether the association between air pollution and metabolic disorders may be attributable to inflammatory processes.

To provide insights into a contribution of inflammation-associated biomarkers, Lucht and colleagues conducted mediation analyses for adiponectin, high-sensitivity C-reactive protein, and IL-6 receptor antagonist when investigating associations of air pollution exposure with a 10-year incidence of type 2 diabetes (Lucht et al. 2020). Of relevance, both adiponectin and IL-6 receptor antagonist have roles in both inflammation and metabolism. Adiponectin is negatively correlated with inflammation as well as fasting insulin levels (Lontchi-Yimagou et al. 2013). Moreover, lower levels have been linked to unfavorable metabolism changes in nondiabetic individuals (Herder et al. 2016) as well as in people with type 2 diabetes (Herder et al. 2013). IL-6 receptor antagonist has been linked to outcomes related to long-term diabetes (Luotola et al. 2011). The study by Lucht and colleagues (2020) found that traffic-specific exposures (PM_{10}, $PM_{2.5}$, and NO_2) were associated with diabetes risk for all air pollutants and the results of the mediation analysis indicated that adiponectin may play a potential role along the causal pathway.

Pregnant rats exposed to unfiltered ambient Beijing air 2 km away from a major artery road of the city ($PM_{2.5}$ 73.5 ± 61.3 μg/m^3) from gestational day 4 until their offspring were 3 or 8 weeks of age were significantly heavier at the end of pregnancy than those exposed to filtered air (Wei et al. 2016). At 8 weeks old the offspring prenatally and postnatally exposed to unfiltered air were also significantly heavier. In both rat dams and their offspring after continuous exposure to unfiltered air, enhanced pulmonary inflammation, tissue and systemic oxidative stress, dyslipidemia, and inflammatory status of epididymal fat were observed. Exposure of mice for 12 weeks to fine concentrated ambient particles (324.2 ± 45.2 μg/m^3 $PM_{2.5}$), from a district in Shanghai where ambient $PM_{2.5}$ mostly comes from traffic exhaust, induced glucose intolerance, insulin resistance, and lipid metabolism disorders and disturbed energy metabolism (Pan et al. 2019). These impairments were accompanied by a respiratory, systemic, and visceral fat inflammatory response, characterized by the release of IL-6 and TNFα in these compartments.

3.3.2.3 Fatty Acid and Amino Acid Metabolism

Metabolomic studies not only suggest that increased TRAP exposure is associated with dysregulated metabolism of fatty acids and amino acids (Liang et al. 2018), but also links alterations in these metabolites with increased adiposity (Hu and Narasimhan 2014; Park et al. 2015), glucose intolerance (Ho et al. 2013; Menni et al. 2013) and insulin resistance (Newgard et al. 2009; Palmer et al. 2015). Targeted metabolomics has been performed on 173 young adults (18–23 yr; a critical age in the development of cardiometabolic diseases) from eight Southern Californian communities participating in the Children's Health Study to examine the influence of near roadway air pollution (estimated using modeled NO_x at residential addresses) exposures on indices of fatty acid and amino acid metabolism (Chen et al. 2019). Higher near-roadway air pollution exposure was associated with higher concentrations of nonesterified fatty acid oxidation byproducts with effect sizes larger among obese individuals. These results indicate that exposure to near-roadway air pollution could contribute to the metabolic perturbation in adolescents and young adults via altered fatty acid metabolism; the effect modification by obesity status indicates that increased near-roadway air pollution exposure could exacerbate obesity-induced metabolic dysfunction.

3.3.3 SUMMARY

A large evidence base, dominated by studies investigating DE and DEP exposures, describes effects including vascular dysfunction, increased susceptibility of the heart to ischemic damage through an acceleration of atherosclerosis, increased propensity for thrombosis, and imbalance of the autonomic nervous system. Substantial progress has been made in determining the underlying biological mechanisms behind these multifaceted effects and continues to support a role for enhanced oxidative stress.

Far fewer studies have investigated mechanisms underlying potential cardiovascular effects following NO_2 exposures. Although controlled human exposure studies have shown that acute adverse vascular effects of TRAP are mediated by components other than NO_2, repeated exposures of the gas in rodents and in vitro work have reported an increased presence of markers for oxidative stress and inflammation, evidence of endothelial dysfunction and atherogenic effects.

There is little experimental evidence that TRAP would exacerbate stroke. However, impaired circulatory control as a consequence of atherosclerosis of extra- or intracranial arteries could result in inadequate perfusion of organs and potentially ischemic damage, in addition to an increased propensity for thromboembolism.

Animal studies provide evidence that exposure to high concentrations of traffic particles may be a risk factor in the development of diabetes, particularly in those individuals who have existing insulin resistance, and that maternal exposure to DEP may persistently influence glucose homeostasis.

Studies evaluating mechanistic pathways underlying such metabolic perturbations induced by urban PM and near-roadway air pollution have identified possible contributory roles played by inflammation and altered fatty acid metabolism, respectively.

3.4 BIRTH OUTCOMES

Adverse birth outcomes, as a consequence of exposure to TRAP, could be caused by the action of detrimental effects on the mother, fetus, and/or placenta (Kannan et al. 2006). They may reflect systemic consequences of events in the mother,

the placenta, and/or the fetus and may involve a range of biological processes induced by pollutants before and during pregnancy. It is also plausible that ultrafine particles may translocate from the maternal blood circulation in the placenta toward the fetus where several organ systems may be affected (Hougaard et al. 2015). Indeed, the presence of carbon and metal-bearing nanoparticles have been detected in human placenta of mothers (Bové et al. 2019; Liu 2021). Of note, Bové and colleagues (2019) reported an accumulation of black carbon particles in placental villous tissue of mothers exposed to relatively low annual ambient black carbon concentrations (annual average: 0.63–2.42 μg/m^3 in the study area of northern part of Belgium). It remains unclear, however, whether what appears to be a small number of particles (relative to PM in the lung) have the capacity to alter placental development and function and adversely affect the developing fetus. It is likely that the mechanisms through which TRAP could influence birth weight or a premature delivery are dependent not only on the TRAP mixture, but also the gestational window of exposure owing to changes in physiological maturity of the placenta and fetus as pregnancy ensues.

Experimental work, summarized below, has utilized human mechanistic studies and animal research focusing on placental dysfunction, oxidative stress, inflammation, and epigenetic alterations. Human studies are vital because most laboratory animals have fundamental differences in gestational sac structure, placentation, circulations, fetal/placental weight ratios, organogenesis phases, and gestational length. The latter reduces the likelihood of observing chronic adaptive mechanisms that could occur during a 9-month human pregnancy. Furthermore, spontaneous preterm birth is rare in most species. Other potential mechanisms, which have primarily been studied in highly polluted areas impacted by industry rather than traffic, include those induced by heavy metals and polycyclic aromatic hydrocarbons and involve DNA damage in the mother, placenta, and fetus as well as endocrine and metabolic changes.

It is recognized that there is a case for the vascular effects of TRAP (e.g., via systemic endothelial dysfunction) to contribute to preeclampsia (National Toxicology Program 2019), and that infants born to mothers with hypertension during pregnancy are at higher risk for preterm delivery and low birth weight (Doyle 2008). Mechanisms underlying effects of TRAP on the birth outcomes evaluated in this report as a consequence of increasing maternal blood pressure during pregnancy is however not discussed further in this chapter. Instead, readers are directed to the National Toxicology Program monograph on the systematic review of traffic-related pollution and hypertensive disorders of pregnancy that considers mechanistic data (National Toxicology Program 2019). Details of all references cited below are presented in Appendix Table 3F (available on the HEI website).

3.4.1 ALTERED GROWTH, DEVELOPMENT, AND FUNCTION OF THE PLACENTA AND UMBILICAL CORD CIRCULATION

The placenta plays critical roles in facilitating essential nutrient, gas, and waste exchange between the physically separate maternal and fetal circulations and is an important endocrine organ producing hormones that regulate both maternal and fetal physiology during pregnancy. Factors affecting this will therefore impact fetal growth, development, and survival (Kingdom et al. 2000). Moreover, placental weight is a principal influence on the achieved birth weight (Salafia et al. 2006).

Epidemiological studies with a mechanistic component, although not fully supportive, may suggest that exposure of women to higher concentrations of ambient NO_2/NO_x may affect placental growth and function by eliciting abnormal vascularization and/or hemodynamics (Carvalho et al. 2016; Contreras et al. 2018; van den Hooven et al. 2012b). A study embedded in the Generation R Study, a population-based prospective cohort in Rotterdam (characterized by high emissions from road traffic, shipping, households, and industry), found that among 7,801 women, concentrations of NO_2 averaged over total pregnancy were associated with lower placental growth factor (important for placental development and angiogenesis) and higher levels of soluble fms-like tyrosine kinase 1 (a tyrosine kinase protein with antiangiogenic properties) in fetal cord (but not maternal) blood, consistent with an anti-angiogenic state (van den Hooven et al. 2012b). No associations were observed between NO_2 concentrations and either second or third trimester placental resistance (a parameter of the fetal circulation). Other studies have demonstrated elevated blood soluble fms-like tyrosine kinase 1 levels or reduced blood lower placental growth factor levels in women whose pregnancies were complicated by intrauterine growth restriction (Åsvold et al. 2011). Van den Hooven and colleagues (2012b) also observed associations between NO_2 concentrations and lower placental weight and a significant reduction in birth weight.

The few animal studies undertaken to date describe disturbances in placental morphology and function and umbilical cord structure following maternal exposure to particulate air pollutants in real-world environments with high traffic density (Veras et al. 2008, 2012) and DE (Valentino et al. 2016; Weldy et al. 2014). Exposure of mice to filtered or unfiltered particulate urban air pollution in São Paulo (chambers placed close to roadside with high traffic density) throughout pregnancy affects the placental functional morphology (mean $PM_{2.5}$ 27.5 μg/m^3) and changes the structural integrity of the umbilical cord (mean $PM_{2.5}$ 32.8 μg/m^3) (Veras et al. 2008, 2012). The cords were thinner and less voluminous due to loss of mucoid connective tissue and reduced collagen content. Despite findings indicative of feto-placental adaptations to improve diffusive transport across the placenta, fetal weights were significantly reduced. Gestational exposure to DE (1,000 μg/m^3;

25KVA Loxam engine) decreased placental blood flow and fetal capillary numbers in rabbits (Valentino et al. 2016). In mice, DE (300 μg/m^3; single cylinder Yanmar diesel engine, model YDG5500EV-6EI) induced hemorrhage and compaction of the vascular spaces of the placental labyrinth (a structure on the fetal side of the placenta and the interface for gas and nutrient exchange) (Weldy et al. 2014).

3.4.2 OXIDATIVE STRESS

There is suggestive evidence from human mechanistic studies (Clemente et al. 2016; Janssen et al. 2012; Saenen et al. 2016) that increased exposure to TRAP (including residential proximity to source and particulate urban air pollution) is associated with oxidative/nitrosative stress and mitochondrial (mt) DNA content in the placenta and/or maternal/cord blood. In regulating energy, mitochondria within the cells of the placenta are essential for the nourishment, growth, and development of the fetus. Mitochondria are also the major intracellular sources and primary targets of ROS and, compared to nuclear DNA, mtDNA is more sensitive to oxidative stress due a lack of repair capacity (Lee and Wei 2000; Payne et al. 2013). Abnormalities in the content of mtDNA in a cell can therefore be used as a biomarker of mitochondrial dysfunction in the presence of oxidative damage. It is noteworthy that a lower mtDNA content in umbilical cord blood has been associated with abnormal fetal growth (Gemma et al. 2006).

Within 330 mother-newborn pairs of the ENVIRONAGE birth cohort, situated in Belgium, Saenen and colleagues observed that each interquartile range increment in entire-pregnancy black carbon exposure resulted in a 13.9% increase in placental 3-nitrotyrosine (the stable product of tyrosine nitration and a marker of oxidative stress and inflammation) levels (Saenen et al. 2016). No significant associations were found between placental 3-nitrotyrosine and NO_2 exposure or placental 3-nitrotyrosine and birth weight or length. Nitration of placental proteins is evident in normal pregnancies but at higher levels, may disturb placental function, as reported in placental vessels in states of preeclampsia (Bosco et al. 2012). Moreover, the presence of nitrative stress has also been linked with diminished vascular reactivity of the fetal placental circulation (Myatt 2010). Animal studies, described above, that cited adverse effects of TRAP on the placenta and umbilical cord (Section 3.2.1) also observed evidence of nitrosative/oxidative stress (Veras et al. 2012; Weldy et al. 2014).

Using data from the ENVIRONAGE (N = 550) and INMA (N = 376; Spain) birth cohorts, a 10-μg/m^3 increment in average NO_2 exposure during pregnancy was found to be associated with a 4.9% decrease in placental mtDNA content and a 48-g decrease in birth weight (Clemente et al. 2016). The association with birth weight was significant for INMA (–66 g) but not for ENVIRONAGE (–20 g).

3.4.3 INFLAMMATION

Pregnancy per se, may be viewed as an inflammatory condition. As a result of the inflammatory response to pregnancy, maternal C-reactive protein concentrations increase slightly during normal pregnancies (Thornton 2010; von Versen-Hoeynck et al. 2009). However further increases in concentrations have been reported in women whose pregnancies are complicated by suboptimal fetal growth and preterm delivery (Guven et al. 2009; Pitiphat et al. 2005; Trevisanuto et al. 2007). Placental inflammation may also affect its growth, development, and function, which in turn can lead to fetal growth restriction (Williams et al. 2000). Evidence exists that cytokines can cross the placental barrier and interfere with fetal development (Jonakait 2007).

Surprisingly, few studies in either humans (Lee et al. 2011; van den Hooven et al. 2012a) or animals (de Melo et al. 2015; Fujimoto et al. 2005; Weldy et al. 2014) have investigated the potential of TRAP exposure during pregnancy to induce an inflammatory response in maternal, placental, or fetal tissues. Studies involving 1,696 women from the Prenatal Exposures and Preeclampsia Prevention study in Allegheny County (Lee et al. 2011) and 5,067 women from the Generation R Study in Rotterdam (van den Hooven et al. 2012a) did not find an association between ambient NO_2 and high-sensitivity C-reactive protein levels in maternal blood during early pregnancy. However, the Generation R Study did observe elevated concentrations in cord blood (n = 4,450). in association with higher concentrations of NO_2 during total pregnancy (van den Hooven et al. 2012a).

3.4.4 DNA METHYLATION

Studies are beginning to demonstrate that exposure to air pollution modifies epigenetic mechanisms; this may have long-lasting effects on health and future health risk. Epigenetic mechanisms, such as DNA methylation, histone modification, and noncoding RNA, regulate gene expression of a cell by being responsive to environmental changes. The fetal epigenome may provide a biologically plausible link between early life exposure to environmental factors and adverse pregnancy outcomes because DNA synthesis rates are high and epigenetic remodeling is extensive through critical stages of ontogenesis (Hochberg et al. 2011). For instance, during the prenatal period, the embryo undergoes genome-wide DNA methylation (the covalent addition of a methyl group to a cytosine primarily in the context of a cytosine-guanine dinucleotide [CpG]), demethylation, and remethylation (Chaillet et al. 1991). Modification by toxicants of epigenetic patterns that control the expression of genes involved in key placental cellular processes therefore has the potential to contribute to abnormal placental or fetal development.

There is suggestive evidence from human mechanistic studies that increased exposure to TRAP during pregnancy is associated with alterations in DNA methylation in the placenta

or cord whole blood (Gruzieva et al. 2017; Herbstman et al. 2012; Kingsley et al. 2016; Ladd-Acosta et al. 2019; Maghbooli et al. 2018). Personally monitored prenatal exposure to polycyclic aromatic hydrocarbons among a longitudinal cohort study (The Columbia Children's Center for Environmental Health Northern Manhattan Mothers and Newborns Study) of 164 nonsmoking women in New York City, during the third trimester was associated with decreased genomic methylation in cord blood (Herbstman et al. 2012). In a cohort of 471 mother–infant pairs from the Rhode Island Child Health Study, living closer to a major roadway was associated with decreased placental methylation at long interspersed nuclear element-1 (LINE-1; used as a surrogate marker for global methylation) repetitive elements (Kingsley et al. 2016). A meta-analysis of four European and North American birth cohort studies (n = 1,508), reported that prenatal NO_2 concentrations were associated with significant epigenome-wide cord blood DNA methylation differences in several mitochondria-related genes as well as expression of genes involved in antioxidant defense pathways (Gruzieva et al. 2017). The studies described above have not however extended their analysis to look at a mediating effect of disrupted DNA methylation patterns on the relationship between air pollution exposure during pregnancy and birth outcomes or found no significant effect.

3.4.5 SUMMARY

Limited evidence from human mechanistic studies suggest that exposure of women to higher concentrations of ambient NO_2/NO_x may affect placental growth and function.

The few animal studies undertaken to date demonstrate disturbances in placental morphology and function and umbilical cord structure following maternal exposure to (1) particulate air pollutants in real-world environments with high traffic density and (2) DE.

There is some evidence from human and animal studies that increased exposure to TRAP (including residential proximity to source and particulate urban air pollution) is associated with inflammation, oxidative/nitrosative stress, and a lower degree of DNA methylation in the placenta and cord blood.

Evidence exists that inhaled particles have the capacity to accumulate in placental tissue. It remains unclear however whether what appears to be a small number of particles (relative to PM in the lung) have the capacity to alter placental development and function and adversely affect the developing fetus.

3.5 DISCUSSION AND CONCLUSION

Experimental data generated by a substantial body of mechanistic research have demonstrated that exposure to TRAP has the potential to lead to multiple health effects, elicited by adverse events brought about by a number of plausible mechanistic pathways in various organs around the body. These mechanisms all feature in the hallmarks of environmental insults, described by Peters and colleagues as providing a framework to understanding how environmental insults, even at relatively low concentrations, can manifest chronic diseases (Peters et al. 2021).

The mechanistic evidence to support (or refute) epidemiological findings presented in this review is more developed for certain health outcomes than others. For example, a substantive and well-established literature base of experimental studies exists describing characteristic features of asthma (i.e., airway inflammation, airway hyperresponsiveness, and oxidative stress) following exposures to NO_2 and DE (using a variety of mostly older diesel engines to generate exhaust with high concentrations of PM and NO_2). For NO_2, the experimental evidence base is deemed sufficient to support short-term effects on the exacerbation of asthma and (to a lesser extent) long-term effects on the development of the disease. For DE, mechanistic studies have been particularly focused on acute effects and such research is well developed in defining underlying pathways involved in the modulation of epithelial function and inflammatory mediators. Findings that DEPs can directly interact with airway C-fiber afferents to elicit respiratory reflexes provide another mechanistic insight as to how exposure to urban air pollution could initiate exacerbating symptoms (Robinson et al. 2018). Studies also support interactions between gaseous and particulate traffic pollutants and the epigenome in contributing to the development and persistence of disease, and particularly an impact of early life TRAP exposure on developing persistent wheezing and asthma (Brunst et al. 2013; Perera et al. 2009).

Although features relevant in the development of COPD (e.g., oxidative stress, inflammation, amplification of infections, and compromised pulmonary function) are also established effects of exposures to TRAP, relatively little experimental research has been conducted in this area. The 2016 EPA ISA on Oxides of Nitrogen did not include experimental studies in the evaluation of COPD (U.S. EPA 2016). Recent animal studies utilizing real-world traffic exposures for varying periods up to 7 months have observed changes in the airways of rats consistent with those in COPD patients, in association with the release of multiple cytokines from airway cells and a greater role for the PM fraction compared with gaseous components in causing lung damage and lung function decline (He et al. 2017; Jheng et al. 2021). Furthermore, a controlled human study of exposure to DE (6.0 kW generator with Yanmar engine [installed in 2009]) has identified a potential new inflammatory biomarker, neutrophil extracellular traps, the release of which represents a possible mechanism to explain how TRAP contributes to the airway pathophysiology of COPD (Wooding et al. 2020).

An older group of experimental studies describes mechanisms by which long-term exposure to NO_2 and DE/DEP could increase susceptibility to both bacterial and viral pathogens.

Biological plausibility, albeit from studies that invariably used high exposure concentrations, stems from findings that include impaired pulmonary clearance of bacterial infections, reduced capacity of alveolar macrophages to internalize bacteria, and increased susceptibility and response to viral respiratory infections.

A large literature base, dominated by studies investigating DE/DEP exposures, describes the multifaceted nature of cardiovascular effects, including vascular dysfunction (disturbed vascular homeostasis), increased susceptibility of the heart to ischemic damage through an acceleration of atherosclerosis, and an increased propensity for thrombosis. Substantial progress has also been made in determining the underlying biological mechanisms. The evidence continues to support a role for enhanced oxidative stress in the fundamental machinery. Far fewer studies have investigated mechanisms underlying potential cardiovascular effects following NO_2 exposures. Although controlled human exposure studies suggest that acute adverse vascular effects of TRAP are mediated by components other than NO_2, repeated exposures to this gaseous pollutant in rodents and in vitro work have demonstrated the presence of markers for cardiovascular effects and effects consistent with initial events in the development of vascular disease.

Animal studies provide evidence that exposure to high concentrations of traffic particles may be a risk factor in the development of diabetes, particularly in those who have existing insulin resistance, and that maternal exposure to DEP may persistently influence glucose homeostasis. There is little experimental evidence that TRAP would exacerbate stroke. Although it is challenging to fully reproduce the causes and consequences, it is reasonable to assume that the vascular effects of air pollution seen in many other areas of the body will be relevant to the brain. For example, impaired circulatory control because of atherosclerosis could result in inadequate perfusion of organs and potentially ischemic damage when combined with an increased propensity for thromboembolism.

Investigation into mechanisms underlying possible TRAP-related effects on fetal growth and preterm birth is a relatively new area of research. Evidence from human mechanistic studies suggests that exposure of women to higher concentrations of ambient NO_2/NO_x may affect placental growth and function. Studies have also reported associations between particulate and gaseous TRAP and oxidative/nitrosative stress as well as alterations in DNA methylation in the placenta and cord blood. However, only a limited number of studies have investigated a given mechanism. This prevents any firm conclusions relating to weight of evidence between different constituents of the TRAP mix and critical time windows of exposure during pregnancy. Because impaired fetal growth and prematurity have been linked to increased risk of several diseases, such as asthma, heart diseases, and type 2 diabetes—associations that form the basis for the "fetal origins" or the "Barker hypothesis" (Barker 2004)—any air pollution–mediated adverse birth outcome might have long-term consequences. However, it is not known whether associations between birth outcomes and health in childhood and adulthood are attributable to a causal effect of a given birth outcome and/or some of the determinants of the latter. For example, hypothesized mechanisms underlying the association between low birth weight or preterm birth and a subsequent increased risk of asthma involve genetic, perinatal, and environmental factors.

Throughout the mechanistic literature, and certainly since the mid-1990s, there has been an emphasis on particles in vehicle exhaust—especially on DE. Their small size engenders a large reactive surface area, to which redox active metals and polycyclic aromatic hydrocarbons can adhere. This allows the particles to penetrate deep into the respiratory tract. From there they can enter the circulation to elicit widespread effects on different organs of the body. As a consequence, a working principle has been established not without some support that these very small particles pose the greatest threat to human health. Along the way however, the toxicity of traffic-related pollutant gases and other volatile components per se, as well as possible synergistic effects with particles, has become neglected. The findings of Wooding and colleagues (2019) that removing particles from DE did not protect against the allergen-induced effects and that the procedure not only decreased particles, but also total volatile organic compounds and gases, with the exception of NO_2, strongly implicates NO_2 associated with DE as an important adjuvant factor enhancing allergen sensitization (Wooding et al. 2019). Others have demonstrated lower levels of thrombus formation and improved response to vasodilators after exposure to particle-depleted exhaust relative to regular exhaust in healthy male volunteers (Lucking et al. 2011) and the prevention of pro-atherosclerotic effects of DEP in rodents after addition of additives that reduce particle numbers (Cassee et al. 2012). Overall, these results emphasize the importance of delineating the effects of particle traps across a range of exposure conditions and biological endpoints. In addition, studies using new technology diesel engines with enhanced particle and NO_x emission control technologies show very few effects (McDonald et al. 2015). The need for more experimental studies investigating nonexhaust sources from brake wear, tire wear, road surface wear and resuspended road dust is also acknowledged (Amato et al. 2014), especially because they are becoming a significant component of urban air pollution. This is supported by the study quoted earlier in this chapter, demonstrating a broadly equivalent impairment of bacterial phagocytosis by brake dust and DEPs (Selley et al. 2020).

There are also relatively few experimental studies that have used real-world traffic exposures to evaluate the risk of TRAP more accurately on individuals who live near highways and those who commute frequently. Examples include

panel studies that have investigated associations between traffic pollutants and changes in lung function (McCreanor et al. 2007), vascular function (Pettit et al. 2015; Zhang et al. 2016), thrombotic biomarkers (Delfino et al. 2009; Strak et al. 2013; Wu et al. 2012) and heart rate variability (Hemmingsen et al. 2015; Langrish et al. 2012; Sarnat et al. 2014). Others have demonstrated that occupational exposure to vehicle emissions leads to several markers of oxidative stress and increased oxidation of circulating lipids (Bagryantseva et al. 2010; Brucker et al. 2013). Animal studies employing inhalation exposures to traffic-dominated urban air have uncovered several potential molecular features associated with early lung damage with relevance to COPD (Jheng et al. 2021). Others have shown that in real-world environments high traffic density can potentiate the atherosclerotic process (Soares et al. 2009), increase the risk of obesity and metabolic syndrome (Wei et al. 2016), and disturb the functional morphology of the placenta (Veras et al. 2008) and structure of the umbilical cord (Veras et al. 2012).

The focus of the epidemiological evaluations in this report is on long-term exposures to TRAP. As a consequence of the concentrations at which humans are typically exposed in the real world, depending on dose plus other factors such as susceptibility and other environmental influences, an organism or organ is likely to show no response or an adaptive response and finally a pathological response. Examining the potential steps of such a pathway through data generated in mechanistic research is challenging. This not only pertains to the frequent need to (1) extrapolate findings from acute exposures of high dose studies in animals/tissues to long-term, lower dose exposures in humans, but also (2) judge as to what extent alterations that have rapid onset, persist post exposure or lead to a pathological endpoint.

In addition, the animal research that employs weeks to months of inhalation exposures very often undertakes endpoint measures at the end of the study rather than at intervals to define a pathological pathway. Examples of findings that may help in deciphering such concepts include the feasibility that activation of uncoupled NO synthase after DE exposure (Cherng et al. 2011; Miller et al. 2009) may result in prolonged endothelial dysfunction that is slow to reverse (owing to the need for de novo production of NO synthase protein/cofactors and a reduction in circulating ET-1) by which time a subsequent exposure may have ensued. Furthermore, investigating the effects of DEP after (1) an acute (5 hr/day for 2 days) and (2) a 16-week episodic exposure that demonstrated small effects on ET-1 and MMPs after acute exposure, versus observations of oxidative stress, thrombosis, vasoconstriction, and proteolysis after 16 weeks suggest that acute effects may be critical in the progression of vascular effects over a long period (Kodavanti et al. 2011). Further discussion of research approaches needed to validate and give greater insight into such conceptual issues are described in Chapter 14.

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MATERIALS AVAILABLE ON THE HEI WEBSITE

Appendices 3A to 3F contain supplemental material not included in the main report. They are available on the HEI website at *www.healtheffects.org/publications*.

Appendices

3A Asthma

3B Chronic Obstructive Pulmonary Disease

3C Acute Lower Respiratory Infection

3D Cardiovascular Disease

3E Diabetes

3F Birth Outcomes

ABBREVIATIONS

COPD	chronic obstructive pulmonary disease
DE	diesel exhaust
DEP	diesel exhaust particles
ET-1	endothelin-1
GST	glutathione-S-transferase
HDL	high density lipoprotein
HRV	heart rate variability
ICAM-1	intercellular adhesion molecule-1
IFN	interferon
IL	interleukin
ISA	Integrated Science Assessment
LDL	low density lipoprotein
MMP	matrix metalloproteinase
mt	mitochondrial
NADPH	nicotinamide adenine dinucleotide phosphate
NO	nitric oxide
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
NOD	nucleotide-binding and oligomerization domain
oxLDL	oxidized LDL
PM	particulate matter
PM_1	particulate matter ≤1 µm in aerodynamic diameter
$PM_{2.5}$	particulate matter ≤2.5 µm in aerodynamic diameter
PM_{10}	particulate matter ≤10 µm in aerodynamic diameter
ROS	reactive oxygen species
sICAM-1	soluble sICAM-1
sLOX-1	plasma-soluble lectin-like oxidized low density lipoprotein receptor
SRM	standard reference material
sVCAM-1	soluble VCAM-1
Th2	helper T cell
TNF	tumor necrosis factor
TRAP	traffic-related air pollution
TRPA1	transient receptor potential Ankyrin-1
VCAM-1	vascular cell adhesion molecule 1
vWF	von Willebrand factor

PART A: BACKGROUND MATERIAL

Chapter 4

Health Effects of Short-Term Exposure to Traffic-Related Air Pollution

CONTENTS

CHAPTER 4

Health Effects of Short-Term Exposure to Traffic-Related Air Pollution

4.1 BACKGROUND AND APPROACH

Adverse health effects of long-term and short-term exposures to ambient air pollution are well established. Recognizing the importance of exposure duration, air quality regulatory standards worldwide have been established using both daily and annual metrics to protect public health. In addition to the health effects of long-term exposures to high levels of air pollution, short-term exposures may (1) trigger pathological processes that lead to clinical events and premature deaths among susceptible individuals, and (2) exacerbate symptoms of underlying health conditions, such as asthma and chronic obstructive pulmonary disease (COPD*). Establishing health effects of short-term exposures is critical because of their impacts on public health, health care systems, and individual quality of life (Pascal et al. 2013; Wei et al. 2019; Williams et al. 2019). This knowledge also may help support risk communications as air quality alerts from health agencies operate on the hourly or daily scales that may lead to adaptive behaviors and reduce short-term health effects of ambient air pollution. Finally, it has been hypothesized that persistent short-term exposures and accumulation of short-term health effects over time may contribute to the observed health effects associated with long-term air pollution exposures. Although the 2010 HEI Traffic Review considered both short-term and long-term exposures in its critical review, this report has limited the scope to only long-term exposures. The main objective of this chapter is to provide a summary of current literature on health effects associated with short-term traffic-related air pollution (TRAP) exposures. This background information will serve as complementary and supporting evidence to the current HEI Traffic Review's systematic evaluation on long-term exposures.

Studies on short-term exposures rely on changes in air pollution levels from day to day or even within hours. Rapid changes in an individual's exposure can result from regional changes in air quality due to meteorology, as well as from an individual's mobility or behavior, whereas studies on long-term exposures focus on spatial contrasts in air pollution levels over months or years. See Sidebar 4.1 for descriptions of commonly used study designs for short-term exposures (i.e., time-series, case-crossover, and panel). One challenge in assessing results from studies on short-term exposures is that daily variation in estimated exposures to TRAP can be influenced by pollutants from regional sources travelling with air masses (e.g., power plant, wildfires, and industrial operations) and not by local traffic sources alone. Studies that utilize measurements from sparse monitoring networks also cannot fully capture pollutants that exhibit high spatial heterogeneity, especially those reflecting primary emissions from traffic. For some studies, temporal variation in exposures may indeed reflect TRAP well at the population- or individual level. However, the degree to which this is true is likely to vary across traffic-related air pollutants, study locations, and time periods.

Given the above challenges, the 2010 HEI Traffic Review included only a few studies on short-term exposures that were determined to have adequately estimated traffic exposures. The numbers of studies on short-term exposures were limited in the 2010 HEI Traffic Review because of the roadside

Highlights

- A substantial number of time-series, case-crossover, and panel studies have been conducted to examine health effects of short-term exposures to traffic-related air pollution. Particularly for NO_2 and CO, large meta-analyses have demonstrated consistent positive associations between daily variation in traffic-related air pollution and mortality and morbidity outcomes that are robust across geographical regions and age groups. Since the 2010 HEI Traffic Review, studies on elemental carbon, ultrafine particles, and traffic-related air pollution exposures derived from source apportionment have also increased.
- Although still limited in number, these studies provide further supporting evidence on health effects of short-term traffic-related air pollution exposures. Finally, recent panel studies with crossover designs and scripted real-world exposures that specifically target traffic-related air pollution have investigated a wide range of biomarkers, subclinical measures, and symptoms. These studies provide important insights into potential pathways for linking traffic-related air pollution exposures to acute and chronic adverse health outcomes.

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* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

SIDEBAR 4.1 STUDY DESIGNS FOR HEALTH EFFECTS OF SHORT-TERM EXPOSURE

- Health effects of short-term exposure to ambient air pollution are typically investigated by time-series, case-crossover, and panel studies for exposure windows ranging from hours to a few weeks. Time-series studies aim to estimate associations between short-term variation in air pollution over a study region and daily counts of adverse events, such as hospital admissions and deaths, often in study populations of several million people followed for several years (Bhaskaran et al. 2013). A case-crossover analysis is conducted at the individual level by identifying matched reference time periods for each adverse event and utilizing within-individual exposure variation to estimate health effects (Carracedo-Martínez et al. 2010).
- Both time-series and case-crossover studies are case-only designs that can leverage large health administrative databases. Time-series and case-crossover studies examine the entire underlying at-risk populations that are often defined by geographical regions or catchment areas of cases. In contrast, panel studies focus on linking repeatedly assessed individual health endpoints, sometimes accompanied by detailed personal exposure characterizations among a small number of (usually more susceptible) study participants (Janes et al. 2008). Despite use of selected groups of individuals, the panel studies are particularly useful for elucidating possible biological mechanisms linking exposure, biomarkers, physiological responses and symptoms.
- Panel studies often can provide detailed records of behaviors, exposures, and other triggers for acute health outcomes and can assess various outcomes with fine temporal resolution, such as symptoms, medication use, and physiological responses. Some cohort studies with repeated clinical assessments also have the ability to investigate health effects of short-term exposures, mimicking a panel design. Finally, a specific type of panel study, particularly for examining traffic exposures, involves scripted real-world exposures in a crossover design where, as part of the study design, each participant spends time in environments with varying pollution levels.

monitoring requirement laid out in the exposure framework for the 2010 review. For example, only four time-series or case-crossover studies were included for all-cause and cardiovascular mortality, only six panel studies contributed to the assessment of cardiovascular morbidity, and only two panel studies on lung function contributed to respiratory morbidity. Included studies either estimated traffic exposures using source-apportionment methods or had study participants residing in near-road environments. Most time-series and case-crossover studies were excluded because they either utilized background monitors to represent daily variation of air pollution for large geographical regions, or an average of multiple monitors that may reflect a mix of both background and local levels.

Since the 2010 HEI Traffic Review, several developments in exposure assessment have strengthened our ability to attribute observed associations with short-term air pollution exposures to traffic. First, the availability of daily particulate matter ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$) constituents, nitrogen dioxide (NO_2) and carbon monoxide (CO) data from monitoring networks have increased considerably, especially in regions outside of North America and Europe. This has encouraged a larger number of recent time-series and case-crossover studies. Second, ultrafine particles (UFPs) and elemental carbon (EC) are increasingly being used to characterize near-road environments and urban backgrounds. Within cities, tailpipe emission is the most important source contributing to UFPs and EC, which includes black carbon (BC), black smoke, and $PM_{2.5}$ absorbance (Briggs and Long 2016; Kumar et al. 2014). Third, multipollutant analyses where traffic exposure indicators are adjusted for regional pollutants (e.g., ozone and total $PM_{2.5}$ mass) have become more common. Fourth, various source-apportionment methods have been developed to better quantify daily contributions of traffic-related sources (Hopke 2016). Using concentrations of multiple pollutants, these source-apportionment methods aim to estimate contributions of shared emission sources using either known source profiles (e.g., chemical mass balance methods) or observed correlations between pollutant concentrations (e.g., positive matrix factorization [PMF] methods). Studies utilizing source-apportionment methods have also been increasing due to the availability of $PM_{2.5}$ species measurements. Finally, hybrid approaches that integrate multiple data streams, including monitor-based measurements, satellite imageries, and simulations from chemical transport and dispersion models are increasingly being used to estimate short-term exposures (Diao et al. 2019). These data products provide more spatially resolved estimates of traffic-related air pollutants, particularly for NO_2 and EC, that can be assigned to individuals in case-crossover studies or to estimate population-averaged exposures for time-series studies.

The goal of this chapter is to provide a summary of recent studies on effects of short-term exposures that may contribute to our understanding of the health effects of TRAP. Due to the

above-mentioned recent developments in exposure assessment, the consideration of the HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution was not restricted to studies that utilized source apportionment or populations in proximity to major roads. Specifically, the Panel also considered time-series and case-crossover studies on traffic-related air pollutants, such as NO_2, CO, EC, and UFPs as indicators of the TRAP mixture. Recent findings from short-term $PM_{2.5}$ studies based on background monitoring data are not the topic of this review, because of the large number of sources other than traffic and significant secondary particle formation that contribute to $PM_{2.5}$ concentrations. Health effects of short-term exposures to general $PM_{2.5}$ are well recognized, particularly from recent large population studies and systematic reviews (e.g., Atkinson et al. 2014; Liu et al. 2019a; Lu et al. 2015).

The chapter is organized by three broad health outcomes of interest: respiratory morbidity, cardiovascular morbidity, and mortality. Birth outcomes are excluded because of limited studies that reported acute exposures at the daily or weekly scale. Birth outcome studies focusing on trimester or pregnancy exposures are included in the systematic review and hence described in Chapter 8. For each outcome, studies are categorized into three sections, starting with time-series or case-crossover studies of adverse health outcomes with measured or modeled traffic-related air pollutants. Given the large number of existing studies, here we summarize recent meta-analysis results or large multicity analyses when available. These meta-analyses often combine estimates of different exposure lags and outcomes (e.g., hospitalization and emergency department visits) across studies. Then, studies using source-apportionment methods for exposure assessment are described, focusing on results based on TRAP-related sources. Most of these studies also applied a time-series or case-crossover design. Because the number of studies employing source-apportionment methods was small and meta-analyses were not available, the Panel reported results from selected individual studies that were more recent and had large study populations. Finally, we describe evidence from a diverse group of studies, mostly from panel studies with personal exposure assessments, that linked short-term exposures to biomarkers, subclinical measures, and morbidity. A particular emphasis is on crossover designs with scripted exposures to specifically assess effects of traffic exposures. Because this chapter is not a comprehensive evaluation of the complete literature, the Panel reported only on selected representative studies to illustrate specific aspects of TRAP effects on physiological outcomes or disease endpoints.

4.2 RESPIRATORY MORBIDITY

In time-series and case-crossover studies of respiratory morbidity, the most often examined health outcomes are hospital admissions or emergency department visits for specific respiratory conditions, particularly asthma, ascertained using diagnosis codes from medical or billing records. Studies often also examine patient groups with specific respiratory diseases that may respond to increased exposure levels with exacerbations of existing conditions (e.g., asthma or COPD) or with increased vulnerability to severe outcomes, such as those related to pneumonia and acute lower respiratory infections. In panel studies, a wide range of subclinical outcomes related to lung function and pulmonary inflammation have been examined. Time-series studies are typically based on the general population, whereas case-crossover studies typically include patient populations. In panel studies, healthy participants or specific samples from patient populations are typically included, especially when clinical outcomes such as respiratory symptoms are being assessed.

4.2.1 TIME-SERIES AND CASE-CROSSOVER STUDIES

A large number of time-series and case-crossover studies have also been conducted for asthma morbidity to capture exacerbations among those with active or poorly controlled asthma. Overall, most meta-analyses of time-series and case-crossover studies on various traffic-related air pollutants have identified positive associations of short-term exposure and asthma morbidity. Zheng et al. 2015 conducted the largest meta-analysis to date that combined asthma hospital admissions and emergency department visits results from 87 studies. The summary estimate and 95% confidence interval (CI), pooled regardless of age groups, was estimated to be 1.018 (95% CI: 1.014–1.022) per 10-μg/m^3 increase in NO_2 across 66 studies, and 1.045 (1.029–1.061) per 1-mg/m^3 increase in CO across 42 studies. In subgroup analyses, the authors noted similar magnitudes of associations within populations of children and people 65 years and older. In general, higher relative risks (RRs) were observed during the warm season. More recently, Orellano and colleagues (2017) reported a meta-analysis of only case-crossover studies for asthma-related hospital admissions and emergency department visits. With 22 studies from mostly high-income countries, Orellano and colleagues (2017) reported a summary estimate of 1.024 (1.005–1.043) per 10-ppb increase in NO_2 and 1.045 (1.005–1.086) per 1-ppm increase in CO for asthma morbidity. In a subgroup analysis of 12 studies focusing on children under the age of 18, the RR of NO_2 was elevated to 1.040 (1.001–1.081). These findings from meta-analyses are consistent with recent multicity analyses on NO_2 and asthma morbidity (Alhanti et al. 2015; Lu et al. 2020).

Time-series and case-crossover studies on other specific diagnoses of respiratory disease are more limited. For COPD morbidity, DeVries and colleagues (2017) combined nine hospital admissions and emergency department visit studies from Europe, East Asia, and North and South America and calculated a summary estimate of 1.030 (95% CI: 1.020–1.040) for NO_2 per 1-μg/m^3 using the strongest single-day lagged-associations

from these studies. A parallel effort for COPD with largely overlapping studies by Zhang and colleagues (2018), and also including studies with nitrogen oxides, reported a similar summary estimate of 1.013 (1.005–1.021) per 10-μg/m^3 for 14 hospital admission studies. Finally, Nhung and colleagues (2017) performed a meta-analysis of hospital admissions and emergency department visits for pneumonia—including more general acute lower respiratory infections—in children. Among 17 studies, with 12 from either Brazil or the United States, the summary estimate was 1.014 (1.004–1.024) per 10-ppb increase in NO_2 and 1.009 (1.000–1.019) per 1-ppm increase in CO for various lags.

Studies on broad respiratory morbidity are less common. Mills and colleagues (2015) conducted the largest meta-analysis of 15 multisite time-series studies for NO_2 and hospital admissions, including 204 study locations from North America, Europe, India, Australia, and East Asia. They reported a positive association between 24-hour NO_2 and all-age hospital admissions for respiratory diseases with a summary estimate of 1.006 (95% CI: 1.003–1.008) per 10-μg/m^3 increase in various lags. Positive associations were also identified when the analysis was restricted to children (RR = 1.012; 1.004–1.021) and people 65 years and older (RR = 1.007, 1.002–1.012). The largest meta-analysis for UFPs and broad respiratory outcomes was conducted by Samoli and colleagues (2020). They reported a summary effect estimates from 15 cities (11 from Europe, 1 from China, 3 from the United States, and 1 from Chile) and found that among children aged 0–14 years, a 10,000-particles/cm^3 increase in UFP exposure at 2-day lags was associated with an RR of 1.01 (1.00–1.02) in respiratory hospital admissions. Summary effect estimates at other lags were positive but with larger uncertainties; associations in other age groups were generally null.

4.2.2 TIME-SERIES AND CASE-CROSSOVER STUDIES USING SOURCE APPORTIONMENT

Due to the lack of meta-analyses, here we describe several recent individual studies that have examined associations with short-term exposure to source-apportioned traffic PM and respiratory morbidity outcomes. We begin by describing studies on hospital admissions. First, Pun and colleagues (2015) estimated traffic-related PM ≤10 μm in aerodynamic diameter (PM_{10}) in Hong Kong (2001–2018) using PMF and found positive associations with respiratory hospital admissions. Specifically, the RR was estimated to be 1.021 (95% CI: 1.004–1.030) per 4.6-μg/m^3 increase in exposure to vehicle exhaust in a 0 to 5-day distributed lag model. Results were also robust at individual lags, particularly at lags 0, 3, 4, and 5. Also examining hospital admissions, Ebisu and colleagues (2019) applied PMF to eight locations in California (2002–2009) and conducted time-series analyses. They reported positive associations between $PM_{2.5}$ from vehicular emission and pediatric respiratory hospital admissions with an RR of 1.038 (1.009–1.064) per 2.86-μg/m^3 change in exposure at lag 2. Associations at lags 0 and 1 showed consistent positive associations but with larger CIs. The associations in Ebisu and colleagues (2019) were also robust in a two-pollutant model that adjusted for the remaining $PM_{2.5}$ mass. However, several previous studies have found null associations between source-apportioned traffic exposures and respiratory hospital admissions among adults ≥65 years of age. These include a 2-year study in New York (Lall et al. 2011), a 4-year study of four counties in northeast United States (Bell et al. 2014), and a 2-year study in London (Samoli et al. 2016). We note that the above three studies may have considerably less statistical power compared with Pun and colleagues (2015) and Ebisu and colleagues (2019) because of the shorter study duration and smaller number of events.

Studies on respiratory emergency department visits with exposure estimated from source-apportionment methods are also limited and have mixed findings. First, Krall and colleagues (2017) examined source-specific $PM_{2.5}$ with all-age respiratory emergency department visits in four U.S. cities (Atlanta, Birmingham, St. Louis, and Dallas) and reported null associations with $PM_{2.5}$ from traffic sources. When restricted to only pediatric asthma emergency department visits in Atlanta (2002–2015), Gass and colleagues (2015), using the same source-apportionment method, found increased risks of 1.020 (95% CI: 0.990–1.051) for $PM_{2.5}$ from diesel-fueled vehicles, and 1.072 (1.004–1.144) for $PM_{2.5}$ from gasoline vehicles per 1-μg/m^3 increase over lags 0–7 days. These results were generally robust when adjusted for other sources in a multipollutant model, although the association with $PM_{2.5}$ from diesel-fueled vehicles was attenuated when adjusted for ozone. Also focusing on pediatric asthma, Huang and colleagues (2019) conducted a study using source-specific $PM_{2.5}$ estimated from a chemical transport model in the Georgia (2005–2005). They reported positive associations between pediatric asthma emergency department visits and $PM_{2.5}$ from on-road mobile diesel (OR = 1.031; 1.003–1.060) and on-road mobile gasoline (OR = 1.015; 1.003–1.026) per 1-μg/m^3 increase over a 3-day moving average exposure. Finally, Chi and colleagues (2019) derived source-specific $PM_{2.5}$ in Beijing, a location with considerably higher air pollution levels than other studies described in this section. They reported that $PM_{2.5}$ from a traffic-related source was associated with all-age emergency department visits for all respiratory diseases at lag 1 with an RR of 1.058 (1.001–1.120) per IQR range in exposure; however, this association was not consistent at longer lags.

4.2.3 PANEL STUDIES ON BIOMARKERS, SUBCLINICAL MEASURES, AND SYMPTOMS

There is an extensive literature on the use of panel designs to investigate effects of short-term exposures to air pollution on repeated outcome measurements of various biomarkers, subclinical measures, and symptoms related to respiratory

diseases. The three most common outcomes are fractional exhaled nitric oxide as a biomarker for lung inflammation, lung function measured by spirometry, and asthma symptoms. Panel studies are often highly heterogenous in sample size, study population, experimental designs, and exposure assessment methods. The 2010 HEI Traffic Review only included two panel studies on short-term TRAP exposures and lung function. Most studies for asthma symptoms relied on long-term exposure in cohort or cross-sectional studies. Here we describe illustrative examples that highlight possible links between short-term TRAP exposures and physiological responses related to respiratory morbidity.

Fractional exhaled nitric oxide is a noninvasive biomarker for lung inflammation that has received interest in clinical applications, including as a prognostic biomarker for subsequent asthma exacerbations, phenotyping lung diseases, and guiding disease management (Buhl et al. 2020; Kim et al. 2016; Scichilone et al. 2013). Recently, Chen and colleagues (2020) conducted a meta-analysis of associations between short-term ambient air pollution and fractional exhaled nitric oxide from panel studies. From nine panel studies that included both healthy adults and children with or without asthma in the United States, Japan, and China, a 10-μg/m^3 increase in NO_2 exposure was associated with a 4.90% (95% CI: 1.98%–7.81%) increase in fractional exhaled nitric oxide; a positive association was also found by pooling six studies for BC (3.42%; 1.34%–5.50%). It should be noted that the meta-analysis found high between-study variability (I^2 of 93% for NO_2 and 88% for EC). Effect estimates from individual studies are often positive and statistically significant but have large variations in magnitude. This may be because of large variations in sample size, study populations, and covariate adjustment. In general, subgroup analyses suggested higher effects among children.

Weinmayr and colleagues (2010) conducted a systematic review and meta-analysis on NO_2 and asthma symptoms among children with physician-diagnosed asthma, children with reported asthma symptoms, or children who took asthma medication. These panel studies add important additional information because the predominant literature on hospital and emergency department visits reflects only severe cases, whereas the panel studies can identify mild and subclinical health effects. Across 24 panel studies mostly from Europe and the United States, an increase of 10-μg/m^3 NO_2 was associated with an increase in asthma symptoms by 3.1% (95% CI: 0.1%–6.2%). Definitions of asthma symptoms varied across studies, including wheeze, chest tightness, sputum production, shortness of breath, and asthma attacks.

Several panel studies have employed a crossover design with scripted exposure to examine how short-term exposure to high traffic acts on the body and leads to acute and transient physiological responses, possibly explaining the exacerbation of respiratory disease leading to hospital admissions and emergency department visits. The use of scripted exposure is particularly important as the quasi-experimental design allows for attributing observed changes to traffic exposures within a person. Lung function measures, such as forced expiratory volume in 1 second and forced vital capacity, are often measured prior to exposure and at multiple time points after exposure. These lung function measures are common endpoints for assessing asthma control and for diagnosing COPD. One illustrative example of this group of studies is the McCreanor and colleagues (2007) study, which recruited 60 adults with mild or moderate asthma. Each participant spent 2 hours walking along a busy road and through a nearby traffic-free park. The road-side environment showed considerably higher levels of NO_2, EC, and UFPs. Results demonstrated traffic exposure reduced forced expiratory volume in 1 second and forced vital capacity by up to 6.1% and up to 5.4%, respectively. Sinharay and colleagues (2018) followed a similar design and found participants with COPD reported worsening of respiratory symptoms as well as reduced lung function with increased exposure to traffic. More recently, Moshammer and colleagues (2019) conducted scripted walks that also assessed the role of concurrent traffic noise; personal exposures to various pollutants were found to be consistently associated with reduced lung function, irrespective of traffic noise exposure.

Other studies examined the physiological changes after short-term in-vehicle exposure, which is known to include very high levels of TRAP. One typical example of this group of studies is Sarnat and colleagues (2014), who recruited participants to carry out a 2-hour scripted highway commute in Atlanta. Results showed elevated fractional exhaled nitric oxide postcommute compared with baseline but no change in lung function measurements. Because participants drove their own vehicles, Sarnat and colleagues (2014) controlled for stress by including salivary cortisol concentration in the statistical models and found that associations with air pollutants were robust. A follow-up study by Golan and colleagues (2018) added a nonfreeway commute and a no-commute session, showing that on-road exposure may be acutely impacting lung function. Finally, another example is Zuurbier and colleagues (2011), who recruited 34 healthy adults with different 2-hour morning commute modes (bicycle, car, and bus). Personal measurements of UFPs and $PM_{2.5}$ absorbance were associated with changes in lung function, with some evidence that effects were stronger in participants who took car or bus trips.

4.3 CARDIOVASCULAR MORBIDITY

Time-series and case-crossover studies of short-term TRAP exposures and cardiovascular morbidity have predominantly examined hospital admissions, whereas emergency department visits are less frequently examined when compared with

respiratory morbidity. In contrast to long-term studies that often focus on incidence of cardiovascular diseases, short-term studies often cannot be restricted to the first clinical event. Common subcategories of cardiovascular disease outcomes in time-series and case-crossover studies include hospital admissions for myocardial infarction, heart failure, cardiac arrhythmia, and stroke. In panel studies, a wide range of subclinical markers of cardiovascular function have been investigated. These often reflect potential mediating pathways through which air pollution exposure may elicit adverse responses such as systemic inflammation, oxidative stress, and blood pressure (Franklin et al. 2015). Although long-term exposure studies address structural markers that reflect the underlying pathology of atherosclerosis and do not change rapidly over time (e.g., coronary calcification, carotid plaque, carotid intima-media thickness, ankle-brachial index), short-term exposure studies often focus on rapid and transient physiological changes (e.g., endothelial dysfunction, heart rate variability [HRV]), blood pressure, and levels of circulating biomarkers for inflammation, coagulation, and oxidative stress.

4.3.1 TIME-SERIES AND CASE-CROSSOVER STUDIES

Overall, most meta-analyses of time-series and case-crossover studies on various traffic-related air pollutants have identified positive associations between short-term exposures and cardiovascular disease outcomes, particularly for NO_2 and CO. For example, in a meta-analysis of seven single-city and multicity time-series studies from Europe, Australia, and East Asia, Mills and colleagues (2015) reported a positive association between 24-hour NO_2 and all cardiovascular hospital admissions, with a summary estimate of 1.007 (95% CI: 1.003–1.010) per 10-μg/m^3 increase for various lags.

Several large meta-analyses with global coverage, except Africa, have addressed specific cardiovascular disease subgroups such as ischemic heart disease, myocardial infarction, stroke, congestive heart failure, arrhythmias, and hypertension and found consistently positive associations. For ischemic heart disease hospital admissions and emergency department visits, Stieb and colleagues (2020) identified 48 time-series and 38 case-crossover studies. The summary estimate, by combining estimates from different lags, was 1.012 (95% CI: 1.008–1.015) for time-series studies and 1.038 (1.027–1.050) for case-crossover studies per 10-μg/m^3 increase in NO_2. For myocardial infarction hospital admissions and emergency department visits, Mustafic and colleagues (2012) reported a summary estimate of 1.011 (1.006–1.016) per 10-μg/m^3 increase in NO_2 across 21 studies, and a summary estimate of 1.048 (1.026–1.070) per 1-mg/m^3 increase in CO across 20 studies with various lags. The CO result is consistent with a more recent systematic review of 26 studies (Lee et al. 2020) that reported a summary estimate of 1.052 (1.017, 1.089) per 1-mg/m^3 increase in CO. Three studies from Mustafic and colleagues (2012) were excluded from Lee and colleagues (2020) due a more stringent outcome definition. Finally, Shah and colleagues (2015) identified 45 studies for hospital admissions specifically for stroke. The summary estimate was 1.011 (0.999–1.023) per 1-ppm increase in CO and 1.006 (1.003–1.009) per 1-μg/m^3 increase in NO_2; there was also evidence that the strongest association was with lag 0 with both pollutants. For heart failure hospital admissions and emergency department visits, Shah and colleagues (2013) estimated a summary estimate of 1.035 (1.025–1.045) per 1-ppm increase in CO across 27 estimates, and a summary estimate of 1.071 (1.012–1.022) per 10-ppb increase in NO_2 across 28 estimates of various lags. For cardiac arrhythmia hospital admissions, Song and colleagues (2016) estimated a summary estimate of 1.041 (1.017–1.065) per 1-ppm increase in CO across eight studies, and a summary estimate of 1.036 (1.020–1.053) per 10-ppb increase in NO_2 across nine studies from Asia, Europe, and North America. Finally, for hypertension hospital admissions and emergency department visits, Cai and colleagues (2016) reported a positive association for 3-day lagged NO_2 (RR = 1.069; 1.003–1.183 per 10-μg/m^3) from three studies in Canada and China.

4.3.2 TIME-SERIES AND CASE-CROSSOVER STUDIES USING SOURCE APPORTIONMENT

Because of the lack of systematic review or meta-analysis, here we describe several recent studies that have examined associations with short-term exposure to pollutants from traffic sources. We begin by describing illustrative studies on hospital admissions. Lall and colleagues (2011) estimated traffic-related $PM_{2.5}$ in New York (2001–2002) using PMF and found positive associations with over 72,000 hospital admissions for cardiovascular causes among older people. The RR was estimated to be 1.041 (95% CI: 1.005, 1.077) per 2.8-μg/m^3 increase in a 0–3 day distributed lag model with the strongest association observed at lag 0. In their 2011–2012 study, Samoli and colleagues (2016) estimated daily PM_{10} from traffic sources in London using PMF and found a positive association with cardiovascular hospital admissions among people ages 15–64 at lag 1 with an RR of 1.010 (1.00–1.020) per 0.3-μg/m^3 increase in exposure; the association was robust against adjustment for other sources and remaining PM_{10} mass. In a large California (2002–2009) study, Ebisu and colleagues (2019) applied PMF to eight locations in California to estimate $PM_{2.5}$ from vehicular emission. They reported a positive association between traffic exposure and cardiovascular hospital admissions among those ages 65 or above with an RR of 1.015 (1.003–1.028) per 2.86-μg/m^3 change in exposure at lag 1. Similar magnitude of association was found at lag 0 but not at lag 2.

Studies on cardiovascular emergency department visits with exposure estimated from source-apportionment methods are also limited. Sarnat and colleagues (2008) performed PMF and a modified chemical mass balance approach to source apportion daily $PM_{2.5}$ in Atlanta during the period 1998 to 2002. Exposures to mobile sources derived from both methods

were positively associated with same-day cardiovascular emergency department visits. For PMF-based exposures, RRs were estimated to be 1.025 (95% CI: 1.014–1.036) for diesel mobile source per 2.23-μg/m^3 increase, and 1.019 (1.010–1.029) for gasoline mobile source per 1.23-μg/m^3 increase. A follow-up study by Pennington and colleagues (2019) that extended the study period to 2010 and used an updated source-apportionment method also reported positive associations between cardiovascular emergency department visits and same-day diesel-source exposure (RR = 1.005; 1.010–1.020 per 1-μg/m^3 increase) and same-day gasoline-source exposure (RR = 1.005; 0.998–1.013 per 1-μg/m^3 increase). The strongest associations were observed for ischemic stroke, and results were slightly attenuated after adjusting for other sources.

4.3.3 PANEL STUDIES ON BIOMARKERS, SUBCLINICAL MEASURES, AND SYMPTOMS

Several preclinical markers for cardiovascular diseases are routinely used to identify potential short-term mechanistic responses to air pollution exposures. Both noninvasive physiological measurements and circulating biomarkers have been employed to investigate how air pollution may acutely impact different potential pathways, including inflammation, oxidative stress, endothelial dysfunction, autonomic imbalance, and thrombogenesis (Franklin et al. 2015). One commonly used measure of impaired cardiac autonomic function is reduced HRV, which has been used as a predictor for cardiovascular outcomes (Huikuri and Stein 2013; Lees et al. 2018). Other physiological measures include arterial blood pressure and various measures of vascular function such as reactive hyperemia index and retinal arteriole diameter.

For circulating biomarkers, high sensitivity C-reactive protein is often used to reflect vascular inflammation, and elevated levels are associated with a higher risk for subsequent cardiovascular events (Arroyo-Espliguero et al. 2021). Other biomarkers for systematic inflammation and oxidative stress include, but are not limited to, intracellular adhesion molecule, vascular cell adhesion molecule, interleukins (IL-1β, IL-6, IL-8), 8-oxo-2′-deoxyguanosine, and tumor necrosis factor. Several biomarkers have also been used to reflect coagulation, thrombosis potential, and atherosclerosis progression (platelet-monocyte aggregation, tissue-type plasminogen activator, plasminogen activator inhibitor-1 and von Willebrand factor). Identification of novel biomarkers to develop prediction algorithms for subclinical and clinical cardiovascular outcomes is an active area of research. As such, the set of biomarkers for different pathophysiological pathways in air pollution research is increasing as new panel studies are designed and longitudinal follow-ups for established cohorts are being conducted.

Systematic reviews and meta-analysis for short-term $PM_{2.5}$ exposures have been conducted for HRV (Niu et al. 2020; Pieters et al. 2012) and high sensitivity C-reactive protein (Liu et al. 2019b), generally finding positive associations. In contrast, the number of studies that focus on traffic-related air pollutants is more limited. Buteau and Goldberg (2016) provided a structured review of panel studies on short-term exposure to air pollution and HRV, with 12 studies identified for NO_2. However, they noted the small number of high-quality studies, mixed findings, and heterogeneous study populations and measurements make synthesis of evidence difficult. Results for HRV in the systematic review of UFP health effects by Ohlwein and colleagues (2019) were also mixed; 16 studies examined HRV metrics with 11 reporting associations with at least one HRV outcome. Ohlwein and colleagues (2019) also reviewed 20 studies that examined associations between UFPs and other biomarkers, noting suggestive associations with blood pressure and systemic inflammation. Despite the lack of meta-analyses on other traffic-related air pollutants and markers of inflammation and oxidative stress, these associations are increasingly being examined in cohort studies (Bind et al. 2012; Li et al. 2016, 2017).

Four illustrative crossover studies utilized scripted exposure specifically targeting TRAP. In a commuter study, Weichenthal and colleagues (2014) recruited participants in Montreal to cycle for two hours on scripted high- and low-traffic routes. Personal NO_2 exposure was associated with decreased low frequency HRV, and UFPs were associated with increased diastolic blood pressure and decreased reactive hyperemia index. However, UFP exposures were not associated with increased standard deviation of normal-to-normal intervals, a measure of overall HRV. This is in contrast to the scripted car commuter study of Sarnat and colleagues (2014), which found decreases in standard deviations of normal-to-normal intervals three hours post commute for all participants, with the largest decrease seen among people with asthma. The exposure levels of Sarnat and colleagues (2014) were higher than those of Weichenthal and colleagues (2014) (e.g., mean BC was 6.6 μg/m^3 vs. 1.7 μg/m^3). In Moshammer and colleagues (2019), healthy young adults completed 1-hour walks along a busy road. Although noise exposures were consistently negatively associated with all six HRV metrics considered, associations between personal air pollution and HRV were all null. In another related study, Mirowsky and colleagues (2015) recruited healthy adults to participate in scripted walks with different traffic types. Personal exposures to EC were associated with two of the five HRV metrics without controlling for noise. Overall, while the above studies indicate suggestive associations of short-term TRAP exposures and biomarkers for cardiovascular risks, synthesis of finding is challenging, due to the different study design and inconsistent findings across HRV metrics.

4.4 MORTALITY

Time-series and case-crossover studies on mortality represent the largest body of literature on health effects associated with short-term exposures to TRAP, likely due to the relative

ease of accessing death records from administrative databases. These studies often examine all-cause mortality, as well as respiratory and cardiovascular mortality outcomes.

4.4.1 TIME-SERIES AND CASE-CROSSOVER STUDIES

Several meta-analyses have been conducted for short-term exposures to EC on all-cause and cause-specific mortality. A recent study by Achilleos and colleagues (2017) identified 41 time-series and case-crossover studies, mostly from Europe and North America. A 2.6-μg/m^3 increase in EC, using lags of the strongest association in each study, was associated with all-cause mortality (RR = 1.006; 95% CI: 1.002–1.010) and cardiovascular mortality (RR = 1.006; 1.002–1.010) but not with respiratory mortality. These findings are consistent with previous meta-analyses with smaller numbers of studies (Levy et al. 2012; Atkinson et al. 2015) and when $PM_{2.5}$ is included in two-pollutant models (Yang et al. 2019).

Orellano and colleagues (2020) carried out the most recent meta-analysis of mortality and NO_2, with the majority of studies from Asia, Europe, and North and South America. The estimated overall RRs were 1.007 (95% CI: 1.006–1.008) per 10-μg/m^3 increase in 24-hour NO_2 across 54 studies and 1.0024 (0.9995–1.0053) for 1-hour maximum NO_2 across 10 studies of various lags. These results are consistent with several previous meta-analyses on all-cause and cause-specific mortality (Atkinson et al. 2014; Mills et al. 2015; Requia et al. 2018; Shah et al. 2013). They also agree with a recent multisite analysis of 272 cities in China (Chen et al. 2018; Liu et al. 2018), which also demonstrated robustness of NO_2 and CO associations in two-pollutant models with ozone or $PM_{2.5}$. Similarly, Mills and colleagues (2016) conducted a meta-analysis focusing specifically on two-pollutant models. Among 15 study-specific estimates with various lags, they found that adjusted estimates of NO_2 associations were generally independent of PM mass. Specifically, for all-cause mortality, a 10-μg/m^3 increase in 24-hour NO_2 was associated with an RR of 1.008 (1.005–1.011) increased risk, which was reduced to 1.006 (1.003–1.009) after adjusting for PM.

Current studies on the association between UFPs and mortality are limited with mixed findings. In 2013, HEI published Perspectives 3, *Understanding the Health Effects of Ambient Ultrafine Particles*, (HEI 2013) which identified 11 short-term UFP exposure studies on mortality for cardiovascular and respiratory diseases mostly from European cities. Only six studies reported positive associations, and Perspectives 3 concludes that these studies provide only suggestive evidence, citing not only the limited number of studies, but also analytical challenges such as confounding by copollutant, variations in measurement techniques and potential measurement error. In a recent systematic review, Ohlwein and colleagues (2019) updated Perspectives 3 by identifying seven additional studies from Europe and China on short-term UFP exposures and mortality, again noting inconsistent findings across studies.

4.4.2 TIME-SERIES AND CASE-CROSSOVER STUDIES USING SOURCE APPORTIONMENT

Only three mortality studies that utilized source-specific exposure estimates were identified. First, Heo and colleagues (2014) conducted source apportionment of $PM_{2.5}$ in Seoul, Korea, during the period 2003 to 2007 using PMF. They reported positive associations between respiratory deaths and same-day $PM_{2.5}$ from gasoline emissions (RR = 1.055; 95% CI: 1.005–1.107 per 6.48-μg/m^3) and same-day $PM_{2.5}$ from diesel emissions (RR = 1.067; 1.002–1.137 per 5.23-μg/m^3). However, no associations were identified at other lags or with cardiovascular mortality. Tobías and colleagues (2018) estimated UFPs emitted by vehicle exhaust in Barcelona (2009–2014) and found a positive same-day association with daily all-cause mortality (RR = 1.016; 1.007–1.025 per 3,277 particles/cm^3); this association was similar for lag 1 and lag 2 exposure. However, in the 2-year London study by Samoli and colleagues (2016), traffic exposures derived from source-apportioned PM_{10} and size distribution of UFPs were not found to be associated with all-cause and cause-specific mortality.

4.5 SUMMARY

Overall, existing evidence is consistent in reporting positive associations between short-term exposures to TRAP and adverse health outcomes. Observed associations range from early, preclinical adverse health effects assessed by repeated in-depth examinations of pulmonary and systemic inflammation, lung function, blood pressure, endothelial function, and autonomic function to symptom exacerbation, relief medication use, and increased health services use (i.e., hospital admissions and emergency department visits), and finally to increased mortality observed at the population level. The substantial number of time-series and case-crossover studies for short-term TRAP exposures, particularly for NO_2 and CO, have demonstrated that associations are robust across different geographical regions, study periods, age groups, and study populations. Recent studies have also suggested the independent health effects of NO_2 and other air pollutants in multipollutant models. Studies that aim to better capture temporal variation in traffic signal using source-apportionment methods and more specific traffic-related air pollutants (e.g., EC and UFPs) have reported positive associations; however, they are currently limited in the study locations and outcomes assessed. Panel studies focusing on TRAP are more limited and heterogenous compared with $PM_{2.5}$ and ozone. However, findings from crossover designs that mimic an experimental design provide additional evidence linking short-term TRAP exposures and physiological responses.

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ABBREVIATIONS

BC	black carbon
CI	confidence interval
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
EC	elemental carbon
HRV	heart rate variability
NO_2	nitrogen dioxide
OR	odds ratio
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 µm in aerodynamic diameter
PM_{10}	particulate matter ≤10 µm in aerodynamic diameter
PMF	positive matrix factorization
RR	relative risk
TRAP	traffic-related air pollution
UFPs	ultrafine particles

PART B: METHODS

Chapter 5

General Methods

CONTENTS

CHAPTER 5

General Methods

5.1 SUMMARY

The Panel used a rigorous and systematic approach to search the literature, select studies for inclusion in the review, assess study quality, summarize results, and reach conclusions about the confidence in the body of evidence. The Panel's approach was largely based on standards set by Cochrane, World Health Organization (WHO*), and the National Institute of Environmental Health Sciences. To this end, a review protocol was published in 2019 (HEI 2019), and registered in Prospero, a registry of systematic reviews.

Health outcomes were selected by the Panel based on evidence of causality (causal or likely causal), according to the latest determination for general air pollution from available authoritative integrated science assessments and based other considerations such as relevance for public health and policy. Selected health outcomes were clinical (rather than preclinical) outcomes and included birth outcomes, respiratory outcomes, cardiometabolic outcomes, and all-cause and cause-specific mortality.

A PECOS question (Population, Exposure, Comparator, Outcome, and Study) was developed and then inclusion and exclusion criteria were listed for each PECOS domain in relation to the selected health effects of long-term exposure to traffic-related air pollution (TRAP). The focus of the review was on health effects observed in the general population. The Panel developed a novel framework for assessing the potential of different exposure assessment approaches used in epidemiological studies to be indicative of exposure to TRAP, including the near-road and neighborhood environments.

An extensive search was conducted of literature published between January 1980 and July 2019. Studies were checked for eligibility by two reviewers. Data from all included studies were extracted and evaluated extensively, including key information for meta-analysis such as outcome, pollutants, the effect estimate, increment, and 95% confidence interval. A random-effects meta-analysis was performed when at least three studies were available for a specific exposure–outcome pair. Risk of bias was assessed for all exposure–outcome associations that were included in meta-analyses using a modified version of the tool developed for the risk of bias assessment in the WHO Air Quality Guidelines (AQG) review (WHO 2020, 2021). Additional analyses were performed to assess consistency across geographic region and time period, for example. An adapted GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment of the confidence in the quality of the body of evidence was made using the Office of Health Assessment and Translation (OHAT) method as a guide (OHAT 2019). The Panel also took a broader approach and developed a narrative assessment to evaluate the level of confidence in the presence of an association.

The assessments based on the modified OHAT approach and the narrative assessment were combined into an overall confidence assessment, with the two approaches considered complementary.

In addition to the systematic review of key health outcomes as described above, literature reviews were developed for neurodevelopmental outcomes in children as well as Parkinson disease and dementia-related outcomes in adults. Those literature reviews were added because the Panel thought these were important emerging areas that should be represented in the report, even as a larger body of evidence develops.

Highlights

- The Panel used a rigorous and systematic approach to search the literature, select studies for inclusion in the review, assess study quality, summarize results, and reach conclusions about the confidence in the body of evidence.
- An extensive search was conducted of literature published between January 1980 and July 2019 on selected health outcomes.
- Meta-analyses were performed where three or more studies were identified for the same exposure and health outcome.
- Conclusions were based on a narrative assessment and a modified OHAT approach, with the two approaches considered complementary.

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* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

5.2 INTRODUCTION

The Panel used a systematic approach to search the literature, assess study quality, summarize results, and reach conclusions about the associations. To this end, a review protocol was published in 2019 (HEI 2019) and registered in Prospero, a registry of systematic reviews. The methods were largely based on standards set by the Cochrane organization (Higgins et al. 2020), the National Institutes of Environmental Health Sciences OHAT handbook (OHAT 2019). The systematic reviews were conducted as part of the new WHO AQG (Chen and Hoek 2020; Huangfu and Atkinson 2020; WHO 2021). The Panel also took note of the newly published recommendations for the conduct of systematic reviews (Whaley et al. 2020).

This chapter builds on the published protocol, describes additional considerations, and lists differences between the protocol and the actual review undertaken. It describes the selection of health outcomes and prioritization; the review question; and the methods to search the literature, assess study quality, summarize results, and reach conclusions about the level of confidence in the presence of an association.

HEI hired a contractor team at the Swiss Tropical and Public Health Institute, Switzerland, to execute certain parts of the review, particularly bibliographic searches and data extraction, in close collaboration with HEI staff and Panel members.

5.3 SELECTION OF HEALTH OUTCOMES AND PRIORITIZATION

Reviewing the evidence systematically for all potential adverse health effects related to long-term exposure to TRAP was infeasible considering the available resources. Health outcomes were selected by the Panel based on evidence on causality (causal or likely causal) according to the latest determination for general air pollution (broader than TRAP) from the U.S. Environmental Protection Agency (EPA), the International Agency for Research on Cancer, Health Canada, or other authoritative integrated science assessments. Additional criteria included relevance for public health, policy, and feasibility. The Panel only included health outcomes that were linked to long-term traffic-related exposure, which was defined as a duration of months to years, similar to the definition of the WHO AQG (WHO 2021). Table 5.1 lists the health outcomes included in the systematic review.

The selection of health outcomes and prioritization of the traffic review was discussed extensively because initial

Table 5.1. Selected Health Effects of Long-Term Exposure to TRAP in the Systematic Review

Health Outcome Category	Subcategory (ICD-10 codes from the WHO, version 2016, where applicable)
Birth outcomes	• Low birth weight (<2,500 g) (P07.0–P07.1) • Birth weight (continuous measure) • Small for gestational age (e.g., <10th percentile of birth weight for gestational age) • Preterm birth (<37th week) (P07.2–P07.3)
Respiratory outcomes (assessed separately for children and adults)	• Asthma (J45–J46) and asthma-related symptoms (wheeze) • Acute lower respiratory infections (J12–J18, J20–J22) • Chronic obstructive pulmonary diseases (J44)
Cardiometabolic outcomes	• Ischemic heart disease events (I20–I25) ◦ Coronary events such as fatal and nonfatal myocardial infarction (I21) and cardiac arrest (I46) • Stroke events (I60–I69) • Type 2 diabetes mellitus (E11)

Mortality	• Nonaccidental mortality (A00–R99) or all–cause mortality (A00–Z99)
	• Circulatory mortality (I00–I99)
	  ◦ Ischemic heart disease (I20–I25)
	  ◦ Stroke (I60–I69)
	• Respiratory mortality (J00–J99)
	  ◦ Chronic obstructive pulmonary disease (J44)
	  ◦ Acute lower respiratory infections (J12–J18, J20–J22)
	• Lung cancer mortality (C33–C34)

literature searches identified a large number of studies. The Panel discussed the difference between clinical outcomes, clinical-relevant outcomes, subclinical outcomes useful for disease diagnosis, and other subclinical and physiological outcomes primarily relevant to elucidating disease mechanisms. This selection process was guided by the joint statement of the American Thoracic Society and the European Respiratory Society on this topic (Thurston et al. 2017). The Panel ultimately decided to focus efforts on reviewing the evidence for a selected number of clinical outcomes, rather than trying to review every possible important outcome. Therefore, the Panel opted not to review studies on, for example, lung function, atherosclerosis, hypertension, and some other outcomes initially considered. Appendix 5A (available on the HEI website) lists the main rationales for exclusion of health outcomes initially considered in the traffic review.

The Panel acknowledged the limitations in the selection of health outcomes and prioritization, in particularly the omission of neurological outcomes, which have recently received a likely to be causal determination in the U.S. EPA's Integrated Science Assessment on general particulate matter with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) (U.S. EPA 2019). Therefore, literature reviews were developed for neurodevelopmental outcomes in children as well as Parkinson disease and dementia-related outcomes in adults.

The selected health outcomes were measured in various ways across studies. Hence, the *International Classification of Diseases, Tenth Revision* (ICD-10) codes listed in Table 5.1 served only as a guide, because some studies used equivalent definitions using *International Classification of Diseases, Ninth Revision* (ICD-9) or other versions or subsets or definitions based on their own assessments and other data. The Panel did not pose restrictions regarding the source of outcome data (e.g., official registry, hospital data, controlled examinations, and questionnaires) except for COPD morbidity, where the Panel excluded questionnaire-based definitions. For all morbidity outcomes, both incidence and prevalence studies were included, where available (see Sections 5.3.2 and 5.3.3). Details related to the selection of studies for meta-analysis are described in Section 5.10.2.

5.3.1 BIRTH OUTCOMES

The Panel considered low birth weight (LBW) (<2,500 g) as a dichotomous measure and birth weight (BW) as a continuous measure. The latter is not a clinical outcome, but the Panel included it for completeness. Studies investigating other cutoff points for LBW were excluded: for example, studies investigating birth weights only between 2,500 and 3,000 g (e.g., Slama et al. 2007). The Panel distinguished between (L) BW restricted to term births (births at ≥37 weeks gestation) versus all births.

Small for gestational age (SGA) was included as a dichotomous outcome. SGA is most commonly defined as a weight below the tenth percentile for the gestational age. The Panel also allowed the use of birth weight-for-gestational age *z*-scores. Other measures of fetal growth, such as intrauterine growth restriction and the proportion of optimal birth weight and head circumference, were beyond the scope of the review.

For preterm birth (PTB), the Panel included all relevant studies on PTB, irrespective of whether they grouped all PTB according to the standard definition of <37 weeks gestational age at birth or specified subcategories such as moderately or very PTB.

5.3.2 RESPIRATORY OUTCOMES

For respiratory outcomes, the Panel selected asthma and asthma-related symptoms (wheeze), chronic obstructive pulmonary diseases (COPD), and acute lower respiratory infections (ALRI). Respiratory outcomes were separately assessed for children (<18 years) and adults (18+ years).

5.3.2.1 Asthma

Asthma is a complex and poorly defined syndrome characterized by several phenotypes as a result of different etiologies, especially in children (Martinez et al. 1995). There are recent suggestions to use the term *asthma* solely as a descriptive label for a collection of symptoms, with no assumptions about the pathophysiology (Pavord et al. 2018). In fact, the previously widespread belief that asthma is an allergic/atopic disease caused by allergen exposure has been questioned (Pearce et al. 1999) and it is clear now that nonatopic asthma is much more important than has been recognized until recently (Pavord et al. 2018). Because childhood asthma and adult asthma might be distinct phenotypes with different etiological patterns, the Panel distinguished between children and adult studies.

The Panel considered evidence of the impacts of TRAP on incidence of asthma, prevalence of asthma, and exacerbation of the disease among individuals with pre-existing asthma. Prevalence was further divided into asthma ever and active asthma. Most previous studies have used self-administered questionnaires to define asthma and asthma-like symptoms, with parents responding for their children (Kemp et al. 1996). Incidence of asthma is the first appearance of the disease during the life course (asthma onset). Asthma incidence has been mainly defined by a positive response to a questionnaire about a medical diagnosis of the disease (physician diagnosis of asthma) or an algorithm based on medication and health services used for that condition. Prevalence of asthma ever (or lifetime asthma) (mainly based on questionnaire responses but also on medical records or drug prescriptions) indicates the proportion of people who have had a diagnosis of the disease during their lifetime. Finally, active (or current) asthma refers to a prevalence measure based on questionnaires (based on either asthma diagnosis in the last 12 months or asthma symptoms in the last 12 months when an asthma diagnosis was given in the past). Active asthma is also based on the use of medical services (emergency room visits and hospital admissions).

Asthma exacerbations are common in children and adults with asthma and the main goal of asthma management is the prevention of exacerbations and airflow limitation. Asthma exacerbations can range from mild to severe with the most severe forms generally requiring an emergency room visit and likely hospitalization. Several studies have assessed the role of acute exposure to air pollutants on asthma exacerbations using a panel design, time-series, or case-cross over analyses (Weinmayr et al. 2010; Orellano et al. 2017) but few studies are available on the associations of long-term exposures to air pollutants on asthma exacerbations. These studies are usually cohort studies of patients with asthma based on emergency room visits and hospitalizations, but cross-sectional studies have also been employed with asthma control questions.

5.3.2.2 Wheeze

The categorization of asthma by means of different outcomes might be sufficient using a physician diagnosis of asthma but several studies have indicated that the medical diagnosis of the condition can overestimate or underestimate the real occurrence of the disease in the population. These difficulties are particularly present in children of young age. In preschool children, wheezing (the dominant symptom of asthma)—but also chest tightness, breathlessness, and coughing—may be related to viral infections rather than to a true asthmatic condition (*transient wheezing*, Martinez et al. 1995) and it may be too early for a medical diagnosis of asthma. On the other hand, a medical diagnosis is a function of the health care system (Kemp et al. 1996).

For those reasons, the Panel also included studies of wheeze. The Panel distinguished between studies assessing prevalence of active wheeze (wheezing or other asthma-like symptoms in the last 12 months) and those assessing prevalence of ever-wheeze (any episode of wheeze occurring during the lifetime). Because there are many different ways to assess the manifestations of wheeze, the Panel developed an order of preference for the assessment of wheeze when it was reported multiple ways in the same paper. If available, they extracted results for wheeze (without further specification). If not available, they extracted recurrent wheeze or persistent wheeze in that order. If no measure of wheeze was reported as an indication of asthma, the Panel extracted another asthma-related symptom in the following order of preference: shortness of breath, dyspnea, or night cough. If those were not available, use of asthma medication was extracted. Studies reporting only other respiratory symptoms such as phlegm or cough were excluded.

5.3.2.3 ALRI

The Panel accepted studies using both hospital-based and questionnaire-based definitions of ALRI. For children, the Panel considered respiratory infections such as bronchiolitis, pneumonia, bronchitis, and croup; while for adults, the Panel considered pneumonia as an acceptable measure of ALRI (e.g., Neupane et al. 2010). Preference was given to a composite definition of ALRI, if reported. In case separate estimates were given for pneumonia and bronchiolitis in children (e.g., Kennedy et al. 2018), bronchiolitis was extracted.

The Panel considered all ALRI studies as incidence studies given the acute nature and expected absence of the infection prior to diagnosis and/or between repeated infections in the same individual.

5.3.2.4 COPD

Population studies on COPD have used a variety of operational diagnostic criteria, usually based on lung function, respiratory symptoms, and/or controlled examination. More recently, the Global Initiative for Chronic Obstructive Lung Disease global strategy for diagnosis, management and prevention of COPD, referred to as the GOLD initiative, has provided guidelines that are useful also for epidemiological studies and involves the use of a lung function test (Pauwels et al. 2001). For this reason, the Panel restricted the review to studies with lung function tests for the COPD definition and thus excluded studies based only on respiratory questionnaires. A similar restriction was applied in an earlier review of COPD (Schikowski et al. 2014).

The Panel separately evaluated studies on incidence of COPD, prevalence of COPD, and exacerbations of COPD. For the exacerbations of COPD, the Panel searched studies evaluating long-term exposures associated with emergency room visits or hospitalizations among participants with COPD.

5.3.3 CARDIOMETABOLIC OUTCOMES

For cardiometabolic outcomes, the Panel selected ischemic heart disease (IHD), coronary and stroke events, and diabetes. For each of these outcomes, incidence and prevalence were investigated.

5.3.3.1 IHD, Coronary, and Stroke Events

For the diagnosis of IHD, the Panel included studies considering at least one diagnosis from ICD-9 410–414 or ICD-10 I20–I25, or procedural codes/diagnoses for revascularization. The outcome coronary events included fatal and nonfatal myocardial infarction and cardiac arrest. Stroke events included incidence or prevalence measures of different types of stroke including ischemic and hemorrhagic stroke. Note that if a study reported separately on fatal, nonfatal, or combined events, all that met the inclusion criteria were extracted.

Incidence studies of fatal events were included in the cardiovascular section when the study population was free of the disease at baseline and in the mortality section when participants included those with pre-existing cardiovascular disease.

5.3.3.2 Diabetes

Though the focus was on type 2 diabetes, the Panel selected studies with a broader definition of diabetes as well, such as studies that included type 1 diabetes in their definition, because type 1 diabetes is typically a small fraction of diabetes cases in adult studies (e.g., Andersen et al. 2012c). Gestational diabetes was excluded (e.g., Malmqvist et al. 2011; van den Hooven et al. 2009). Diabetes had to be doctor-diagnosed or based on controlled examinations, registry-based, or indicated by the use of antidiabetic medications, following an earlier review (Eze et al. 2015).

5.3.4 MORTALITY

The all-cause and cause-specific mortality outcomes selected were similar to those used in the 2015 Global Burden of Disease study of ambient air pollution (Cohen et al. 2017). The included causes of death were the broad categories of circulatory and respiratory disease and the more specific causes of IHD, stroke, COPD, ALRI, and lung cancer. The Panel accepted different definitions of circulatory and respiratory disease. The Panel did not include diabetes mortality, which was in the initial search and included in the most recent version of the Global Burden of Disease study (Abrams et al. 2020), because the Panel preferred the inclusion of diabetes morbidity given the significant underreporting of diabetes mortality as the primary cause of death on death certificates (Pinault et al. 2018).

For all-cause mortality, the preference was given to nonaccidental (natural) mortality, and all-cause mortality was only used if nonaccidental mortality was not available. Natural-cause mortality or nonaccidental mortality is mortality from all causes except external causes such as accidents, suicide, and homicide. We considered natural-cause mortality equivalent to all-cause mortality as natural-cause mortality accounts for the majority of all-cause mortality and there is no clear evidence that air pollution is associated with accidental mortality (Chen and Hoek 2020).

In the few studies that reported on cardiorespiratory mortality without separately reporting circulatory and respiratory mortality, the Panel considered this as a measure of circulatory mortality because circulatory mortality dominates the combined category (e.g., Kloog et al. 2013).

5.4 DEVELOPMENT OF PECOS QUESTION AND ELIGIBILITY CRITERIA

As is customary in systematic reviews, a PECOS framework was used to develop the review question (Higgins et al. 2020). The following PECOS question was developed in relation to exposure to TRAP:

> In the general population, including subgroups of adults and children, what is the increase in risk of health effect *X* for a change in long-term exposure to traffic-related air pollution, observed in studies relevant for the health outcome and exposure duration of interest?

Table 5.2 presents inclusion and exclusion criteria for each PECOS domain in relation to the selected health effects of long-term exposure to TRAP. The focus of the review was on the general population, and studies in selected representative

Table 5.2. Inclusion and Exclusion Criteria for Each PECOS Domain in Relation to the Selected Health Effects of Long-Term Exposure to TRAP

PECOS	Inclusion	Exclusion
Population	General human population, of all ages, developed and developing areas, both urban and rural; no geographical restrictions Asthma and chronic obstructive pulmonary disease patients for assessing disease exacerbation Selected patient populations, specifically with ischemic heart disease, stroke, diabetes, heart failure, and hypertension, but only for all-cause and cause-specific mortality	Populations exposed in occupational settings or exclusively indoors
Exposure	Long-term exposure (months to years) to TRAP; indirect measures of TRAP, such as distance to or traffic density at nearest road Include studies regardless of whether they adjust for copollutant exposures See the section on the exposure framework for additional inclusion criteria	Short-term exposure studies (minutes to months)
Comparator	Exposure to lower levels of TRAP in the same or in a referent population	

Continues next page

Table 5.2 (*Continued*). Inclusion and Exclusion Criteria for Each PECOS Domain in Relation to the Selected Health Effects of Long-Term Exposure to TRAP

PECOS	Inclusion	Exclusion
Outcome	See Table 5.1 for the selected health outcomes	
Study	Human studies include cohort studies, case–cohort, case–control, cross-sectional studies, and intervention studies Only human studies that are published (or accepted for publication (i.e., in press) between January 1980 and July 2019, in peer-reviewed journal articles and written in English Studies that report a quantitative measure of association and a measure of precision	Qualitative studies, studies reporting only unadjusted results, and clear evidence of an analytical error Studies without individual level data (i.e., fully ecological outcome, exposure, and covariates data) Studies where no original data were analysed, reviews, or methodological papers Genome-wide association study (GWAS) and all other *-omics* studies Nonhuman studies (in vivo, in vitro, other) and controlled exposure (chamber) studies Grey literature, conference abstracts, conference papers, notes, editorials, letters, and unpublished data

population subgroups (e.g., California Teachers study and the Nurses' Health study) were considered to be population-based for the purposes of this review. Only studies in very selective subgroups, such as the CATHGEN study investigating participants who received a cardiac catheterization (Ward-Caviness et al. 2018), were excluded from the review. Cohort, case-control, cross-sectional, and intervention studies using individual-level health outcome data.

For all-cause and cause-specific mortality, as well as for exacerbation of asthma and COPD, the Panel additionally evaluated whether associations between TRAP and these outcomes are more pronounced for specific subgroups (patients) than in the general population (Table 5.2). It was unfeasible to evaluate patient populations for all selected outcomes.

5.5 EXPOSURE FRAMEWORK

To guide selection and evaluation of epidemiological studies on TRAP, the Panel developed a new framework for assessing the potential of different exposure assessment approaches used in epidemiological studies to be indicative of exposure to TRAP, including both in the near-roadway and neighborhood environments. The acceptance criteria in the exposure framework were designed to identify studies with a clear traffic signal in the exposure contrast. The framework builds on the 2010 HEI Traffic Review.

The Panel followed the 2010 HEI Traffic Review in recognizing that a major challenge for epidemiological research is that no commonly measured or modeled pollutant is specific to traffic sources. Other (combustion) sources also contribute to commonly used indicators of TRAP, such as nitrogen dioxide (NO_2), elemental carbon (EC), and ultrafine particles (UFPs). The Panel developed three strategies to determine whether a study was sufficiently traffic-specific, namely the selection of traffic-related pollutants, the exposure assessment method, and its spatial resolution. The Panel decided to be inclusive in the selection of the studies. The Panel acknowledged that a quantitative determination of the contribution of traffic emissions to the exposure contrast in individual studies is not possible. The Panel also developed a traffic specificity indicator (high or moderate) based on stricter criteria for the three elements of the general framework. Chapter 6 describes the different exposure assessment approaches to TRAP and lays out the exposure framework and additional criteria considerations in detail.

5.6 LITERATURE SEARCH STRATEGY

The PubMed electronic database was searched comprehensively for studies matching the PECOS question from January 1, 1980, through July 31, 2019. The search strategy was developed by the contractor team, borrowing from other reviews as much as possible (see Appendix 5B for the search strategy).

Initial literature searches with some test outcomes including diabetes and birth outcomes revealed that the addition of a second electronic database, Web of Science, added very few relevant papers to the PubMed search but added a large number of records to screen (about two- to seven-fold of the number of records in PubMed). For example, the test-search

for diabetes in December 2018 yielded 443 studies in PubMed and 3,468 studies in Web of Science. Thereof, 58 studies from the PubMed search were included and 40 of those needed further exposure screening. Web of Science added no definitely included studies and four studies for further exposure screening. Thus, the Panel decided to restrict the search to PubMed. In addition to PubMed, the LUDOK database was checked for potentially relevant studies. The LUDOK database (*https://www.swisstph.ch/de/projects/ludok/*) is developed and maintained by the contractor team and provides a rich compilation of air pollution and health studies since 1985. LUDOK stems from monthly searches in PubMed and hand searches in selected relevant journals not listed in PubMed (for article titles such as Atmospheric Environment and Air Quality and Atmosphere & Health). In addition, references found in reviews identified by the search were scanned for possible inclusion. To further ensure that relevant published studies not captured through the search were included in the review, the Panel checked with the individual bibliographic databases curated by HEI and Panel members. The Panel also checked against the selected studies included in the 2010 HEI Traffic Review. The list of reviews searched is included in Chapter 7.

5.7 DATA MANAGEMENT AND SELECTION PROCESS

DistillerSR, a web-based, systematic review software program by Evidence Partners was used to ensure standardization of the process. All references were screened using structured forms developed in DistillerSR. For each included study, relevant data were extracted using another structured form, which was also built in DistillerSR. Data from Distiller were exported to Excel spreadsheets for data synthesis and preparation of summary tables. Summary tables were written using a custom script in R 3.5.1.

Two reviewers from the contractor team independently screened titles and abstracts of the search results to determine whether each identified reference met the inclusion criteria. Disagreements between screeners were resolved through discussion involving HEI staff and Panel members, as necessary.

After completion of the title and abstract screening, full-text articles and supplements were retrieved for those studies that either clearly met the inclusion criteria or for which it was not possible to make a clear assessment from the bibliographic information and abstract alone. For those studies, full-text review for relevant health outcomes and exposure assessment was independently conducted by two reviewers from the contractor team and HEI staff. Disagreements were resolved by discussion involving HEI staff and Panel members. The reason for exclusion at the full-text review stage was annotated. A second level of full-text screening was conducted on studies that remained in the review to confirm that effect estimates were reported for outcomes of interest and to check in detail that the exposure framework criteria were met. To obtain information about the exposure assessment, the Panel also used information reported in the cited exposure papers, if needed. All exclusions at the full-text stage were checked by HEI staff.

5.8 DATA EXTRACTION

First, minimal data extraction was performed by one reviewer from the contractor team, including extracting key information for meta-analysis such as study name, outcome, pollutants, effect estimates, increments, and 95% confidence intervals. Second, full data extraction was conducted by another person from the contractor team or HEI staff, which entailed evaluating the data extracted in the minimal data extraction phase and adding relevant additional information, such as details on the study population, study design, and analysis. Further, among the selected studies those that evaluated the shape of the exposure–response function were identified. To ensure comparability of data extracted by different members of the team, a data extraction manual was developed. Moreover, the contractor team conducted full double entry for 70 studies to ensure high quality. We reported the results of a reliability study of duplicate data on a subset of studies in Additional Materials, Section 5.1 (available on the HEI website), demonstrating high quality of the data extracted.

In case multiple effect estimates were reported with different sets of confounders, the Panel extracted the effect estimates from the main model (defined as the one in the abstract and otherwise preferred by the authors) except when the inclusion criteria for the review were only met for models other than the main analyses. An example of the latter is a nationwide study (e.g., Crouse et al. 2015) that we only accepted if appropriate adjustment for region of the country was made for the pollutants (see Chapter 6). Another example was the PIAMA study where the Panel extracted estimates from a sensitivity analysis of participants living in the western and middle parts of the Netherlands (Brauer et al. 2002) or from a sensitivity analysis corrected for region (e.g., Gehring et al. 2010). Moreover, adjusted models without potential mediators, such as pre-existing comorbidities, were preferred. In most cases, the main model was also the most adjusted model.

Effect estimates from single-pollutant models were selected as the effect estimates for the meta-analysis. Additionally, effect estimates were extracted from selected multipollutant models (general $PM_{2.5}$ and ozone) or adjusted for traffic noise, where available.

When results were reported for multiple exposure timings or durations, the preferred exposure window was that most representative of long-term exposure. This general rule meant that only one exposure window estimate per study was extracted, which was in most cases a cumulative or annual average. However, this general rule was not applied to birth

outcomes and respiratory outcomes in children because of the importance of prenatal and early life exposures. For birth outcomes, both total pregnancy and trimester-specific estimates in the studies were extracted. No monthly specific estimates were extracted. For respiratory outcomes in children, up to three exposure windows were extracted, if available: a full pregnancy estimate (thus, not trimester-specific), an estimate of the first year of life, and a cumulative childhood exposure estimate.

Limited attempts were made to contact authors of included studies to obtain missing data considered important for evaluating key study findings (e.g., data required to conduct a meta-analysis). Specifically, the Panel contacted the authors from the DDCH study in Denmark to clarify whether log-transformation was applied in the modeling, and it was confirmed this was not the case for multiple studies (Andersen et al. 2012a, 2012b, 2012c). Also the Panel approached the authors from a Canadian study to obtain missing increments (Poirier et al. 2015) and from a Swedish study to obtain a missing confidence interval for coronary events and NO_2 (Rosenlund et al. 2006).

5.9 RISK OF BIAS ASSESSMENT

A critical step in the systematic review process was the assessment of the risk of bias of included studies. Risk of bias is the potential for the results of an individual study to be biased and does not inform on actual bias existing in a particular study. Neither does a score of moderate or high risk of bias inform about the size of a potential bias (e.g., while risk of bias can be high due to a methodological problem, actual bias might be very small and vice versa). Although various risk of bias tools exist, there is currently no consensus about the best approach for assessing risk of bias in observational study designs (Bero et al. 2018; Savitz et al. 2019).

The Panel decided to use the risk of bias tool and guidance used in the WHO AQG review because the tool was designed for assessment of risk of bias in observational air pollution epidemiology studies (WHO 2020). In brief, the risk of bias tool guides assessment of each study across six domains: (1) confounding, (2) selection bias, (3) exposure assessment, (4) outcome measurement, (5) missing data, and (6) selective reporting. Most domains have subdomains. Each subdomain and an overall rating per domain were derived using three categories (low, moderate, or high). No summary classification was derived across the domains (WHO 2020). A rationale for each judgement is provided in Additional Materials to the report.

For each domain and subdomain the WHO provided guidance for making a judgment about whether the study presents low, moderate, or high risk of bias. To come to an overall judgment for a domain the WHO formulated the following rules: if any of the subdomains had a rating of high risk of bias, the whole domain was rated as high risk of bias; if all the subdomains had a rating of low risk of bias, the whole domain was rated as low risk of bias; when at least one subdomain had a rating of moderate risk of bias and none of the other subdomains were at high risk of bias, the whole domain was rated as moderate risk of bias (WHO 2020).

The tool was modified based upon Panel members' expert judgement and experience in applying the tool in the systematic reviews of the WHO AQG (Chen and Hoek 2020; Huangfu and Atkinson 2020). The final risk of bias tool used by the Panel can be found in Additional Materials, Section 5.2. It includes a summary of guidance to aid interpretation. Specifically,

- The large WHO list of confounders (10 in total in the original tool) was condensed. Confounding is not always easy to recognize, and it differs widely between study populations and settings. Typically, risk factors of health outcomes may be generalizable, but the relationship between exposure and the potential confounder differs across populations. Directed acyclic graphs (DAGs) may help identify the potential of confounding and the causal relations among variables. To this end, the Panel developed a DAG for mortality, containing all 10 confounders used in the WHO AQG reviews (Figure 5.1). Evaluation of the DAGs revealed two possible minimal adjustment sets, which were then applied in further considerations. In the DAG, lifestyle was used as a combined measure of diet, physical activity, and body mass index (BMI). The identified potential important confounders were age, sex, individual-level or neighborhood socioeconomic status (SES), BMI, and smoking. BMI was not included for respiratory mortality and morbidity outcomes, similar to the WHO AQG guidance. Also, sex was not considered a potential important confounder for birth outcomes. The condensed critical list is flexible to include multiple ways of accounting for the potential important confounders through study design or adjustment of statistical models. For example, individual or neighborhood SES contained variables related to education, employment, income, or ethnicity measures; BMI included measures of weight or waist or hip circumference, physical activity, nutrition index, or related measure. Likewise, the correction for smoking included maternal smoking during pregnancy in birth outcome studies or environmental tobacco smoke in home for children's respiratory studies, for example. The Panel chose not to include *year of enrollment* as a potential important confounder because it is only a confounder for very specific settings (e.g., when there are actually multiple years of entry in the cohort, which is often not the case), and it depends on how exposure is modeled (static or dynamic).

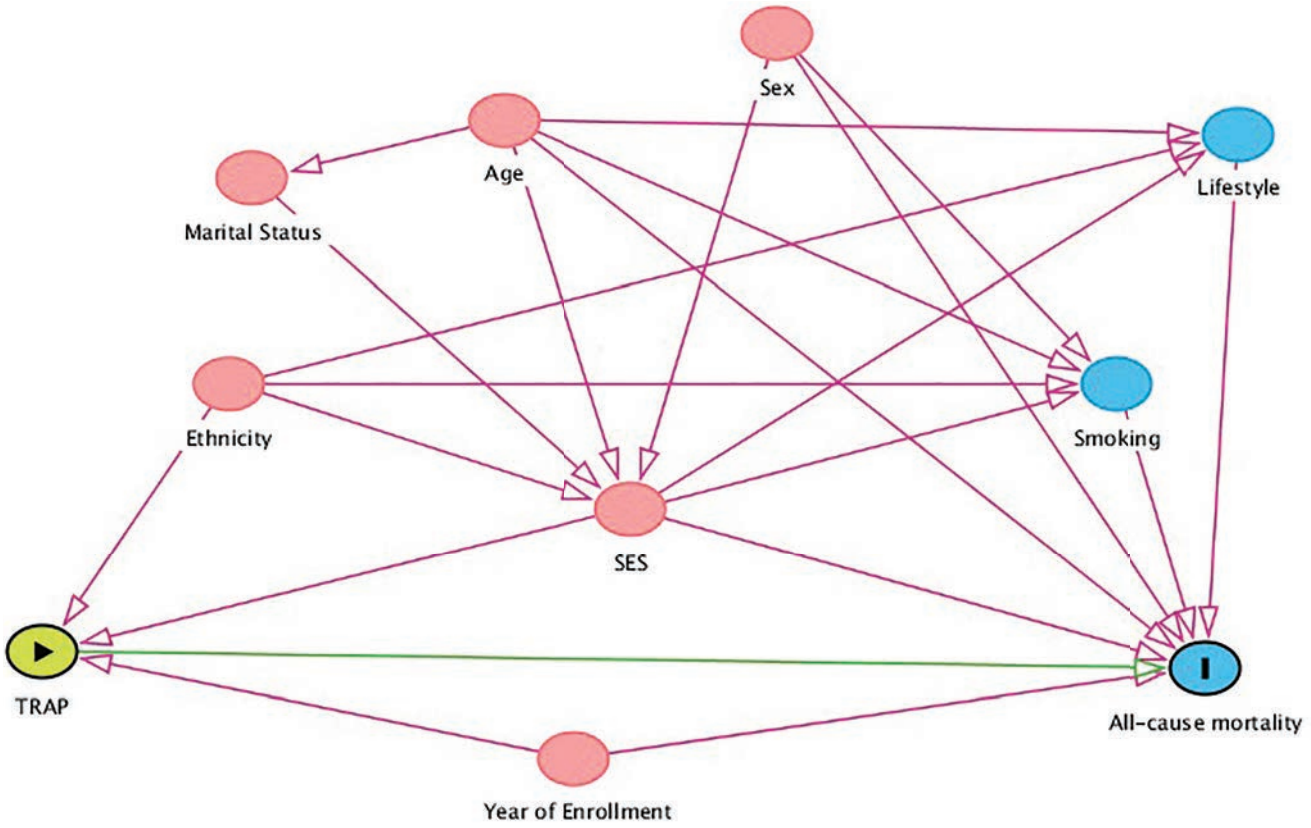

Figure 5.1. DAG for TRAP and all-cause mortality using the list of potential confounders as identified in the risk of bias tool and guidance used in the WHO AQG review. The application of DAG rules yielded two minimal sufficient adjustment sets: (1) age, sex, lifestyle, SES, smoking, and year of enrollment or (2) ethnicity, SES, and year of enrollment. Lifestyle includes diet, physical activity, and BMI.

- The Panel disregarded the risk of bias item on exposure contrast (e.g., low risk of bias if exposure contrast was large compared with the precision of exposure assessment (i.e., between-persons variance larger than within-person variance). The Panel argued that a small exposure contrast results primarily in a large confidence interval and those studies received a low weight in the meta-analysis. In addition, the question was difficult to answer as within-person variance of the exposure is almost never reported, and has led to a classification of low risk of bias in almost all long-term studies in the WHO AQG reviews (Chen and Hoek 2020; Huangfu and Atkinson 2020).
- The Panel modified the missing data items and some other items for clarity and provided additional guidance to distinguish between aspects more explicitly in the different domains. Specifically, in the item selection bias, the Panel considered potential bias that may happen when selecting participants into the study. In the item missing outcome data, bias due to loss-to-follow-up (attrition bias) was considered.

The risk of bias assessment was conducted for each exposure–outcome pair. Thus, should an individual study report on two relevant effect estimates, the risk of bias was evaluated twice. The Panel reported the risk of bias per study but indicated if it differs within a study. One member of the Panel or HEI staff assessed the risk of bias in each study. The assessments were checked by HEI staff and other Panel members for completeness, accuracy, and consistency. Disagreements were resolved through discussions with additional members of the Panel and HEI staff. In addition, detailed quality checks were conducted by HEI staff to ensure comparability and subsequently discussed by the Panel.

Sensitivity meta-analyses were performed per risk of bias domain across studies, grouping studies at high risk of bias versus studies at moderate and low risk of bias for that domain, provided there were a sufficient number of studies. Similar to the WHO systematic reviews, the risk of bias assessment was only conducted for exposure–outcome associations that were included in meta–analyses. In addition, the risk of bias assessments informed the overall confidence assessment of the epidemiological evidence.

5.10 DATA SYNTHESIS

To synthesize the evidence and provide a quantitative summary, a meta-analysis was performed where three or more studies were identified for the same exposure and health outcome, similar to Chen and Hoek (2020). The Panel noted that any number of required studies for meta-analysis is arbitrary and the Panel had more confidence in a meta-analysis with a larger number of studies compared with a meta-analysis with only three studies. Results were quantitatively combined using random-effects models (DerSimonian and Laird 1986; Veroniki et al. 2016). The restricted maximum likelihood method was used to estimate the between-study variance. In a few cases (with only three studies) the method did not converge, and the between-study variance was estimated by an empirical Bayes approach instead. Random-effects models were chosen a priori because of the expected differences in populations and pollution mixtures. The Panel reported the summary estimate, which is the mean effect size across the study populations, and the 95% confidence interval, which is a measure of how precisely the average is estimated.

Statistical heterogeneity was assessed using various measures, such as Cochran's Q (chi-square, χ^2), I^2, and τ^2 (tau-squared). Tau-squared was presented in the form of a 95% prediction interval around the mean effect of the random-effects meta-analysis (Borenstein et al. 2017). There are well known limitations of statistical tests for heterogeneity, and they are less reliable when there are only a few studies. Given these limitations, the Panel decided to primarily interpret I^2—where I^2 values of <50% were interpreted as low, between 50 and 75 as moderate, and >75 as high degree of heterogeneity (Woodward 2013). Note that thresholds for the interpretation of I^2 can be misleading, since its value also depends on the magnitude, direction, and precision of the effect estimates from the individual studies (Rücker et al. 2008). The Panel used the statistical program R (version 3.6.0), and the libraries *metafor* (v.2.4-0), *meta*, (v. 4.16-2), *forestplot* (v.1.10.1), and *ggplot* (v. 3.3.3) for the analyses and plots.

Hazard ratios, risk ratios, rate ratios, and odds ratios were included in the same meta-analyses on the assumption that when relative risk estimates are close to the null, all those measures approximate the risk ratio (Davies et al. 1998). This approach has been used previously (e.g., Anderson et al. 2013; Khreis et al. 2017). We use relative risk in the review as a nonspecific term to indicate any of the ratio measures, although we report the exact measures used in the summary tables.

The Panel has provided forest plots with meta-analysis estimates, where appropriate. The forest plots are accompanied by summary tables with additional information on the studies. The summary tables included all studies, thus not only the studies that were included in the meta-analyses. The plots include the point estimate and the 95% confidence interval as well as study descriptors of the individual studies. In addition, summary plots were also developed for each outcome, displaying all meta-analyses estimates with the respective 95% confidence intervals and the number of studies included in the meta-analyses.

5.10.1 STANDARDIZATION OF EFFECT ESTIMATES

The Panel conducted separate meta-analyses for each pollutant included in the review (standardization of pollutant). The Panel converted a variety of indicators, such as black carbon (BC), black smoke (BS), and PM absorption (soot), into EC-equivalent estimates (Cyrys et al. 2003; Janssen et al. 2013). The Panel acknowledged that the conversion of these metrics results in additional uncertainty, which may not be adequately reflected in the meta-analytic summary estimates.

Effect estimates for pollutants expressed as ppb or ppm were converted to μg/m³, or mg/m³ (CO) using standard WHO scaling factors (standardization of units). For example, 1 ppb NO_2 = 1.88 μg/m³, assuming an ambient pressure of 1 atmosphere and a temperature of 25°C (Department for Environment, Food and Rural Affairs 2005).

In addition, effect estimates were expressed using a standardized increment in exposure and assuming a linear exposure–response function (standardization of pollutant-specific increments). The Panel decided to use the pollutant concentration increments from the ESCAPE study to reflect a realistic range of exposure contrasts in most studies (Beelen et al. 2014, 2015). The following increments were used: 10 μg/m³ for NO_2, 1 μg/m³ for EC, and 5 μg/m³ for $PM_{2.5}$. See Appendix 5C for the conversions that have been applied and for the increments for all pollutants. Caution is warranted when comparing effect estimates across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrasts in exposure for all pollutants. The increments used are in the same range as other reviews (e.g., Chen and Hoek 2020; Huangfu and Atkinson 2020; Khreis et al. 2017).

For PM, the Panel made a distinction between studies of total ambient PM (mass) and studies of ambient PM attributed to traffic sources (referred to as *traffic PM* for short). An important reason for this decision was that the relevant increments for total PM and traffic PM are not comparable, thus hampering the meta-analyses. Moreover, no meta-analysis was conducted for traffic PM studies due to the methodological differences in exposure assessment. For the same reason, the Panel excluded the few personal exposure studies considering time–activity patterns from the meta-analyses (Hasunuma et al. 2016; Mölter et al. 2014). All results are kept in the summary tables and are part of the narrative description and evaluation.

In addition, the Panel did not pursue meta-analyses of indirect traffic measures, such as distance to major roadways and traffic density, because the varying definitions across the

studies precluded such analyses. The results for the indirect traffic measure studies were presented in forest plots for descriptive purposes.

5.10.2 INCLUSION AND EXCLUSION CRITERIA FOR META-ANALYSIS

Table 5.3 summarizes the main inclusion and exclusion criteria for meta-analyses. Only studies that have analyzed the pollutant exposure as a linear continuous term were used in meta-analyses. If a study reported two or more estimates for subgroups of the study population separately only (e.g., male and female, age groups, such as Naess et al. 2007), the Panel combined the estimates by a fixed-effect meta-analysis first before entering the random-effects model.

Regarding the inclusion of multiple estimates from the same study population and cohorts in a single meta-analysis, the Panel decided to be inclusive; thus, the default was that studies were included unless the same study population was used in several publications on the *same* exposure–outcome pair. Hence, a study was not automatically excluded from meta-analysis if the same cohort was also analyzed in a multicohort analysis (e.g., in ESCAPE unless the same population and exposure assessment was used in multiple studies). Likewise, studies that have used the same population, but using a different exposure assessment approach (e.g., land use regression estimates and monitoring) for the same pollutant were allowed in the same meta-analysis. The Panel acknowledged this may be an imperfect solution because the random-effects models assume independent estimates. At the same time, the correlation between different exposure assessments was often rather low and depends on many factors. In addition, in some cases, it was not obvious which exposure estimate would be *better* and more specific to traffic. In the specific chapters, the actual occurrence of this issue was discussed.

5.10.2.1 Birth Outcomes

Separate meta-analyses were conducted for term LBW (binary outcome), term BW (continuous outcome), SGA, and PTB. Separate meta-analyses were conducted for four-exposure windows (full pregnancy and trimester-specific). In case only trimester-specific results were reported, the Panel did not combine those results into one full pregnancy estimate.

All but one study in meta-analysis defined PTB as <37 weeks gestational age at birth. One study documented separate results for moderately preterm (30–37 weeks) and very preterm (<30 weeks) birth, but not *total* preterm (Gehring et al. 2014). In this case, the moderately preterm birth estimates were used in the meta-analysis because this estimate is more comparable to the PTB outcome in the other studies. Note that the vast majority of preterm births are in the moderate-to-late preterm range (32 to <37 weeks) (March of Dimes/WHO 2012).

For LBW and BW studies, the Panel decided to conduct meta-analyses only on studies that restricted data to term births (birth at ≥37 weeks gestation) to disentangle the associations of TRAP on gestational age from the associations on growth restriction.

Table 5.3. Inclusion and Exclusion Criteria for Meta-Analyses

Inclusion Criteria
General population studies, and studies in selected *representative* population subgroups (e.g., California Teachers study, Nurses' Health study)
Adjusted risk estimates from single-pollutant model result. If single-pollutant model results were not reported, multipollutant results were selected
Adjusted risk estimates from the full study population. If a study reported two or more estimates for subgroups of the study population separately only (e.g., male and female, age groups), the Panel combined the estimates by a fixed-effect meta-analysis first before entering the random-effects model
Ability to standardize the results (see text)
Studies were included unless the same study population and exposure assessment was used in several publications on the same exposure–outcome pair. When the same study population was used in several publications on the same exposure–outcome, selection was basis of the following order: • largest population sample size, number of events, or number of cases • most appropriate adjustment for confounders • most recent publication date
Exclusion Criteria
Exposure metric analyzed as log-transformed terms, categories, such as quartiles of exposures, high versus low
Indirect traffic measures (distance and traffic density measures) and personal exposure studies
Insufficient information available to standardize estimates and precision (e.g., not reported, pollutant increment not clear)

Because gestational age can be considered a potential confounder in (L)BW studies, but was not included in the reduced list of potential important confounders for the assessment of risk of bias, the Panel conducted an additional sensitivity analysis excluding term (L)BW studies that did not adjust for gestational age. Whether to correct (L)BW studies for gestational age is debatable; some would argue that gestational age should be viewed as a mediator and on the causal pathway between exposure and outcome (Delbaere et al. 2007). An additional sensitivity analysis comparing birth outcome results with and without a correction for BMI was conducted because of similar concerns—BMI may be mediator of the exposure–outcome association.

5.10.2.2 Respiratory Outcomes

For respiratory outcomes, studies in children (<18 years) and adults (≥18 years) were analyzed separately because of the distinct phenotypes with different etiological patterns. Because asthma is very difficult to diagnose at an early age, the Panel favored estimates in school-age children for the studies that report an estimate separately for preschool and school-age (e.g., Mölter et al. 2015; Sbihi et al. 2016). Likewise, for different publications on the same children at different ages, the older ages were favored (e.g., for PIAMA Gehring et al. 2011 was chosen, instead of Brauer et al. 2008).

For respiratory outcomes in children reporting different exposure windows estimates, the Panel developed an order of preference for the meta-analysis when it was reported in multiple ways in the same paper. If available, they chose results for pregnancy, or an estimate at birth, but if not, they selected for first year of life or cumulative average in that order. If no such measure was available, they chose an estimate of recent years. This order of preference was applied to all respiratory outcomes in children. Because of concerns combining studies where exposure is during pregnancy, early childhood, or cumulative, especially because the relevant exposure window may differ per respiratory outcome (e.g., for asthma incidence the early life exposure seems to be more important than for active asthma in children), the Panel conducted a sensitivity analysis reversing the order of preference. Also, incidence and prevalence studies were analyzed separately, where relevant.

5.10.2.3 Cardiometabolic Outcomes

Some studies reported only nonfatal events, some of them combined fatal and nonfatal events, and a few reported on fatal estimates only. For selection into the main meta-analysis, the Panel preferred combined nonfatal and fatal events, and where that was not available the Panel preferred nonfatal events over fatal events. For sensitivity analyses by fatality where sufficient studies existed, the Panel included all available estimates regardless of inclusion in the main analysis. Results for fatal, nonfatal, and combined events were all included in summary tables. Similar to respiratory outcomes, incidence and prevalence measures were analyzed separately.

5.10.2.4 Mortality

In the main meta-analysis the Panel did not include studies conducted in patient groups because the patient population is very different from the general population, and the main interest of the review is to evaluate the strength of the evidence in the general population. In sensitivity analysis, the Panel reviewed the meta-analysis results in the different selected patient populations.

5.10.3 HETEROGENEITY

The primary aim of the heterogeneity assessment is to inform the evaluation of consistency of a given exposure–outcome association across subgroups of studies or populations, which is one of the factors listed in the overall evaluation of the epidemiological evidence (Section 5.11). An exhaustive exploration of all sources of heterogeneity is beyond the scope of the review. The Panel identified a priori subgroups of interest for potential sensitivity analyses, provided there were sufficient studies:

- general population versus selected patient subgroups (only for mortality outcomes)
- time period (e.g., studies from 2008 [cutoff date of 2010 HEI Traffic Review] or earlier vs. newer studies)
- geographical region (e.g., North America vs. Europe vs. Asia)
- high risk of bias versus lower risk of bias per domain of the risk of bias tool
- confounder adjustment for individual-level behavioral factors (i.e., smoking)
- high versus moderate traffic specificity
- study design

Note that the stratification by confounder adjustment for individual-level behavioral factors (i.e., smoking) is typically the same as the stratification by traditional cohorts versus cohorts based on administrative data.

5.10.4 PUBLICATION BIAS

Publication bias, and other small-study biases, may be detected using graphical and statistical techniques. The funnel plot (Light and Pillemer 1986) is a simple graphical technique in which study estimates are plotted against their standard errors. Visual asymmetry in the funnel plot suggests omission of small studies from the included literature. Asymmetry can also be assessed using a simple statistical

test based upon the intercept from a regression of standard normal deviates against precision (Egger et al. 1997). However, the performance of this test under certain conditions has been questioned and application of the test is recommended only when there are 10 or more studies available for meta-analysis (Sterne et al. 2011). The Panel therefore included this limitation into our protocol and investigated publication bias only when sufficient studies were available. Furthermore, as heterogeneity in study estimates may also contribute to funnel plot asymmetry (Lau et al. 2006), the Panel therefore exercised caution when interpreting analyses of publication bias.

When evidence from the funnel plot and Egger's test suggested the presence of publication bias, the trim-and-fill procedure was applied to assess the potential impact of these biases (Duval and Tweedie 2000). The trim-and-fill procedure first *identifies* studies causing asymmetry, removes these studies from the meta-analysis, recalculates (using a fixed- or random-effects model) a new summary estimate, and then replaces the omitted results together with their *mirror image* results, creating symmetry in the funnel plot. A revised summary estimate can then be calculated based upon observed and imputed studies free from asymmetry. However, there is no guarantee that the filled summary estimates would reflect the real situation in the absence of publication bias and does not account for reasons for funnel plot asymmetry other than publication bias, for example, due to heterogeneity (Peters et al. 2007). The Panel therefore applied the trim-and-fill technique as a sensitivity analysis only and interpreted the results with caution.

There are additional tools for detecting potential publication bias: tracking of conference abstracts that do not make it into publications within 3 to 4 years; examining the role of funding source; and evaluating early positive studies, especially when studies are small. The last approach was also explored in the traffic review. First, a sensitivity analysis was conducted for studies before versus after 2008. Second, the Panel prepared plots of the number of participants versus publication year, colored by statistical significance of results for all estimates and for only those included in meta-analysis.

5.11 OVERALL ASSESSMENT OF THE EPIDEMIOLOGICAL EVIDENCE

The Panel assessed the level of confidence in the evidence that TRAP is associated with the selected health outcomes. This assessment was based on rating the confidence for a given health outcome by considering the strengths and weaknesses in a collection of human studies that constitute the body of evidence. For this purpose, the Panel decided to follow the methods proposed by the OHAT (OHAT 2019). OHAT serves as an environmental health resource to the public and to health research and regulatory agencies in the United States. It conducts technical assessments focused on understanding the potential for adverse effects on human health by agents, substances, mixtures, or exposure circumstances. These evaluations can lead to National Toxicology Program opinions on whether these substances may be of concern given what is known about current human exposure levels.

The OHAT method is based on the methods of GRADE, which has been adopted by Cochrane and many other organizations (Schünemann et al. 2013). In short, using the OHAT methods, available studies on a particular health outcome are initially grouped by key study design features and then each grouping of studies is given an initial confidence rating by those features. This initial confidence rating for the body of evidence from this group of studies is then downgraded for factors that decrease confidence in the body of evidence (risk of bias, unexplained inconsistency, indirectness, imprecision, and publication bias) and upgraded for factors that increase confidence in the body of evidence (large magnitude of effect, exposure–response, consistency, and consideration of residual confounding or other factors that increase the confidence in the body of evidence). Note that OHAT has extended the GRADE approach to include observational human studies in addition to randomized controlled trials. Moreover, OHAT applies the methods separately for animal and human data, which is relevant for the focus of this review on epidemiological studies. Finally, OHAT added an additional upgrading factor, consistency, which was not included in GRADE (Rooney et al. 2014).

The Panel recognized however that the scientific judgments involved in developing these ratings are inherently subjective. A key advantage of the evaluation approach is that it provided a methods to systematically document and explain the decisions made and thus transparency into the scientific basis of judgments made in reaching conclusions. On the other hand, despite the ongoing attempts to apply the GRADE approach to environmental health (Morgan et al. 2019), the application of those methods, in particular the risk of bias tools, has been heavily criticized (Bero et al. 2018; Savitz et al. 2019; Steenland et al. 2020). If not carefully applied, the use of those tools and methods can become a mechanical exercise that may lead to erroneous conclusions, because the assessments may sometimes consider individual studies out of context and do not take a broader approach of the evidence.

The Panel noted several challenges in applying the OHAT methods in its original form in the current review. A major issue is the initial level of confidence assigned to observational studies. Typically, GRADE and OHAT consider randomized controlled trials as the gold standard for judging observational

studies in environmental epidemiology and therefore epidemiological studies have a lower initial confidence. This approach originates from clinical medicine to evaluate treatments and objectively distinguish effective from ineffective ones and places a high priority on avoiding false positive conclusions (e.g., recommending treatments that do not work). This leads to a hierarchy of types of evidence that puts randomized controlled trials at the top. In environmental epidemiology the evidence rarely comes from randomized controlled trials and, rather than avoiding false positives, the greater concern is avoiding false negatives (e.g., failing to detect a specified hazard). Each study design is a proxy of some inherent strengths and weaknesses. Thus, when applying GRADE and OHAT methods, studies may be *penalized* twice for the same issue, such as a lack of randomization of exposure and possibility of residual confounding.

Therefore, the Panel used the OHAT method as a guide and did not apply the methods in a mechanistic way. Some features of the OHAT methods remain controversial. For example, some heterogeneity is expected across studies due to the nature of observational studies in different populations, contexts, and exposure conditions, and does not necessarily reduce confidence in the body of evidence based on inconsistency. Hence, the Panel have slightly modified the OHAT approach to better fit the needs of the Panel.

5.11.1 ADAPTATION OF THE OHAT METHOD FOR THE TRAFFIC REVIEW

OHAT automatically translates confidence ratings in the body of evidence into level of evidence for health effects where it considers the nature of the association (health effects or no health effect). The Panel was convinced that this automatic translation was not appropriate as it transferred the confidence in the body of evidence (mainly the results of the evaluation of the quality of the studies) into an evaluation of the level of the evidence, without considerations of additional relevant factors, such as strength and nature of the association and the consistency of the results from the meta-analyses and the studies not meta-analyzed. Thus, also given the charge of the Panel, the Panel focused on a statement about the confidence in the body of evidence as high, moderate, low, and very low. The Panel noted that convincingly demonstrating no health effect is generally beyond what epidemiological studies can achieve.

Another important choice was whether the downgrading and upgrading of the confidence based on the factors listed above are independent (i.e., an upgrade can occur if the confidence has been downgraded for other factors). The Panel made the choice to evaluate independently the downgrading and upgrading factors without imposing a constraint, following the procedures applied in the WHO systematic reviews of air pollution and traffic noise (Chen and Hoek 2020; Huangfu and Atkinson 2020; WHO 2018).

Because TRAP is a complex mixture, the Panel decided to evaluate the body of evidence separately for each exposure metric included in the review, and then evaluate the body of evidence for the health effects across all included traffic-related air pollutants and indirect traffic measures. Thus, confidence rating for each health endpoint was first developed separately for each exposure metric. Then, the confidence in the body of evidence was considered for the combined TRAP exposure. Conclusions for the combined confidence were primarily based on the evidence with the highest confidence of a pollutant. However, such a conclusion was upgraded or downgraded, if needed, based on the confidence rating of the other pollutants, information from large and informative studies not entering a meta-analysis, as well as considering the traffic specificity sensitivity analyses. For example, when effect estimates from studies with high traffic specificity versus other studies reported a larger magnitude of effect, the Panel considered upgrading the evidence.

The OHAT confidence rating is heavily geared toward the studies entering a meta-analysis. The Panel did not apply the confidence assessment for the exposure–outcome pairs if no meta-analysis was conducted due to few studies. The Panel also did not conduct meta-analysis of studies based on indirect traffic indicator variables, such as distance or traffic density variables, due to limited comparability across studies. The results from studies that did not enter a meta-analysis were mainly considered in the narrative assessment (see below). However, the modified OHAT assessment mentioned those studies, in particular when they were large and informative, to inform the overall evaluation across study designs and different pollutants, but only if an earlier step was completed, meaning that at least one meta-analysis was conducted for an outcome. In Additional Materials, Section 5.3, the OHAT methods and the main modifications are described in detail. In summary, the main modifications for the traffic review were as follows:

- All types of cohort studies were given an initial rating of moderate, not just the *prospective* cohorts.
- Case–control studies based on incidence data were also given an initial rating of moderate in addition to cohort studies.
- The decision to downgrade because of unexplained inconsistency was considered if heterogeneity was high (see Section 5.10) and applied after careful review of the potential sources of heterogeneity (see Section 5.10.3) and considering the direction of the effect estimate rather than its magnitude.
- In its assessment of imprecision, the Panel considered the number of the participants included in the meta-analysis and the width of the 95% confidence intervals

if the interval clearly included unity. The decision to downgrade because of imprecision was considered if the criterion for study power was met, but the effect estimate was imprecise with a wide 95% confidence interval and the confidence interval clearly included unity. For ratio measures (like relative risks), a wide (imprecise) confidence interval was defined as a difference on the log scale >0.1 from the upper to the lower 95% confidence limit (Rothman and Greenland 2018; Zhang et al. 2019).

- To upgrade for exposure response, at least two influential studies should have evaluated the actual form of the relationship (e.g., using splines or quantile analyses) and documented a monotonic exposure–response function. The Panel did not accept a statement of no deviation from linear if the linear association was null.
- The Panel considered upgrading for consistency across populations when there was clear evidence of an association across different populations, specifically in different geographical areas and between different time periods. In addition, the Panel upgraded the confidence when the results were based on different study designs supporting the same conclusions.
- The downgrading factor indirectness and the upgrading factor large magnitude of effect were not considered further.

5.11.2 NARRATIVE ASSESSMENT

Despite modifications, the Panel was convinced that the OHAT methods remain imperfect, and its application was challenging. The Panel thought the application of the OHAT methods was most useful to evaluate the quality of the body of evidence of studies entering a meta-analysis—irrespective of the strength and nature of the association. The Panel thought it was prudent to accompany the OHAT assessment with a broader approach to assess the level of confidence in the presence of an association, considering the meta-analyzed studies as well as other studies not entering the meta-analysis. Note that the goal of the overall evaluation is to establish the collective assessment of confidence in the presence of an association, not of the exact magnitude of the effect estimate. To this end, the Panel also took a broader approach and developed a narrative assessment for each heath outcome.

The narrative assessment included the following aspects: evaluation of the number, size, and location of the evidence base; study design, population, and representativeness; strength (magnitude) and nature (direction) of the association and quality of the studies (e.g., confounding, selection bias, exposure assessment, outcome assessment, missing data, and selective reporting); consistency of the findings (e.g., across locations, age groups, time periods, study designs, and different pollutants and indirect traffic measures, traffic specificity, and adjustment for noise for some outcomes); monotonic exposure–response function; and other considerations. The results of the meta-analyses, as well as the findings from studies not in the meta-analysis, were important for the evaluation, as a larger relative risk (with narrow confidence intervals) was more likely to indicate an association with TRAP than was a smaller and uncertain effect estimate. Associations that were replicated in several studies of the same design, across different populations or across several pollutants, or that used different epidemiological approaches or under different circumstances of exposure were more likely to represent a true association than isolated observations from small single studies. The presence of a monotonic exposure–response function was considered a strong indication of an association. In this way, the narrative assessment took into consideration all the available evidence from both the meta-analytic results and the results of single studies without a meta-analysis and assessed the level of evidence that TRAP is associated with the selected health outcome.

The narrative assessment of the level of confidence in the presence of an association between TRAP and a specific outcome was summarized as high (large number of studies, confounding, other biases, and chance can be reasonably excluded, and consistent associations across multiple populations and pollutants), moderate (moderate/large number of studies, confounding, other biases, and chance cannot be reasonably excluded, and moderate consistency of associations across populations and pollutants), low (small number of studies, confounding, other biases, and chance are likely, and inconsistency of associations across populations and pollutants), or very low (small number of studies, confounding, other biases, and chance very likely, and large inconsistencies of associations across populations and pollutants). These considerations were not applied automatically with set criteria for the issues considered.

Table 5.4 presents a comparison of main similarities and differences between the narrative assessment and the modified OHAT assessment.

5.11.3 OVERALL CONFIDENCE ASSESSMENT

Figure 5.2 gives a summary of the overall confidence assessment taken in the traffic review. The confidence assessment of the narrative and the modified OHAT assessment were combined in an overall evaluation between TRAP and the selected health outcomes. In case of agreement, that was simply high–high leads to high overall; if not in agreement the Panel have listed both (e.g., moderate to high) because the Panel considered both assessments complementary, reflecting the complex issues in determining the level of confidence. Detailed descriptions of the overall confidence assessment are listed in Table 5.5.

Table 5.4. Comparison of Main Similarities and Differences Between the Narrative Assessment and the Modified OHAT Assessment

	Narrative Assessment	Modified OHAT Assessment
Main purpose	To assess confidence in the presence of an association	To assess confidence in the quality of the body of evidence
Inclusion of studies	All studies—both the meta-analytic results and results of studies that were not included in meta-analysis	All studies, though heavily geared toward the studies entering a meta-analysis
Number, location, and size of the evidence base	Yes	Partial
Study design	Yes	Yes
Study population (generalizability)	Yes	No
Direction and magnitude, strength and nature of the association	Yes	No[a]
Risk of bias	Yes	Yes
Confounding	Yes	Yes
Selection bias	Yes	Yes
Exposure assessment	Yes	Yes
Outcome assessment	Yes	Yes
Missing data	Yes	Yes
Selective reporting	Yes	Yes
Consistency of the findings (e.g., across locations, time periods, study designs, and different pollutants and indirect traffic measures)	Yes	Partial
Unexplained inconsistency	Yes	Yes
Imprecision (chance)	Yes	Yes
Publication bias	No	Yes
Exposure–response	Yes	Yes
Residual confounding	Yes	Yes

[a] The OHAT has an upgrading factor for *large magnitude of effect* that applies only if the effect size is large or very large (i.e., large relative risk > 2 or very large relative risk > 5) because residual confounding is then less likely. However, the Panel consider a *large* effect to be both ambiguous to define and unlikely to occur. Thus, the Panel has decided not to consider this specific upgrading factor.

5.12 DIFFERENCES BETWEEN PROTOCOL AND SYSTEMATIC LITERATURE REVIEW

The Panel endeavored to apply the a priori defined methods, as outlined in the published review protocol (HEI 2019), however the Panel decided that certain changes to the methods were necessary, all based solely on methodological considerations and independent of study results. These main changes are described below.

Regarding the inclusion of multiple estimates from the same study population and cohorts in a single meta-analysis, the Panel decided to be inclusive; thus, the default was that studies were included unless the same study population is used in several publications on the same exposure–outcome pair. Exposures were only considered the same if they used the same measurements and/or models for assignment.

The Panel anticipated combining ambient PM mass and PM mass from traffic together in one meta-analysis, but because the increments were not comparable between ambient and traffic PM or between different studies of traffic PM, the Panel conducted meta-analyses of ambient PM mass only, where possible.

As anticipated in the protocol, the Panel elaborated on some methods when the review was already underway: (1) the Panel further elaborated on the overall evaluation of

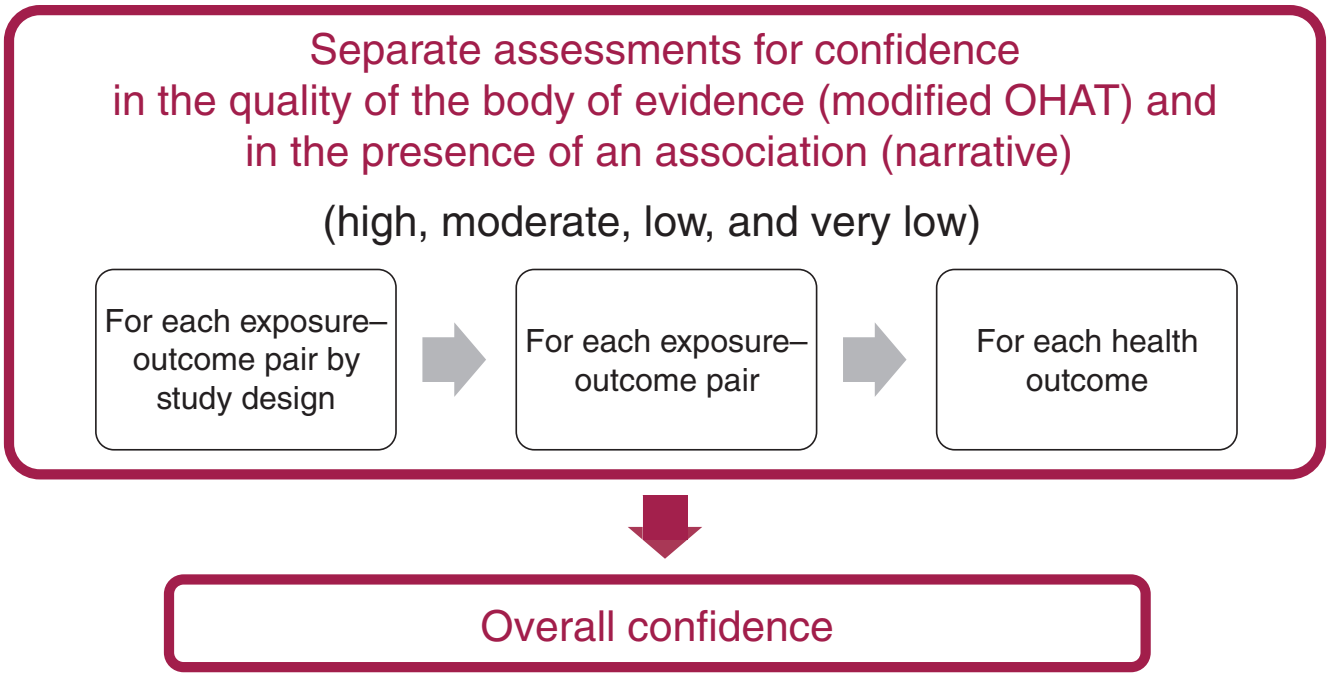

Figure 5.2. Summary of overall confidence assessment for TRAP and selected health outcomes.

Table 5.5. Overall Confidence Assessment: Descriptions of the Level of Confidence in the Evidence for an Association[a]

High	Evidence is sufficient to conclude that the strength of the evidence for an association is high, that is, the exposure has been shown to be associated with health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. The determination is based on multiple high-quality studies conducted in different populations and geographical areas with consistent results for multiple exposure indicators. High confidence in the association between exposure and the outcome
Moderate	Evidence is sufficient to conclude that an association is likely to exist, that is, the exposure has been shown to be associated with health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. The determination is based on some high-quality studies in different populations and geographical areas, but the results are not entirely consistent across areas and for multiple exposure indicators. Moderate confidence in the association between exposure and the outcome
Low	Evidence is suggestive but limited, and chance, confounding, and other biases cannot be ruled out. Generally, the body of evidence is relatively small, with few high-quality studies available and at least one high-quality epidemiological study shows an association with a given health outcome and/or when the body of evidence is relatively large but the evidence from studies of varying quality and across multiple exposure indicators is generally supportive but not entirely consistent. Low confidence in the association between exposure and the outcome
Very low	Evidence is inadequate to determine if an association exists with the relevant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. Very low confidence in the association between exposure and the outcome

[a] The overall assessment of the association of each health outcome with long-term exposure to TRAP is a combination of the narrative assessment and the modified OHAT assessment. The descriptors are modified from OHAT (2019) and U.S. EPA (2015).

the epidemiological evidence; (2) additional considerations were added related to how well exposure contrast in the included studies represents participants' exposure to TRAP (the traffic specificity variable); and (3) exact definitions of some of the selected health outcomes were developed, such as for respiratory and cardiometabolic outcomes.

5.13 METHODS FOR LITERATURE REVIEWS

Literature reviews were developed for neurodevelopmental outcomes in children and Parkinson disease and dementia-related outcomes in adults. Neurological outcomes recently received a *likely to be causal* determination in the U.S. EPA's Integrated Science Assessment on general long-term $PM_{2.5}$ (U.S. EPA 2019), and the Panel thought literature reviews were warranted, even while a larger body of evidence develops.

5.13.1 SEARCH STRATEGY AND STUDY SELECTION

The literature search strategy and the methods for the selection of studies were identical to the selected outcomes in the systematic review. However, the literature review differs from the systematic literature review in some important respects: (1) no meta-analyses were conducted, (2) there was no evaluation of the confidence in the quality of the body of evidence, and (3) there was no formal risk of bias assessment on individual studies.

5.13.2 NEUROLOGICAL OUTCOMES

For the literature review the Panel included as health outcomes in children (18 years and younger) cognitive function, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD). Health outcomes in adults (>18 years) included cognitive function, dementia, and Parkinson disease.

Cognitive function in children was assessed across a range of domains or networks, including verbal and nonverbal intelligence, language, learning and memory, working memory, visuospatial and visual-motor abilities, executive function, attention, inhibitory control, metacognition, and behavioral regulation. The Panel also included rating scales of executive function, attention, hyperactivity/impulsivity, and social behavior. Neuropsychological assessments were administered directly to the child using a range of tests. Behavioral rating scales, such as the Behavioral Regulation Inventory of Executive Function and the Strengths and Difficulties Questionnaire, were completed by parents, teachers, or by self-report.

ADHD is a neurodevelopmental disorder characterized by a persistent pattern of inattention and/or hyperactivity–impulsivity that interferes with functioning or development (American Psychological Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) and *Fourth Edition* (DSM-IV) (APA 1994, 2013). Most included studies used DSM-IV or DSM-5 criteria to define ADHD or ADHD traits. One study used the World Health Organization's *International Classification of Diseases, Tenth Edition* (ICD-10). The Panel included ADHD and associated traits, obtained from parent-, teacher-, and self-report of ADHD-related behaviors in behavioral rating scales and from diagnosis by a pediatrician.

ASD is a developmental disorder characterized by persistent deficits in social communication and social interaction across multiple contexts and by a restrictive and repetitive pattern of behavior, interests, and activities (DSM-5). The Panel included ASD and associated traits, based on reports from physicians, psychologists, or psychiatrists; health care and developmental services records; national registries, and structured interviews with parents and teachers.

For cognitive function in adults, the Panel included cognitive performance, cognitive decline, and mild cognitive impairment in one or more domains. Outcomes were directly assessed using tests such as the Mini-Mental State Examination and the Consortium to Establish a Registry for Alzheimer Disease, as well as intelligence tests such as the Wechsler Adult Intelligence Scales for Adults and the Neurobehavioral Evaluation System 2. Dichotomized and continuous measures of cognitive performance on a single test event and measures of cognitive decline over an interval were accepted as outcomes. Domains assessed by these tests included memory, reasoning, attention, language, executive function, and perceptual-visuomotor-visuospatial ability. One study considered mild cognitive impairment based on participants complaints of cognitive decline accompanied by poor performance on at least one objective test (Tzivian et al. 2016). Most researchers reported prevalent cognitive function; only three of the included studies investigated cognitive decline over an interval between assessments (Colicino et al. 2014; Oudin et al. 2017; Tonne et al. 2014).

Dementia is a major neurodegenerative disorder marked by significant decline from a previously attained cognitive level in one or more cognitive domains and substantial cognitive impairment that interferes with independent completion of instrumental activities of everyday living. The condition can result from a range of neuropathologies and combinations thereof that have different etiologies, symptoms, and trajectories. The Panel accepted as outcomes incident diagnoses of all-cause dementia and subtypes, which were documented in medical registries, health system databases, and death registries. Diagnoses were coded to the (ICD-9-CM, ICD-10-CM, DSM-IV, DSM-5, and READ codes used in the United Kingdom's National Health Service (Dementia Partnerships 2012). One study combined standardized evaluations of participants with data from their medical and death records (Oudin et al. 2016). The accepted outcomes varied in breadth: some included only Alzheimer disease and vascular dementia

(Carey et al. 2018; Oudin et al. 2016), while others included Alzheimer and vascular dementia, dementia from a range of other diseases and conditions, and unspecified dementia (ICD-9-CM codes 46.1, 290.0–290.4, 294, 331.0, 331.1, 331.5, 331.82 and ICD-10 codes F00–F03, G30) (Chen et al. 2017a, 2017b; Ilango et al. 2019).

Parkinson disease is a neurodegenerative disorder that affects movement and is characterized by shaking or resting tremor, bradykinesia, rigidity, and posture instability. For Parkinson disease, the Panel accepted diagnoses documented in medical, hospital and health insurance registries. Accepted codes were ICD-9 332.0 and ICD-10-CM G20.

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MATERIALS AVAILABLE ON THE HEI WEBSITE

Appendices 5A to 5C and Additional Materials 5.1 to 5.3 contain supplemental material not included in the main report. They are available on the HEI website at *www.healtheffects.org/publications.*

Appendices

5A Main Rationales for Exclusion of Health Outcomes Initially Considered in the Traffic Review

5B Search Strategy

5C Scaling and Conversion Factors for Use in Meta-Analysis

Additional Materials

5.1 Quality Control of Screening and Data Extraction

5.2 Modified Risk of Bias Tool

5.3 Overall Assessment of the Epidemiological Evidence—Further Elaborations

ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
ALRI	acute lower respiratory infection
AQG	air quality guidelines
ASD	autism spectrum disorder
BC	black carbon
BMI	body mass index
BS	black smoke
BW	birth weight
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
DAGs	directed acyclic graphs
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
EC	elemental carbon
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICD-10	*International Classification of Diseases, Tenth Revision*
ICD-9	*International Classification of Diseases, Ninth Revision*
IHD	ischemic heart disease
LBW	low birth weight
NO_2	nitrogen dioxide
OHAT	Office of Health Assessment and Translation
PECOS	Population, Exposure, Comparator, Outcome, and Study
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
PTB	preterm birth
SES	socioeconomic status
SGA	small for gestational age
TRAP	traffic-related air pollution
U.S. EPA	United States Environmental Protection Agency
UFPs	ultrafine particles
WHO	World Health Organization

PART B: METHODS

Chapter 6

Assessment of Exposure to Traffic-Related Air Pollution

CONTENTS

CHAPTER 6

Assessment of Exposure to Traffic-Related Air Pollution

6.1 OVERVIEW

To guide transparent selection and evaluation of epidemiological studies, the Panel developed a novel framework of exposure to traffic-related air pollution (TRAP*). This framework was necessary to identify studies in the systematic literature search and to select studies where the Panel had confidence that the exposure contrast(s) used in quantifying associations with the health outcomes of interest were due to TRAP. This step was critical because there are numerous epidemiological studies of air pollution, especially $PM_{2.5}$, but not all of them had considered exposure contrasts related to TRAP as opposed to all sources.

The Panel built on the exposure framework of the 2010 HEI Traffic Review (HEI 2010) that extensively discussed traffic-related emissions and exposures and based on that, identified acceptable exposure assessment methods. The Panel agreed that the fundamental exposure concepts laid out in Chapter 3: Assessment of Exposure to Traffic-Related Air Pollution and Chapter 4: Health Effects: Epidemiology of Traffic-Related Air Pollution of the 2010 HEI Traffic Review were still valid and thus did not require significant updating.

This chapter first provides a concise background on TRAP in Section 6.2, building on Chapter 2 on traffic emissions and the 2010 HEI Traffic Review. Section 6.3 discusses the 2010 exposure framework that formed the basis of the exposure framework in this review. Section 6.4 provides the exposure framework used to identify minimum inclusion criteria in the current review and report. Section 6.5 discusses how the framework was applied, and Section 6.6 describes a traffic specificity ranking that was used for more in-depth evaluation of the epidemiological evidence. A summary of the chapter and conclusions are provided in Section 6.7.

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* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

Highlights

- The Panel developed a novel framework of exposure to traffic-related air pollution to guide transparent selection and evaluation of epidemiological studies.
- No commonly available indicator pollutant was entirely specific for motorized road traffic sources.
- The pollutant, spatial scale, and exposure assessment methods and their spatial resolutions were considered to select studies where the exposure contrasts are primarily related to traffic emissions.
- A traffic specificity classification was developed for sensitivity analyses comparing studies with different levels of confidence that the reported pollutant signal associated with the outcome(s) represented traffic.

6.2 BACKGROUND

As discussed in Chapter 2, multiple gas- and particle-phase pollutants originate from motor vehicle traffic. Furthermore, within urban emissions inventories, transportation is one of the major sources for several of these pollutants (e.g., nitrogen oxides [NO_x]). Air quality source apportionment studies from multiple geographic regions (e.g., North America, Europe, and Asia) also provide evidence of the importance of TRAP to total air pollutant levels. Although emissions data continue to be uncertain, impacts of primary emissions on population exposure patterns are reasonably well characterized given known factors that influence the amounts produced from tailpipes, from evaporative processes, and from nontailpipe abrasive processes (e.g., Frey 2018). However, there continues to be uncertainty in the magnitude of the contribution of these emissions to urban air quality because they disperse and are subject to multiple chemical and physical processes. Emissions from traffic mix with the urban background, which itself includes pollutants entering urbanized areas as a regional background of air pollutants. Additionally, the newly emitted pollutants undergo chemical transformation into other pollutants leading to diverse secondary products of traffic emissions that contribute to both gas- and particle-phase pollutants, ranging from ozone to secondary organic aerosol to particulate nitrate (Seinfeld and Pandis 2016).

Dispersed primary traffic pollutants and their secondary products undoubtedly exist in and downwind of populated regions and contribute significantly to population exposure.

However, over time as they mix with pollutants from other sources the ability to track their origin as TRAP is lost. This means that at larger distances from sources it is more difficult to examine the separate or unique associations of these dispersed primary traffic pollutants and their secondary products with health effects in epidemiological studies. Nonetheless, TRAP-related health effects are critical to assess given that in most developed countries a relatively large percentage of the population lives within 500 m of major roads or highways. For example, Su et al (2015) estimated that 23% to 96% of the population of seven world cities lived within 300 m of highways or 50 m of major roadways in the early 2000s. Similarly, Perez and colleagues (2013) considered 10 cities in Europe and reported that about one third of the population lived within 50 m of major roads while 53% lived within 150 m.

Figure 6.1 shows the typical patterns of TRAP exposure across a city. In this simplified view, areas of greater TRAP emissions (or other major local sources) occur as areas of enhanced concentration (e.g., traffic areas marked by number 1 in Figure 6.1) above the general urban, regional, and continental backgrounds (other areas in Figure 6.1). Increased air pollutant concentrations in such areas are easily attributed to traffic given knowledge of the configuration of the roadway network and traffic volumes. In general, the air pollutants at a given point in a city can be partitioned into the quantity associated with the regional background entering into the city; the urban background from dispersed primary source emissions, which include traffic; and secondary products of these emissions and other nearby sources (Lenschow et al. 2001; Thunis 2018).

As indicated above, both TRAP levels and the quantitative contribution of TRAP to the urban background vary by pollutant, by season, and geographically. Depending on the amount of TRAP relative to air pollution from other emission sources, TRAP emissions may be the main contributor to spatial patterns in intra-urban concentrations. Most insight regarding how much TRAP contributes to the urban background comes from applications of chemical transport models (CTMs) through scenario analyses (e.g., Godowitch et al. 2010; Samaali et al. 2011; Schnell et al. 2019; Whaley et al. 2020) or tracking of traffic emissions (Beevers et al. 2012; Joe et al. 2014; Venecek et al. 2019). Much of the epidemiological research on TRAP, which is the focus of this current review, comes from being able to assign individual-level exposures that reflect spatial variations in exposure arising from the long-term concentration patterns created by areas of enhanced TRAP concentrations. The remainder of this section provides information about the nature of these areas, the resulting exposure patterns, and how the patterns are characterized.

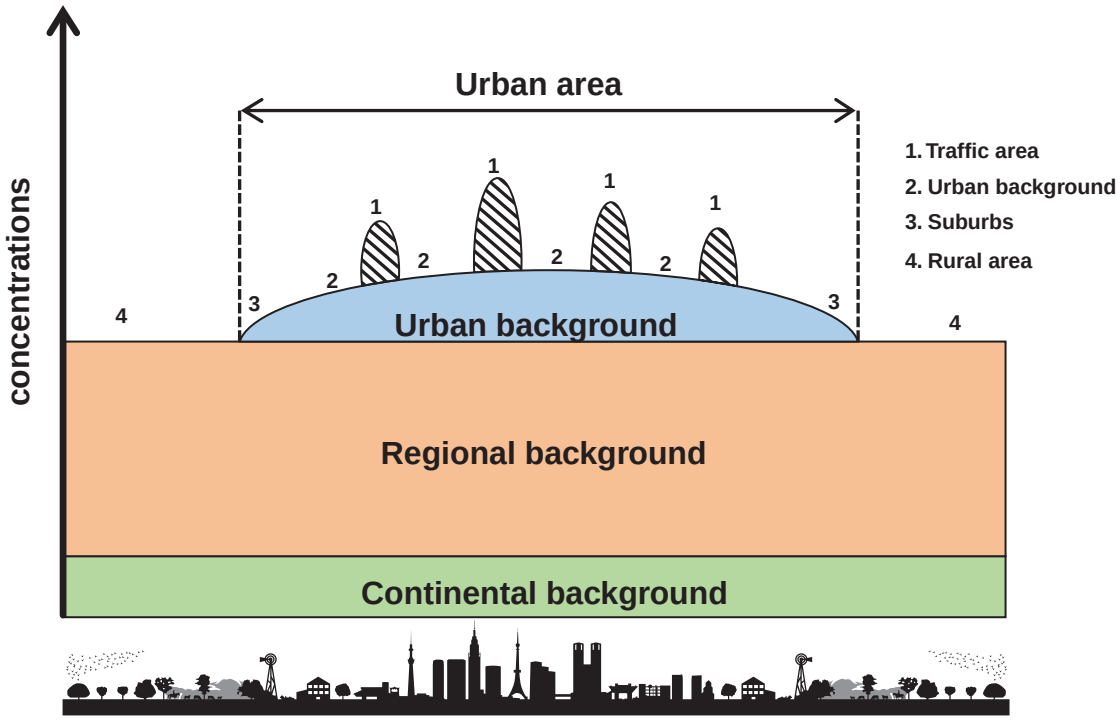


Figure 6.1. Conceptual diagram of urban background and traffic contributions to air pollution over background concentrations at regional and continental scales. (Reproduced from Fuzzi et al. 2015; Creative Commons license CC BY 3.0)

6.2.1 PHYSICAL AND CHEMICAL PROCESSES AFFECTING TRAFFIC-RELATED AIR POLLUTION MIXTURES

In the near-road environment, the strength of the on-road emission sources is the most important factor influencing local downwind concentrations. As indicated in Chapter 2, traffic volume, fleet age and composition (e.g., gasoline or diesel fuel, and light- or heavy-duty vehicles), and driving behavior (e.g., acceleration, speed, and braking) are the major determinants of on-road vehicle emissions (NRC 2000). Additionally, nontailpipe particulate matter emissions contribute to the mix of pollutants from motor vehicles via direct emissions from brakes, tires, and road wear, and via indirect emissions from resuspension of road dust or salt by vehicle motion and wind.

As distance from the roadway increases, steeply declining gradients in concentrations occur for primary species, such as carbon monoxide (CO), nitrous oxide (NO), elemental carbon (EC), and ultrafine particles (UFPs), as well as dust (Karner et al. 2010; Naser et al. 2009) (Figure 6.2). Numerous investigations of hourly monitoring data have observed familiar diurnal patterns for concentrations throughout urban areas (morning and evening peaks associated with higher traffic volumes) and decreases in concentrations with increasing wind speed and vertical mixing (e.g., Gordon et al. 2012a). The occurrence of these diurnal patterns in primary TRAP (e.g., CO, NO_x, and EC) further demonstrate that traffic contributes substantially to air pollution throughout urban areas.

Hot gaseous emissions from motor vehicle exhaust undergo rapid physical and chemical changes in the near-road environment. Dilution from vehicle-induced and atmospheric turbulence is the most important physical process influencing concentrations (Gordon et al. 2012b). However, in the first few seconds after the exhaust mixture leaves the tailpipe (cooling phase), nucleation, condensation, and coagulation are also important, and as the mixture is further diluted during downwind transport, condensation and evaporation (gas-particle partitioning) continue to influence aerosol size and concentrations (Zhang and Wexler 2004; Zhang et al. 2004). In the daytime, concentrations tend to decay to local background levels well within ~500 m of highways and major roads (Gordon et al. 2012a; Zhu et al. 2006), yet at night or during other atmospherically stable conditions, elevated concentrations of traffic-related air pollutants can extend farther from the roadways (up to 2,400 m under worst-case conditions) (Hu et al. 2009). Nontailpipe vehicle emissions from brake and tire wear and resuspended road dust undergo similarly rapid dilution and dispersion as these pollutants are transported away from roadways. Stating a single, specific distance or zone of influence is not justifiable because the magnitude of the gradient (i.e., concentration decrease from very near the road to the point where the concentration is equivalent to the local or neighborhood background) and the distance at

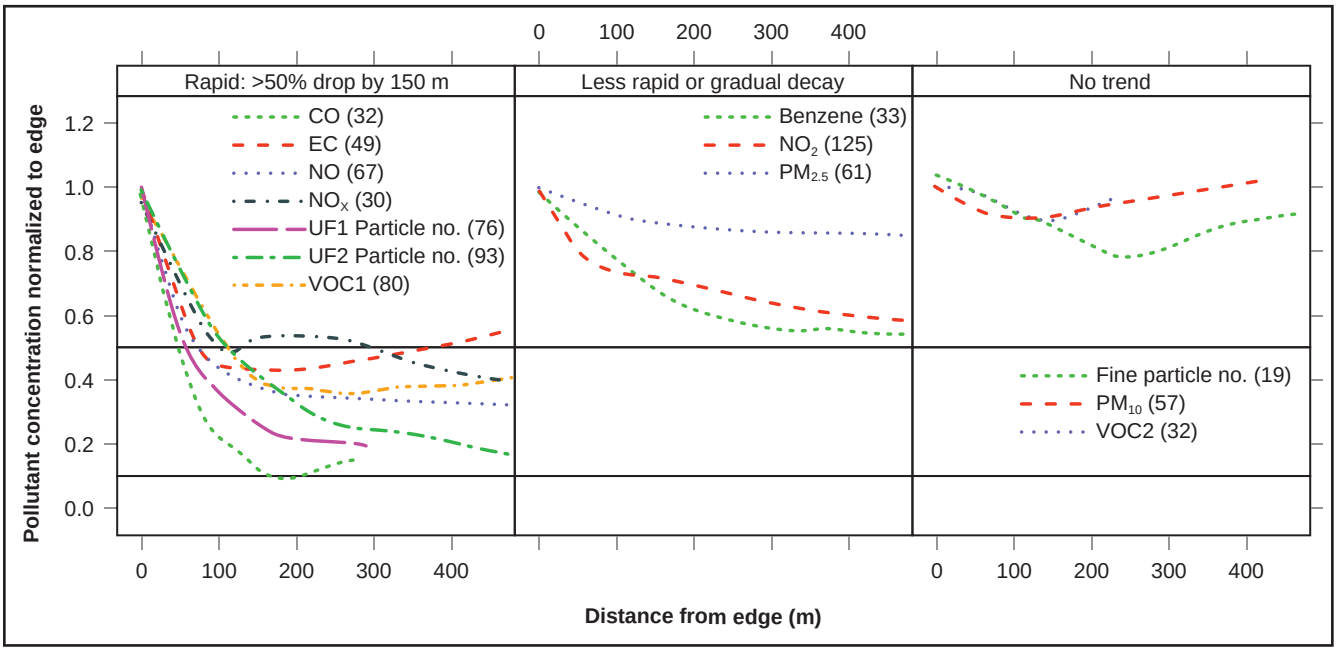


Figure 6.2. Local regression of concentrations on distance relative to the concentrations at the edge of the road. Parenthetical numbers after each pollutant refer to the regression sample size. (Reproduced with permission from Karner et al. 2010; copyright 2010 American Chemical Society)

which elevated concentrations can be detected change temporally and by pollutant (Gordon et al. 2012a). However, considering seasonal and diurnal variations, as well as pollutants that are not rapidly removed via physical or chemical processes, it is reasonable to expect that typically concentrations of TRAP are elevated above the local background up to about 500 m from the edge of the road (e.g., Levy et al. 2014a).

Background or upwind pollutant levels have important effects in the near-road zone. Because of the rapid chemical reaction of NO and ozone, background ozone influences the chemical formation of nitrogen dioxide (NO_2), producing consistently high NO to NO_2 conversion when ozone is high relative to NO_x, but widely varying conversion when ozone is low relative to NO_x (Lurmann et al. 2013). Chemical reactions of organic compounds in the near-road environment are less well-understood and difficult to observe but are expected to be relatively slow because of depressed hydroxyl radical levels in daylight and increased nitrate radical levels at night. The relative amounts of gas- and aerosol-phase organics and the role of oxidation to increase local secondary organic aerosols (SOA) are highly dependent on the volatility distribution (Robinson et al. 2007) of primary organic emissions. There is increasing recognition of the importance of intermediate volatile organic compounds (VOCs) in SOA formation near roads and downwind throughout urbanized areas (Jathar et al. 2014, 2017; Stroud et al. 2014; Zhang et al. 2016). Overall, near-road concentrations of all traffic-related air pollutants and, by extension, potential population exposures are a function of the background concentrations of these pollutants, plus the incremental contribution associated with roadway emissions. The resulting near-road air pollutant mixture is thus highly complex, physically and chemically, containing multiple known toxics (polycyclic aromatic hydrocarbons [PAHs], VOCs, metals, organic nitrates) and likely some unknown or rarely measured toxics (e.g., Moussa et al. 2016; Wren et al. 2018) in both gaseous from and in a wide distribution of particle sizes (~5–300 nm).

As traffic-related air pollutants are transported beyond the near-road environment, they mix with pollutants from other sources and are subject to the chemical and physical process affecting all pollutants on the urban, regional, and global scales. Within the city these become part of the urban background portrayed in Figure 6.1. Horizontal and vertical transport by atmospheric winds and turbulence are coupled with chemical reactions, condensation, evaporation, nucleation, and wet and dry deposition to determine the fate of the pollutants (Seinfeld and Pandis 2016). Daylight photochemical reactions drive ozone formation and the oxidation of NO to NO_2; NO_2 to aerosol nitrate, nitric acid, and organic nitrates; sulfur dioxide to sulfate aerosol, organic compounds to oxidized gases and secondary organic aerosol; and CO and organic compounds, including benzene, to ultimately form carbon dioxide (CO_2). Additional reactions occur at night and within and on the surface of wetted aerosols and cloud droplets that form nitrate, sulfate, and oxidized organic compounds. Furthermore, the complex mixture of atmospheric gases and particles include semivolatile species that transfer to and from the gas and aerosol phases depending on environmental conditions. As mentioned above, indicators for the contribution of traffic-related emissions become increasingly difficult to observe as transport distances increase and pollutants from all sources are mixed and transformed.

6.2.2 CHARACTERIZING TRAP EXPOSURE

The complex mixture of TRAP has frequently been represented in epidemiological studies by the commonly measured indicators NO_2, CO, and EC. Use of UFPs as an indicator is increasing, but data relevant to long-term urban exposure patterns are relatively limited. Although each indicator pollutant has unique behavior near and downwind of traffic (i.e., UFP number concentration decreases rapidly and particles can evaporate and coagulate, EC disperses as a fine particle tracer, and NO_2 initially depends on both direct emissions and conversion from NO via ozone reactions then is subsequently oxidized within and downwind of the city), they each consistently exhibit near-road enhancements in concentration thus making them useful exposure measures for epidemiological research. Figure 6.2 provides typical rates of decrease of some TRAPs away from major roads while Figure 6.3 shows the more complex spatial patterns derived from averaging mobile measurements made on multiple days on roads of different types in a portion of Oakland, California (Apte et al. 2017). These maps reveal differences in the exposure gradient for EC and NO_2 with the latter persisting at higher levels throughout the city relative to the near-road peaks. In Figure 6.3, UFPs tend to behave like EC with sharp increases near the major roads. Although these fine scale differences in spatial behavior among traffic-related air pollutants can be detected and represent true differences in potential exposure patterns, the relationships among pollutants as experienced across large populations are complex. The shared gradients near major roads and across urban areas (Figures 6.2 and 6.3) resulted in a considerable amount of spatial correlation in concentrations of different pollutants ($r \geq 0.7$; Figure 6.3). In this review we will assess multiple indicators of TRAP and not attempt to disentangle health effects of specific pollutants.

Most intraurban exposure surfaces used in epidemiological studies are derived from short-term saturation sampling during selected weeks across a year and increasingly from mobile measurements for strategic time periods. These snapshots of the spatial patterns have frequently been shown to represent the long-term exposure patterns because over the time scales of interest the locations of roads in any given city are mostly fixed and relative traffic volumes on different roads are relatively consistent. By far, NO_2 has been the most commonly used TRAP indicator for epidemiological studies because of data availability. Most monitoring networks include NO_2, sometimes from multiple sites within cities,

Figure 6.3. BC and NO_2 spatial distributions in Oakland, California. (Adapted with permission from Apte et al. 2017; copyright 2017 American Chemical Society)

and NO_2 has been used extensively for exposure model development because it can be measured inexpensively at multiple locations with passive samplers. Particulate matter with aerodynamic diameter ≤2.5 µm ($PM_{2.5}$) includes EC and UFPs and thus it is also enhanced in the near-road environment. As Figure 6.4 shows for measurements in Amsterdam, $PM_{2.5}$ variations across cities can be somewhat correlated with UFPs (r = 0.66) and likely other TRAP indicators, as also evidenced in Figure 6.5 for Montréal (r ~0.4). However, regional and urban background levels of $PM_{2.5}$ are large relative to its local enhancement, meaning distinct exposures of $PM_{2.5}$ specifically attributable to primary TRAP are difficult to resolve. Furthermore, the correlations among measurements of long-term average $PM_{2.5}$ and TRAP indicators will depend on the dominant particle sources in a given city and, as a result, can vary between parts of a city (e.g., airports can be an important source of UFPs that locally alters the relationship between particle mass [usually measured by $PM_{2.5}$] and particle number [usually assumed to represent primarily UFPs]) (Levy et al. 2014b; Saha et al. 2020). The large body of evidence linking $PM_{2.5}$ to health outcomes thus requires scrutiny to determine if the exposure signal driving the epidemiological results was primarily due to $PM_{2.5}$ associated with TRAP or with other sources. The exposure framework described below identifies the conditions for which an epidemiological study using $PM_{2.5}$ can be considered to provide information about the health effects of TRAP.

Overall, the chemical and physical complexity of TRAP mixtures and the correlations among components have important implications for interpreting results of the study. Even though epidemiological studies report separate results for the measured or modeled components of traffic-related air pollutants, the typically high correlation of the components with each other suggests the results are not independent and that each component should be considered as an indicator or surrogate for the mixture. The complexity of the mixture suggests each measured or modeled component is an imperfect indicator for TRAP. As such, the Panel viewed the multiple indicators of traffic exposure as being more useful to assess the overall TRAP mixture than to provide insight on the relative toxicity of any specific indicator.

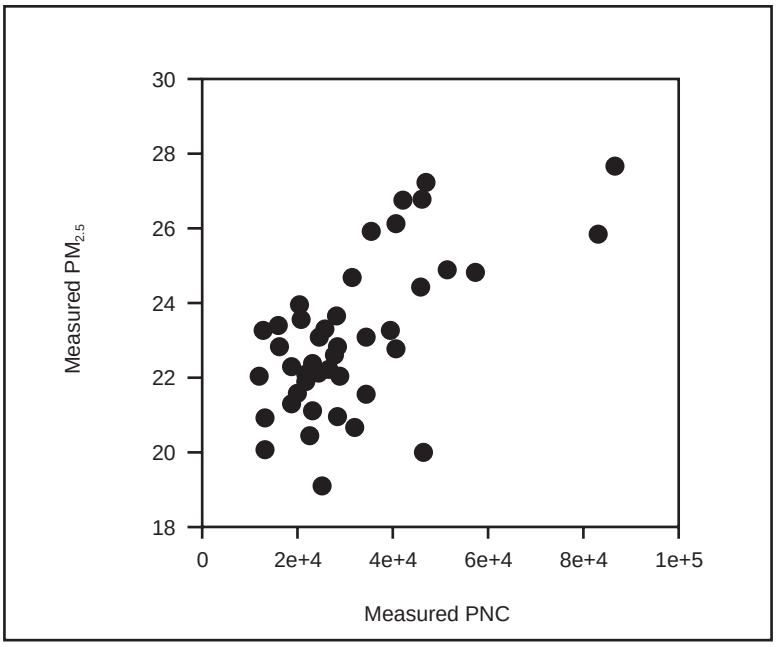


Figure 6.4. Relationship between measured particle number concentration (number/cm³) and measured $PM_{2.5}$ (µg/m³) concentrations in Amsterdam, the Netherlands. (Reproduced with permission from Hoek et al. 2011; copyright 2011 American Chemical Society)

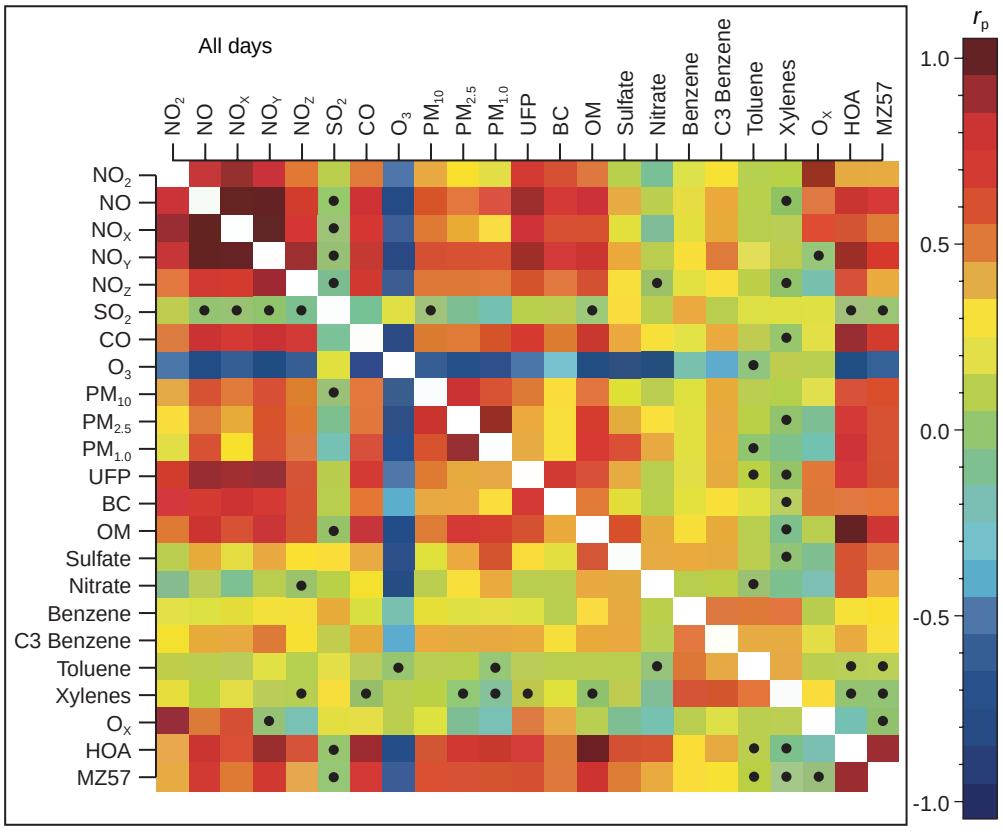


Figure 6.5. Interpollutant spatial correlations based on mobile monitoring on 34 days in 2009 in Montréal, Canada, with colors representing the magnitude of each correlation and black dots indicating nonsignificant correlations ($P > 0.05$). HOA is the hydrocarbon-like organic fraction of PM_1 and MZ57 is also an indicator of this component of the fine particles. O_x is this sum of NO_2 and O_3. Adapted from Levy et al. (2014b).

6.2.3 EXPOSURE AT HOME, WORK, SCHOOL, AND IN TRAVEL

Most epidemiological studies of the health effects of air pollution, including those focused on TRAP, are based on outdoor air pollution exposure assigned to participants' residential addresses. However, due to human behavior patterns, people are often exposed to TRAP throughout their daily activity spaces, including settings such as school, work, or commuting (Dons et al. 2012; Hoek 2017; Zuurbier et al. 2010). The amount of time that individuals spend in these different microenvironments, particularly during travel on roads, can alter individual TRAP exposures considerably (Fruin et al. 2004). However, this additional component is difficult to consider for epidemiological studies given the factors that influence in-vehicle exposures (Dekoninck and Int Panis 2017; Fruin et al. 2011). There is evidence that using residential exposures does not lead to significant bias in epidemiological results (Hoek 2017 and references therein). However, the bias has been shown to depend on the amount of time that people spent away from their home and the distance traveled (Setton et al. 2011), factors that are typically not reported and quantified in epidemiological studies and thus the potential for bias may vary with study location and population (e.g., age, sex, and occupation).

Given that a substantial fraction of an individual's exposure can also occur at locations other than the residential address, some epidemiological studies have exploited exposure contrasts derived from including those other locations. Examples include studying exposures at school addresses (Brunekreef et al. 1997; McConnell et al. 2010), work addresses (Puett et al. 2011), or during commuting (Ragettli et al. 2013; Zuurbier et al. 2010). Some studies were designed to primarily assess exposure at school (Brunekreef et al. 1997), whereas other studies specifically characterized both the residential and school exposures (McConnell et al. 2010). Epidemiological studies of commuting exposures primarily assessed short-term exposures (e.g., Peters et al. 2004), which were not considered in this review.

It is also important to recognize that in addition to spending time in different locations, where the TRAP exposure based on home address may not be representative, people typically spend the majority of time indoors. Depending on the characteristics of the buildings, the extent of indoor infiltration of TRAP will vary (Goldstein et al. 2021; Jones et al. 2000; Wallace 2000; Wheeler et al. 2011). Over larger geographic scales this may be more important as housing stock and behaviors like window opening will reflect local climates, population preferences, and socioeconomic conditions (Janssen et al. 2002). However, the Panel only included studies on TRAP that focused on intra-urban exposure contrasts or adjusted for regional variation if larger study areas were used. Thus, systematic spatial variations in infiltration are less likely to have influenced the epidemiological results. Uncertainty remains, however, as there can be dramatic variations in housing stock within cities based on socioeconomic conditions (Brown et al. 2015). In this regard, areas of high TRAP exposure may have housing with greater infiltration rates given the growing body of evidence of environmental injustices related to air pollution exposure (e.g., Chambliss et al. 2021; Doiron et al. 2020). Clearly, the interactions between socioeconomic conditions, housing, equity, and TRAP exposure are highly complex and require future work to better understand how, where, and when variable infiltration rates could influence the epidemiological findings regarding TRAP. Exposures to indoor sources were not considered because this review was intended to assess only associations with ambient TRAP.

6.3 EXPOSURE FRAMEWORK IN THE 2010 HEI TRAFFIC REVIEW

Chapter 3 of the 2010 HEI Traffic Review provided a detailed discussion of the spatial scale at which traffic emissions affect air quality, surrogate TRAP exposure metrics, modeling techniques, and different pollutants used as indicators for exposure to TRAP (HEI 2010). That chapter also discussed strengths and weaknesses of the different exposure assessment methods considering those supporting chronic and acute health effect studies.

Traffic emissions and their secondary products affect air pollution concentrations at global, regional, urban, and local scales (HEI 2010: Figure 3.1). Regional scale refers to a large area of a country, urban scale refers to differences between urban and more rural areas and differences between neighborhoods of very large cities, and local scale reflects near-roadway traffic impacts. Distinctions were made in the 2010 HEI Traffic Review among regional (100 km to 1,000 km), urban (4 km to 50 km), neighborhood (50 m to 4 km), and household (<50 m) scales. Local was interpreted as within 500 m from a highway or a major road. Additionally, the different surrogate metrics of TRAP exposure (e.g., distance to major roads and traffic density) were evaluated in the context of studying the health effects of long-term or short-term exposures.

Overall, the 2010 HEI Traffic Review highlighted that no pollutant is 100% specific to traffic sources. Other sources contribute to varying degrees to all the pollutants frequently referred to in epidemiological studies as TRAP (e.g., EC, NO_2, and UFPs). In terms of the potential indicator pollutants to consider, the 2010 HEI Traffic Review suggested that an important criterion should be the fraction of their total emissions due to motor vehicles (e.g., on-road vehicle emissions of CO, benzene, and NO_x account for 40% or more of total atmospheric emissions). However, the 2010 HEI Traffic Review recognized that this factor could not be the only criterion. In particular, as discussed above, it is important to carefully assess how much of the spatial contrast in concentration or exposure in a specific setting was due to the different sources. Given these challenges, the studies evaluated in the 2010 HEI Traffic Review, which were selected based only on exposure considerations (i.e., no a priori selection was made in terms of health outcomes),

were limited to those that involved TRAP indicators related to primary emissions and their spatial exposure contrasts at the local scale. The net result of these criteria was that the 2010 HEI Traffic Review only reviewed studies if they used one of the following exposure assessment methods:

1. Measures based on distance or length of roads
2. Measures of traffic density
3. Modeling (dispersion models of TRAP, other techniques such as land use regression [LUR] for TRAP, and traffic-specific source apportionment)
4. Participants in occupations characterized by exposure to TRAP
5. Monitoring of pollutant surrogates of TRAP if the measurements were from roadside monitoring or the study participants lived a short distance (i.e., up to 300 to 500 m) from the monitors. The 2010 HEI Traffic Review acknowledged this method requires judgment with respect to traffic specificity.

Studies that used self-reported traffic exposure measures were excluded. The result of these strict exposure considerations (HEI 2010: Table 4.1) was that most of the long-term exposure studies included in the 2010 HEI Traffic Review were based on indirect traffic measures, such as distance to roadways or traffic density. Despite that eventual focus for the review, the 2010 HEI Traffic Review acknowledged these measures have important limitations because of validity (i.e., such metrics do not necessarily translate to TRAP concentration differences because the concentration differences depend on the nature of the traffic on the roads being considered) and confounding issues (e.g., due to traffic noise). In addition, few short-term exposure studies were included due to the strict exposure criteria (e.g., only four all-cause mortality studies and one UFP study were included in the 2010 HEI Traffic Review). The number of relevant time-series studies in general—especially UFP short-term studies—was restricted by the roadside monitoring requirement. Most of the available time-series studies had selected urban background monitors or averaged all available stations, including background and traffic sites, to represent daily variation of air pollution and were thus excluded from the 2010 HEI Traffic Review (see Chapter 4 for an overview of those studies).

6.4 EXPOSURE FRAMEWORK FOR THE CURRENT REVIEW

For the current review, the Panel developed an updated framework to identify studies of health effects of TRAP exposure. First the full Panel was consulted to develop and test a novel framework on a selection of studies with different features. Second, issues that arose through the initial testing were discussed within the full Panel and further discussed as needed by the subgroup of exposure experts on the Panel; the framework was then refined to sharpen the study selection process. This second step took several iterations as additional issues were identified.

As portrayed in Figure 6.1, exposure to TRAP varies across multiple spatial scales. The Panel classified these scales as local, neighborhood, urban, and regional scales. The highest direct exposures to traffic-related emissions of primary pollutants are likely to occur at the local scale, that is, when a person is in transit (walking, cycling, or in a vehicle) or living or working close to major roads. As discussed in Section 6.2, at greater distances (urban and regional scales), traffic emissions of primary pollutants as well as their secondary products are likely to be mixed with emissions from other sources and thus difficult to apportion or uniquely distinguish from the mixture. However, to allow an inclusive assessment the Panel decided it was important to consider the impact of traffic-related air pollution beyond the local scale where appropriate. As an example, in the European ESCAPE study the exposure contrasts for NO_2 between urban background and nearby rural background and between local major streets and urban background were very similar in magnitude (Cyrys et al. 2012). Although sources other than traffic contributed to the urban background, the emission sources impacting the cities included in ESCAPE were likely dominated by motorized road traffic. Thus, the Panel recognized that contrasts across larger geographic areas (i.e., between urban background and nearby rural background locations) can predominantly be caused by TRAP.

Furthermore, as a large proportion of residences are spread across cities and likely to be located in areas experiencing multiple contrasts (from near-road, to local, to neighborhood, to urban background, to nearby rural background), the exposed populations throughout urban and near-urban areas are expected to experience varying influences from traffic emissions relevant to this assessment. Also important to recognize is that people spend time at locations other than their residence—which is often used to calculate individual spatially refined exposures in air pollution epidemiology studies—and thus the broader neighborhood scales have an important influence on TRAP exposure contrasts (Hoek 2017). In general, the above considerations led the Panel to conclude that for many cities—where traffic is a major source of air pollution—studies exploiting contrasts within and between neighborhoods should be considered for inclusion along with those exploiting local-scale exposures. More specific criteria that recognize these different scales are provided below, and the implications of including studies at different spatial scales on the overall results were evaluated using sensitivity analyses as described in Section 6.6.

The Panel followed the 2010 HEI Traffic Review in recognizing that no commonly available indicator pollutant is entirely specific for motorized road traffic sources. Other sources (including industrial, commercial, and residential combustion sources) contribute to ambient concentrations

of frequently used traffic-related air pollutants such as EC, NO_2, and UFPs (HEI 2013; U.S. EPA 2016, 2019). Therefore, the Panel applied three strategies to increase the likelihood that in a specific study selected for inclusion, the exposure contrasts are primarily related to traffic emissions:

1. Choice of pollutant (Section 6.4.1)
2. Choice of spatial scale (Section 6.4.2)
3. Choice of exposure assessment methods and their spatial resolutions (Section 6.4.3)

A combination of these three strategies was considered by the Panel to be the best approach to select studies that are informative about health effects of TRAP. The Panel applied stricter criteria for spatial scale and exposure assessment methods for those pollutants that were less closely related to traffic (e.g., $PM_{2.5}$, particulate matter with aerodynamic diameter ≤10 µm [PM_{10}], and particulate matter with aerodynamic diameter between 2.5 µm and 10 µm [PM_{coarse}]).

6.4.1 DEFINITION OF TRAFFIC-RELATED AIR POLLUTANTS AND INDICATORS

Many pollutants are considered to be related to traffic based on previous emissions, monitoring, and modeling studies (HEI 2010). Table 6.1 lists the primary pollutants that the Panel judged to be most relevant and were potentially used in epidemiological studies of interest. The guiding principle was that the exposure contrasts characterized through use of the selected pollutant should have an important traffic signal, although no pollutant identified has traffic as its only source.

The Panel considered certain air pollutants (e.g., NO_2) included in the review to typically represent traffic better than others (e.g., benzene and PAHs). In particular, PM_{10}, PM_{coarse}, and $PM_{2.5}$ mass have significant contributions from sources other than traffic and predominantly exhibit regional variation due to longer atmospheric lifetimes, dispersion, and atmospheric transformation processes (secondary organic,

Table 6.1. Traffic-Related Air Pollutants and Exposure Indicators Included in Review

Exposure Metric	Consideration
NO_2, NO_x, NO	Frequently used in epidemiological studies NAAQS or limit values
CO	Frequently used particularly in earlier traffic studies NAAQS or limit values
EC, BC, BS, PM absorption (soot)[a]	Frequently used in epidemiological studies
PM_{10}, PM_{coarse}, and $PM_{2.5}$	Frequently used in epidemiological studies In specific settings PM contrast may have a clearly resolvable relative traffic contribution
Nontailpipe PM trace metals from wearing of brakes and tires or from the resuspension of road dust (e.g., Cu, Fe, and Zn)	Increased interest because of reduction of tailpipe emissions
UFPs, particle number concentration, quasi-ultrafine PM, different particle modes (nucleation, Aitken, accumulation), particle size distribution	Fraction of fine particles produced through combustion and with potentially distinct health effects
PAH	Added for completeness Some PAHs increased by traffic, though not a very specific marker and most human exposure is via diet
Benzene	Added for completeness Some VOCs are increased by traffic, though VOCs are generally not specific for traffic Benzene chosen as a marker for mobile source air toxics
Indirect traffic measures (metrics based on distance or traffic density)	Very specific for local traffic but concerns about validity Indicators represent more than air pollution (e.g., noise) and no quantitative concentration estimates available

[a] Elemental carbon (EC), black carbon (BC), black smoke (BS), and PM absorption (PM_{abs}) are referred to as EC throughout this report. These carbonaceous pollutants are defined by operational measurement techniques rather than by fundamental chemical properties alone. Chapter 5 describes the methods adopted to convert BC, BS, and $PM_{2.5\ abs}$ to EC units for use in meta-analyses.

sulfate, and nitrate formation) (HEI 2010; U.S. EPA 2019). Although the contribution of local and neighborhood traffic to the overall $PM_{2.5}$ concentration is generally small in relative terms, in specific settings such as a single metropolitan area the modest intra-urban spatial contrasts in $PM_{2.5}$ concentrations may be largely due to traffic emissions because the large regional component is broadly constant across such areas. This behavior was demonstrated in Section 6.2.2 above where in two different cities spatial variations in $PM_{2.5}$ were found to be reasonably correlated with the variations in pollutants more strongly linked to TRAP (Hoek et al. 2011; Levy et al. 2014b). Nonetheless, because of the large impact of other sources, both local and regional, the Panel applied stricter inclusion requirements for PM_{10}, PM_{coarse}, and $PM_{2.5}$ than for the other pollutants. The distinction between PM and the other components was furthermore included in the subsequent traffic specificity assessment and in the confidence assessment of the epidemiological evidence. Specifically, if the only evidence for an association of TRAP with a health endpoint was for $PM_{2.5}$ and not for pollutants such as NO_2 or EC as well, the confidence in an association with TRAP was lower compared to the reverse setting.

As in the 2010 HEI Traffic Review, studies that used self-reported traffic exposure measures were excluded. Studies that relied primarily on occupational exposure were also excluded because they would be difficult to combine with general population exposures and were not found to be useful in the 2010 HEI Traffic Review. Objective indirect indicators of traffic exposure that were not pollutants, such as distance to roads and traffic density measures, were included in the review, despite a priori concern about the comparability of these indirect traffic measures across studies. The Panel viewed these indicators for exposure characterization as likely to be very specific markers of variations in traffic exposure in the settings in which they have been applied. However, because of the varying definitions across the studies and because the actual magnitude of the exposure gradient associated with such indicators will vary by study location it was deemed not appropriate to attempt meta-analyses. Because indirect measures of traffic have been applied in a large number of studies and were evaluated in the 2010 HEI Traffic Review, this evidence was considered of significant value in further informing the Panel's overall assessment of the evidence of health effects due to TRAP. Results from studies using indirect measures of exposure to TRAP should be interpreted in the context that there may be confounding effects of socioeconomic status and noise.

6.4.2. DEFINITION OF SCALE OF EXPOSURE CONTRASTS RELATED TO SPECIFIC STUDY DESIGN

The spatial scale of the exploited exposure contrast affects how specifically a study reflects traffic impacts (Table 6.2). The Panel slightly modified the definition of the scales from the 2010 HEI Traffic Review as follows: regional (>50 km), urban (5 km to 50 km), neighborhood (1 km to 5 km), and local scale (<1 km). In the 2010 HEI Traffic Review, local scale was interpreted as less than 500 m from traffic, which is smaller than the Panel's definition of local scale. The Panel acknowledges that the upper range of its definition of local (1 km) is only applicable to major freeways, and that for most major roads, distances of up to 100 to 500 m lead to increased exposure (HEI 2010, Section 6.2). The Panel also noted that 50 km is large for many cities. Scale needs to be interpreted in conjunction with actual land use in a specific study. Hence, the Panel considered the scales to be important criteria in the evaluation of exposure contrasts that need to be used in conjunction with other criteria because of differing processes and inherent uncertainties at different scales, as further developed below.

Due to reasons discussed above, contrasts in TRAP at the urban and regional scales are difficult to isolate from contrasts due to other sources. The Panel therefore judged that it was essential for included studies to characterize TRAP exposures well at the local and neighborhood scales (<5 km). This would ensure that the overall exposure contrast considered in the included epidemiological studies had considerable relevance to TRAP. The Panel also acknowledged that accepting large urban study areas may result in inclusion of studies where other sources contribute significantly to the exposure contrast.

Because of the focus on local and neighborhood scale exposure contrasts, studies that exclusively made use of between-city contrasts, such as the American Cancer Society study (Pope et al. 2002), were not included. Studies that made use of both between- and within-city contrasts were included only if they adjusted for differences between the urban areas in the epidemiological analyses. Most nationwide studies (e.g., Crouse et al. 2015a; Di et al. 2017) were not selected because across these large geographic areas it is very difficult to disentangle TRAP from other sources.

6.4.3. DEFINITION OF SPECIFIC EXPOSURE ASSESSMENT METHODS AND THEIR SPATIAL RESOLUTIONS

The spatial resolution of the exposure assessment method is important to judge how well a specific method characterizes TRAP. The Panel distinguished the spatial resolution of the pollution exposure surface from that of participant locations (i.e., address data). The criteria for the spatial resolution of the pollution surface were selected based on the surface's ability to identify intra-urban contrasts in ambient air pollution down to variations at the local to neighborhood scale that are subsequently exploited

through sufficient spatial resolution of the addresses of the health study participants. In addition, there are intrinsic differences between exposure assessment methods. The spatial resolution criteria are described below and summarized in Table 6.3.

6.4.3.1 Spatial Resolution of Exposure Surface

The first key aspect of the exposure assessment is the spatial resolution of the exposure metrics (e.g., air pollutant concentrations). We distinguish the spatial resolution of the

Table 6.2. Scales of Exposures in TRAP Studies

Scale (area of impact)[a]	Within Scope of Review	Rationale
1. Increase in regional scale (>50 km) average background concentration of secondary pollutants including O_3, nitrates (part of $PM_{2.5}$)	No	Other sources than traffic contribute to contrasts that cannot be reliably separated
2. Increase in regional scale (>50 km) average background concentration of traffic-related air pollutants as listed in Table 6.1	No, when this is the only source of spatial contrast; an example is a study using county-level pollution as the exposure metric or a study evaluating only rural communities where the contrast is derived completely from differences in regional background; a rare study design in this review given that we exclude geographical (ecological or correlation) studies	Other sources than traffic contribute to contrasts that cannot be reliably separated
3. Increase in neighborhood scale (1 km to 5 km) and urban scale (5 km to 50 km) average background concentration of traffic-related air pollutants as listed in Table 6.1. This category also includes nationwide epidemiological studies that evaluate contrast as the sum of regional and urban background	For the assessment, the Panel classified studies based on contrasts: a) Exclusively between city (No) b) Within city and between city (Possibly) c) Within city only (Yes) Studies that exclusively used between-city contrast (i.e., that assigned one value to all participants in a city) were excluded. An exception may be a design in a small nonindustrial region (e.g., <100 km) where the dominant contrast is between major cities and smaller towns. Studies were included if the paper or accompanying exposure paper satisfactorily documented that the contrast between study locations or cities had an important traffic source contribution and was not dominated by other sources (e.g., industry and wood smoke). This was particularly important for studies that included a between-city component.	All three types of contrast studies may contain a traffic signal, though the certainty of attributing contrast to traffic differs The a priori assumption is that category *a* has the most uncertainty in whether the contrast is related to traffic If in category *b* traffic is a documented important source and an adjustment is made for city or area in the epidemiological analysis, the study is more likely to show a traffic signal than if no adjustment is made
4. Increase in local scale (<1 km) average concentration of traffic-related air pollutants as listed in Table 6.1	Yes	Studies included if the contrast between study locations has an important traffic source contribution
5. Increase in commuting exposures for all traffic-related air pollutants as listed in Table 6.1	Yes	Commuting studies consider primary TRAP exposures, but there are likely few of these studies on long-term exposure
6. Increase in occupational exposure (e.g., taxi drivers and postal delivery workers)	No	Not considered useful in 2010 HEI Traffic Review Difficult to combine with general environmental exposures

[a] Scale refers to the geographic extent of the region in which variations are compared. Studies typically have multiple scales; the Panel used the smallest scale to categorize a study.

Table 6.3. Exposure Assessment Methods Eligible for Inclusion in the Review

	Exposure Method	Considerations	Spatial Resolution "Pollution Surface"[a]	Spatial Resolution "Address" (Health) Data[a]
1.	Measures based on distance, as continuous distance (preferably nonlinear) or distance categories	Specific markers for local scale Limited validity[b]	≤1,000 m from a highway or a major road	≤100 m
2.	Measures of traffic density or length of roads	Typically buffers or traffic intensity of nearest street Specific marker for local scale Limited validity	Buffers with radius of ≤1,000 m from address	≤100 m
3.	Dispersion models or CTMs	May include local, neighborhood, and urban scales If a dispersion model or CTM of traffic emissions was used, the study was included, provided it met the scale requirements Studies that used dispersion models or CTMs of all sources combined were considered, although judgment of traffic specificity including study area and modeled sources was needed	≤5 km	≤5 km
4.	Traffic-specific source apportionment	Specific to the extent that source apportionment is successful May cover local, neighborhood, and urban scale Rarely resolved spatially	≤5 km	≤5 km
5.	LUR models: Includes hybrid models with CTM and/or satellite data; universal kriging; Bayesian methods; models by machine learning techniques	Studies that use LUR models require judgment on study area and predictors in the model For inclusion, the Panel required at least one traffic predictor (traffic intensity or road density) or broader surrogate of traffic (e.g., address density, household density, population density, impervious surface)	≤5 km	≤5 km
6.	Surface monitoring: Includes exposure assignment by interpolation methods such as nearest neighbor, Thiessen polygon, inverse distance weighing and kriging without covariates (e.g., ordinary kriging)	Not fully specific for traffic; the main issue is exploited spatial scale of exposure contrast of study PM studies and studies that assigned city averages to all participants were excluded	≤5 km	≤5 km
7.	Satellite monitoring	Less specific for traffic than surface monitoring if used directly If satellite monitoring is combined with other approaches (e.g., hybrid model), the overall specificity may be sufficient PM studies and studies that assigned city averages to all participants were excluded	≤5 km	≤5 km
8.	Personal exposure monitoring or modeling (time weighted average of micro-environment exposures)	Unlikely to be applied in long-term studies Separation of indoor and outdoor sources needed PM studies were excluded	Not applicable	Not applicable

[a] All spatial resolutions are indicative and need to be interpreted in conjunction with actual land use in a specific study. The Panel preferred to use absolute spatial criteria rather than such terms as address or postal code because the resolution of postal codes varies across and within countries and depends on the number of digits of the postal code. The spatial resolution of a pollution surface was selected based on its capacity to identify within-city contrasts in ambient air pollution.

[b] Validity refers to how well the metric reflects actual pollutant concentrations. Indirect measures of TRAP have limited validity because fleet composition, traffic speed, street configuration, and other factors affect emissions and concentrations (see Section 6.2).

air pollution surface (e.g., a 4 × 4 km grid from a CTM), from a location-specific estimate provided by an LUR model that incorporates buffers of specific radii (e.g., 100 m) around a study subject's geographic location (e.g., home address). The spatial resolution of an LUR was estimated as the radius of the smallest buffer in the model. See Sidebar 6.1 for more details on CTMs, LURs and dispersion models.

To be eligible for inclusion in the review, the air pollution surface considered had to be resolved to ≤5 km (i.e., 5 × 5 km grids or equivalent surface); this corresponds to the upper limit of the neighborhood scale. For measures based on distance, length of road, or traffic density (i.e., indirect traffic measures), the acceptable resolution was set at ≤1 km, the upper limit of the local scale definition (i.e., ≤1,000 m away from a highway or a major road; length or traffic density within buffers of ≤1,000 m from address).

6.4.3.2 Spatial Resolution of the Address

The second key aspect of the exposure assessment is the spatial resolution of the address data of the participants in the epidemiological study. Even with the prerequisite for individual-level epidemiological studies in this review, the address in one study versus another may vary from actual address (i.e., an exact address or a detailed ZIP code for a street segment) to a small area. The Panel thus defined the largest acceptable address resolution as 5 km for air pollutants and 100 m for indirect traffic exposure metrics. In some studies, exact addresses of individuals are not available, but other forms of georeferencing (such as ZIP codes, postal codes, and census areas) are used. The resolutions that these identifiers represent varies by country. Additional information was compiled during the review regarding the typical size of ZIP code tabulation areas, ZIP codes, census tracts, and census blocks in cities, suburban areas, and rural areas in the United States, Canada, several European countries, and Australia. This knowledge was used to assist in selection of studies meeting the spatial resolution criteria. Both the input health and air pollution data and the final epidemiological analyses of data matched using appropriate spatial techniques were required to meet the spatial resolution requirements for inclusion. Many of the epidemiological studies considered for this review relied on considerably better than 5-km resolution for subject geolocation.

The Panel included studies based on residential address, school address, and work address. All these environments may represent a considerable amount of time spent and therefore potential exposure to TRAP. When a study reported associations for multiple addresses (e.g., both work and residential), the Panel selected the estimates for the residential address to increase comparability with other studies. The Panel also accepted studies that calculated a weighted average exposure including residence, school, work, and commuting.

6.4.3.3 Intrinsic Differences Between Methods

Exposure assessment methods employed in epidemiological research differ intrinsically in their specificity to represent TRAP. For example, studies using measures based on distance to road or traffic density are very specific for traffic and were automatically included in the review, provided they met the resolution requirements. Dispersion models and CTMs were also always accepted if they were applied specifically for traffic, provided they met the resolution requirements (maximum 5 km × 5 km grids). Further examination was needed to determine whether to include studies that used CTMs of ambient concentrations, LUR models, or monitoring data.

The evaluation of the traffic contribution in studies using monitoring site data to characterize spatial exposure contrasts is challenging, in particular for the neighborhood scale studies. Most of those studies assign the nearest monitor for participants residing within a certain distance of the monitor or use urban background monitors and apply interpolation methods to assign data from monitoring stations to individual participants. The sphere of influence of background monitoring stations is typically about 3 km to 5 km, dependent on the setting. Studies that assign measured city averages to all participants were excluded for all pollutants because the intra-city contrasts in exposure to TRAP could not be determined. In addition, all PM monitoring studies were excluded because it is difficult to be confident that the major source of any observed PM exposure contrast was due to traffic. For the other measured pollutants, the Panel decided that judgments were to be made as to whether traffic was a major contributor to the exposure contrast revealed from the monitoring data. For all monitoring studies, the Panel required that the majority of the population analyzed lived within 5 km of a monitor, which meant in some instances only a subgroup analysis was used from a given study, if provided. The choice to allow 5 km distance between the residence and the monitor is consistent with the scale used for modeling surfaces. If no information about the distance to monitors was available, the Panel required that the average distance between sites be less than 10 km or that the density of sites be more than one site per 50 km^2.

During the review, the Panel determined that more specific definitions of long-term exposure were needed, particularly for the monitoring studies. As the focus of this review was on health effects of long-term exposure, the measurements needed to reflect an annual average or longer. Exceptions were made for birth outcome and childhood respiratory health (e.g., asthma) studies where trimester average exposures or other early life exposure windows were also appropriate. Some studies were based on short duration measurements (e.g., Jedrychowski et al. 2007, 2009). We excluded these studies, unless there was evidence that the measurements were representative of long-term spatial differences in exposure by simultaneous monitoring over one or more weeks in multiple seasons, adjustments were made

SIDEBAR 6.1 KEY EXPOSURE ASSESSMENT DEFINITIONS

Dispersion Model

A dispersion model is a mathematical model that solves the atmospheric dispersion equations for ambient concentration at a spatial location and point in time using air pollution source emission rate data, meteorological parameters (including wind speed, wind direction, atmospheric stability, and planetary boundary layer height), and other physical characteristics of the geographic setting. The simplest dispersion models provide steady-state solutions of the dispersion equation for a line source (i.e., a roadway) or point source based on empirical parameterization of turbulent diffusion. Given estimates of the number of vehicles per hour and their emissions along a roadway, a dispersion model, like the American Meteorological Society/Environmental Protection Agency Regulatory Model (AERMOD) or Research LINE source (RLINE) model, can estimate the ambient concentrations at locations downwind of the roadways from these vehicle emissions. Most simple dispersion models either simulate chemically inert compounds (EC or primary $PM_{2.5}$ mass) or compounds with simple parameterized chemistry (NO_x to NO_2 conversion).

Chemical Transport Model

Chemical transport models (CTMs) solve the atmospheric dispersion equations at many points in space and time using a three-dimensional spatial grid and with consideration of many chemical reactions and physical processes influencing gases and particles. Emissions rate data and meteorological input data are supplied by separate large-scale models (e.g., the meteorology may come from continental-scale weather prediction models). CTMs may have neighborhood, urban, regional, or global spatial coverage, and predict short-term and long-term ambient concentrations of many gases and particles. An example is the Environmental Protection Agency's (EPA's) Community Multiscale Air Quality (CMAQ) modeling system that is designed to simulate the emissions, chemistry, and physics of the atmosphere.

Land Use Regression Model

Land use regression (LUR) models are regression models designed to estimate air pollutant concentrations in space or in space and time. LUR models are developed using air pollution monitoring data at locations spread over the study area and predictor variables usually obtained through geographic information systems (GIS). Monitoring in the first LUR studies was temporally limited: two to four surveys of typically one or two weeks in duration. Significant predictor variables often include various traffic representations, population density, land use, physical geography (e.g., altitude), and meteorological parameters. Hybrid LUR models incorporate data from other models including dispersion model or CTM concentrations, and satellite remote-sensing aerosol optical depth or column density parameters. LUR methods have been applied successfully to model monthly and annual mean concentrations of NO_2, NO_x, $PM_{2.5}$, and components of $PM_{2.5}$ in different settings, including European and North American cities. The performance of the method in urban areas is typically better or equivalent to geostatistical methods, such as kriging, and dispersion models when the goal is to predict concentrations from all sources. LUR model developers often report the relative importance of covariates, which can help identify the dominant sources in a region. LUR models generally quantify average spatial patterns in concentration (assumed to be potential exposure) with high resolution (50 m to 100 m) for a given period of time. Thus, they are useful for estimating long-term or chronic exposure, but are not predictive of future exposures in response to changes in emissions. In contrast, CTMs and dispersion models have this predictive capability, but typically do not provide the spatial resolution of an LUR model. CTMs, in particular, do not usually offer resolution to a scale finer than 1 km × 1 km.

Buffer

LUR models often use the average or total value of parameters in the area surrounding a point of interest (e.g., a residential address or monitoring location) as covariates (i.e., predictors). The areas (typically circular, though they also may be approximated using raster GIS data and functions) for which parameters are averaged are referred to as buffers. For example, covariates may be developed for the average population density or traffic load within circular buffers within 100 m, 500 m, and 1,500-m radii of a point of interest. LUR developers may use stepwise variable selection to identify the most predictive variables and buffer sizes for the regression model. Indirect measures of traffic exposure including traffic density or road length may also be measured within a buffer from a residence.

Source Apportionment Model

Air pollution source apportionment is the practice of using ambient air pollution data to derive information about pollution sources and their contributions to observed concentrations. Various methods are employed, based on differing amounts of information that can be assumed about the number of polluting sources and their compositions. The Chemical Mass Balance model can be used when information on the relative chemical composition of the principal source types in a region is known. Factor analysis techniques, such as positive matrix factorization, can be used when the pollution sources are not well known. Both methods exploit long records of detailed chemical composition data at monitoring sites to statistically estimate the relative importance of various type of sources in a region.

for measurements made sequentially at different locations, or there was control for meteorological conditions. For example, surfaces generated by averaging mobile monitoring measurements in Oakland and Montreal (Apte et al. 2017; Levy et al. 2014a) were judged acceptable because measurements were made over many days and analyses were done to show that a long-term average was approached with fewer days.

Mobile monitoring is usually only conducted during daytime hours and thus the resulting exposure model predictions are probably biased toward daytime exposures. The

implications of this issue are difficult to assess as over diurnal periods nocturnal reductions in mixing height can increase concentrations, but traffic emissions rise and fall with levels of traffic. Furthermore, all locations in a city are similarly affected by these factors such that exposure patterns and gradients, which are of relevance for the epidemiological analyses, are similar from day to night. In the Netherlands, it was shown that this issue especially affects the level of exposure but less the spatial contrast for different times of the day (Downward et al. 2018). Measurements in the ESCAPE study, on which LUR models were developed, were accepted for the review because three 14-day averages of concentrations in different seasons with temporal adjustment were used to derive an annual mean (Cyrys et al. 2012). Several NO_2 studies using exposure surfaces that used one or two monitoring periods of one to two weeks were accepted on the basis that all sites were measured simultaneously (e.g., Crouse et al. 2015b; Dell et al. 2014; Sbihi et al. 2016) and sampled during representative time periods (Henderson et al. 2007).

The Panel considered LUR models to be similar to dispersion models and CTMs that predict concentration patterns arising from emissions of all sources within the domain. This is because LUR models typically attempt to use a variety of predictors to explain the variability in the traffic-related air pollutants as opposed to strictly traffic-based predictors. In evaluating the relevance of an LUR model it was thus important to consider the extent of the study area and the presence of other sources. For selection of the studies using LUR models into the review, the Panel took an inclusive approach. Models that contained at least one traffic predictor (e.g., traffic intensity or road density) or broader surrogate of traffic (e.g., address density, household density, population density, or impervious surface) were accepted. However, it is important to note that it was not feasible for the Panel to retrospectively evaluate individual LURs with regard to their overall sensitivity to TRAP (see Sidebar 6.2). For example, models that also included green space or other variables representing lack of emission sources with negative regression coefficients (i.e., their presence led to lower TRAP exposure) may also be quite indicative of TRAP exposure gradients. The Panel explored the possibility of refining the LUR model criteria by requiring multiple traffic predictors or evidence that the model predicts clear traffic contrasts (e.g., by comparing slopes across predictors). However, it was determined that application of these additional criteria would be impractical to apply because the required information is reported unevenly across studies.

6.4.4 COMBINATION OF STRATEGIES

A combination of these three strategies was considered by the Panel to be the best approach to select studies that are informative about health effects of TRAP (Table 6.4): Informative studies needed to fulfill requirements for pollutant, exposure assessment method, and spatial resolution of pollution surface and residential address. For the pollutants that were accepted in the review but could be less definitively linked to traffic (e.g., PM_{10}, PM_{coarse}, and $PM_{2.5}$), the Panel applied more stringent criteria for the other two domains. For example, the Panel did not accept PM mass monitoring studies.

The spatial extent of the study area also determines whether a given exposure assessment method likely presents a traffic signal. In general, the larger the study area, the less likely a measured or modeled contrast in pollution is primarily due to traffic emissions (i.e., reflecting local to neighborhood scale contrasts in exposure). Nationwide or large statewide (e.g., California) studies are examples of this challenge for interpretation. If an LUR model with traffic and other predictors were applied in a nationwide study, much of the exposure contrast would likely be due to regional concentration differences and nontraffic air pollutant sources. If the same LUR model were applied in a single metropolitan area, the model may be accepted if it met the other inclusion criteria above. Whether or not to accept the generally large and influential nationwide epidemiological studies was not straightforward, and some of the nationwide studies especially for pollutants other than PM mass could be informative for TRAP if the model primarily included traffic predictors. In general, the Panel included nationwide studies only when area adjustments were made in the epidemiological analyses, as small-scale contrasts related to a traffic signal are more likely to be observed after adjustment for large-scale contrasts is made. If these area adjustments were not made, the paper and its supplements were checked for area- or region-specific effect estimates to include in the review. A nationwide epidemiological study based on a high-resolution dispersion model with only road traffic sources was always included. Sometimes the authors expressed in the paper that the exposure patterns represent regional-scale variation, and the Panel excluded those studies.

The contractor team responsible for the literature search put all nationwide epidemiological studies in the "possibly in" category for the exposure subgroup to discuss and make the final decision using the full text of the paper and the accompanying exposure paper. Some highly influential epidemiological studies employing high-resolution exposure assessment required discussion among the full Panel. In the United States, the nationwide American Cancer Society study, the Six Cities study, the Multi-Ethnic Study of Atherosclerosis and Air Pollution study and the Nurses' Health study included very large study populations over expanded geographic areas (Cohen et al. 2009; Hart et al. 2015; Lepeule et al. 2012; Puett et al. 2009; Turner et al. 2016). Analyses from these and similar large-area studies were therefore only included in the review if adjustment for study area was performed. Statewide epidemiological studies (e.g., Jerrett et al. 2013 in California, United States) required the same treatment, as some states in the United States are bigger than some countries in Europe. Most results from these influential studies were excluded after discussion on the basis that the Panel had low confidence that contrasts in the pollutant levels were driven by traffic to such an extent that the exposure contrast in the population represented

SIDEBAR 6.2 EXAMPLES OF NO_2 AND UFP LUR MODELS

NO_2 LUR models from ESCAPE

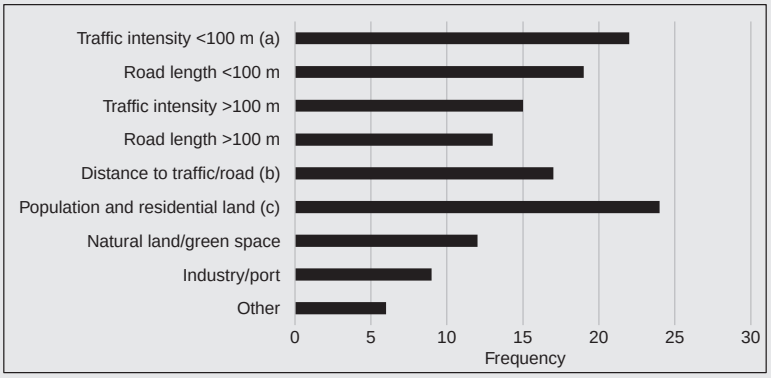
As part of the European Study of Cohorts for Air Pollution Effects (ESCAPE) project, LUR models for annual average NO_2 were developed for 36 study areas in Europe (see Beelen et al. 2013 for details). Traffic, land use, demographic, and geophysical data were used in GIS to provide candidate variables in buffer sizes ranging from 25 m to 5000 m in radius. Separate models were developed for each study area following common protocols for monitoring and model-building. From the large database of possible variables considered in the regression analyses, the final models included two to seven variables (average = four) and the model R^2 ranged from 55% to 92% (median 82%). All the NO_2 models included one or more traffic variables, such as traffic intensity on nearby roads, distance to nearby roads, and traffic intensity in a small buffer around the site.

The frequency of categories of predictor variables in the NO_2 LUR models in all study areas is shown in Sidebar 6.2. Of the 137 predictor variables available for modeling, 86 (63%) were traffic variables. Traffic intensity in buffers smaller than 100 m was the most common traffic variable. All models contained a traffic variable describing small-scale variation, in line with studies that showed that NO_2 concentrations have a large decline in the first 100 m to 200 m near high traffic intensity roads. In addition, most models included traffic variables within a 1,000-m buffer representing larger-area traffic density. Where LUR models include four or five traffic variables and only one or two other variables (e.g., Helsinki, the Netherlands, Munich, and Turin), it is highly likely that they are able to capture the contrast in TRAP exposure across a city. Population density or address density was another common variable, consistent with well documented urban–rural differences related to a variety of sources including traffic and home heating. Although industry and ports are important emission sources of NO_2, few ESCAPE models contained variables representing industry or port emissions. About one third of the models included a variable for natural land or green space, which is considered an important indicator of the lack of air pollution sources in LUR models. Overall, the ESCAPE NO_2 models are important examples of the types of LUR model that met the exposure framework's inclusion criteria.

LUR Models of UFPs

The numbers of LUR models of UFPs being developed for use in assessment of long-term exposure for health studies is growing, and those models have been recently reviewed (Patton et al. 2020). Similar to LUR models for NO_2, developers of LUR models of UFPs tested large numbers (N = 8 to 164) of potential predictors, typically in buffers ranging from 50 m to 3,000 m in radius and included only a small number of variables in the final models. Most UFP LUR models explained less than 50% of spatial variation in UFPs or the natural logarithm of UFPs, which is lower than for most NO_2 and $PM_{2.5}$ models. Nonetheless, many of the models that were identified are being applied in ongoing epidemiological studies.

All of the UFP LUR models identified in the earlier review of LUR models of UFPs included an indicator of traffic as a predictor variable. The traffic variables included measures of traffic intensity (e.g., traffic volume or density) or road length within a buffer, type of road (e.g., major, intersection), and vehicle class (e.g., heavy-duty, bus, car, or motorcycle). Most of the models included a variable related to distance to the nearest road and/or major roads, and the models almost always accounted for traffic intensity or road length. Some models were purely spatial annual averages, whereas others were spatiotemporal models incorporating predictor variables for meteorology, traffic volume at a given time, and factors related to the time of day and week in which a particular measurement was made. Variables related to population density or nontraffic land use (e.g., residential, manufacturing and industry, construction, and commercial land use; ports and airports, rail, or other transportation; and green space, open space, or water) were also often included as predictors in UFP LUR models.



Sidebar 6.2. Frequency of predictor variables in ESCAPE NO_2 LUR models for 36 European study areas. (a) All traffic intensity variables with buffer size <100 m, including traffic intensity on nearest and nearest major road. (b) All variables with distance to a road or traffic, including variables with product of traffic intensity and distance. (c) Population/buildings/residential land/household density. (Source of data: Beelen et al. 2013)

Table 6.4. Combination of Criteria for All Accepted Combinations

Exposure Metric	Exposure Assessment Methods	Spatial Resolution "Pollution Surface"	Spatial Resolution "Address"	Spatial Resolution "Address" for Study Identification	Traffic Contribution to Exposure and Other Considerations[a]
All pollutants from Table 6.1	Dispersion models or CTMs of traffic emissions or traffic-specific source-tracking/ apportionment	≤5 km	≤5 km	Residential address as exact address, neighborhood, census tract or block, or postal code (but not city or county)	Assumed by method
All pollutants from Table 6.1	Dispersion models or CTMs of all sources	≤5 km	≤5 km	Residential address as exact address, neighborhood, census tract or block, or postal code (but not city or county)	Judgement needed (e.g., required area adjustment in epidemiological analysis if spatial extent of the study area was >10,000 km^2, determination of whether exposures met long-term criteria)
All pollutants from Table 6.1	LUR models that contain at least one traffic predictor (e.g., traffic intensity or road density) or broader surrogate of traffic (e.g., address density, household density, population density, impervious surface)	≤5 km	≤5 km	Residential address as exact address, neighborhood, census tract or block, or postal code (but not city or county)	Judgement needed (e.g., required area adjustment if spatial extent of the study area was >10,000 km^2, determining whether exposures met long-term criteria)
All pollutants from Table 6.1 except PM_{10}, PM_{coarse}, and $PM_{2.5}$	Surface, satellite, and personal monitoring	≤5 km; operationalized as up to 5 km between the residence and the monitor, or up to 10 km between monitors, or at least one site per 50 km^2	≤5 km	Residential address as exact address, neighborhood, census tract or block, or postal code (but not city or county)	Judgement needed (e.g., unclear monitor density, determination of whether exposures met long-term criteria)
PM_{10}, PM_{coarse}, $PM_{2.5}$	Surface, satellite, and personal monitoring	Excluded	Excluded	Excluded	Excluded
Indirect traffic measures (metrics based on distance or traffic density)	Objective	≤1,000 m from a highway or a major road	≤100 m	Residential address as exact address or detailed postal code (i.e., street segment)	Assumed by method

[a] In general, the larger the study area, the less likely a measured or modeled contrast in pollution is primarily due to traffic emissions. Therefore, nationwide epidemiological studies were designated as "possibly in" requiring Panel assessment (see text for additional considerations). The spatial resolution of a pollution surface was selected based on its capacity to identify within-city contrasts in ambient air pollution.

differences in TRAP exposure as opposed to differences in ambient air pollution from all sources.

The criteria described above were only used to determine whether the publications would be included in the review. After inclusion and preparation of summary tables, additional criteria described in Chapter 5 were used to determine whether meta-analyses could be conducted. Studies of ambient PM attributed to traffic sources were not combined in meta-analysis with studies of total ambient PM because the exposure contrasts were not comparable. In addition, the differences across studies in exposure assessment methods and definitions of specific components of traffic emissions (e.g., tailpipe and nontailpipe) and indirect measures precluded meta-analyses for ambient PM attributed to traffic sources and for indirect measures.

6.5 APPLICATION OF THE FRAMEWORK

6.5.1 OVERVIEW OF APPLICATION

In summary, to select an epidemiological study for the review, there needed to be evidence that the spatial contrast in exposure was mainly related to traffic sources. This depended on the design and the exposure assessment method. Studies were included that exploited contrast at the local scale but also at the larger neighborhood scales. For the latter, disentangling a traffic signal from other sources was challenging. The exposure framework detailed above was developed to obtain, as confidently and transparently as possible, positive confirmation that exposure contrasts were primarily related to traffic. When there was insufficient information in either the paper reporting the health analysis or an accompanying exposure paper, the study was excluded by the Panel.

The exposure framework was used to support a transparent selection of studies included in the review. In the application of study-selection frameworks some ambiguity is unavoidable. By design the framework used in this assessment was considered by the Panel to be an inclusive approach. In its implementation the contractor team and HEI staff classified the studies identified as definitely included, definitely excluded, and possibly included. The Panel then made a final decision before data extraction by the contractor. A more restricted approach was taken in the evaluation stage and data synthesis by developing an additional classification based on greater traffic specificity. The Panel's framework primarily defines the exposure criteria used to search literature and consider if a study could be included in the review. In Chapter 7 we illustrate that most included studies exceeded the minimum requirements.

The framework was applied to each pollutant or indirect measure individually. It was possible that one exposure metric fulfilled the criteria for inclusion whereas another pollutant or indirect traffic measure did not in the same study. An example would be if one pollutant was assessed by modeling at a fine scale (e.g., NO_2) and another pollutant (e.g., $PM_{2.5}$) was assessed by modeling or monitoring at a larger scale (e.g., Kingsley et al. 2017; Wilhelm et al. 2011). For a study considering both pollutants and indirect measures, it was possible for the available address information to be sufficient for the modeled pollutant but not for the distance to road measure.

6.5.2 GUIDANCE FOR DATA EXTRACTION

In the course of application of the general framework, it was determined that additional guidance was needed to identify which results should be extracted for inclusion in summary tables and potential meta-analyses. First, studies were identified where multiple exposure methods were used with essentially the same health data in one or more papers. When multiple exposure approaches were reported in one paper for the same pollutant, the Panel advised the contractors to extract the results that had higher traffic specificity or were more highly resolved spatially for inclusion.

Second, many studies using distance to major roads or traffic density as an exposure metric reported categorical results for multiple distance categories. In those cases, the Panel suggested the contractors extract data from the groups within about 100 m from the highway or major road because that was likely to be the highest exposed group with enough participants for stable results. If the preferred distance category was not the smallest distance reported (e.g., there were results for <50 m and 50 to 100 m), the contractors also extracted results for smaller distances.

Finally, results from single-pollutant models were prioritized in data extraction given they were required for use in the main meta-analyses. Additionally, effect estimates were extracted for sensitivity analyses from selected multipollutant models (general $PM_{2.5}$ and ozone) or models adjusted for traffic noise, where available, as described in Chapter 5.

6.5.3 DIFFERENCES BETWEEN THE PROTOCOL AND APPLICATION OF THE EXPOSURE FRAMEWORK

The Panel endeavored to apply the a priori defined methods, as outlined in the published review protocol (HEI 2019), however, in practice, refinements to the methods regarding the exposure framework were necessary. These were all based on methodological considerations of the studies being reviewed and independent of these studies' results. The refinements were as follows:

1. Defined a large study domain as >10,000 km^2 or one that included cities more than 100 km apart. In general, the larger the study area, the less likely a measured or modeled contrast in pollution for a given exposure assessment was mainly due to traffic emissions. Consequently, application of the exposure framework was particularly difficult for nationwide or large regional or statewide (e.g., California) studies. To address this challenge, the Panel set specific thresholds for when an area adjustment was required.
2. Defined long-term exposure in a manner that excluded studies based on short duration measurements unless there was evidence that the measurements used for exposure assignments or exposure model development were representative of long-term spatial differences in exposure. For example, simultaneous monitoring over one or more weeks in multiple seasons, adjustments for measurements made sequentially at different locations, or control for meteorological conditions were acceptable methods for ensuring shorter duration measurements were representative of long-term exposure contrasts.
3. Developed more detailed guidance for selecting among epidemiological results when the same paper or series of papers used different exposure models.

4. Created additional traffic specificity criteria to further differentiate between levels of confidence that exposure contrasts in a study reflected differences in TRAP exposure. The use of a traffic-specificity ranking was anticipated in the published protocol (HEI 2019) but not yet developed, and thus is now described below.

6.6 TRAFFIC SPECIFICITY

6.6.1 BACKGROUND

The exposure framework described above specified the general exposure criteria for use in selection of epidemiological studies to be included in the review. The acceptance criteria in this framework were designed to identify studies with a traffic signal in the exposure contrast. A traffic specificity classification was developed to further categorize qualifying studies based on the level of confidence that the reported pollutant signal associated with the outcome(s) represented traffic. The Panel decided that this classification would further differentiate studies according to whether they exhibited moderate or high traffic specificity, given that low traffic specificity studies were already excluded from consideration under the exposure framework. The main intention of this differentiation was to enable subsequent sensitivity analyses during meta-analyses regarding the magnitude and confidence in TRAP health effects. When enough studies were available in the meta-analyses, the comparison of studies with moderate and high specificity informed the confidence ratings assigned to the findings in the overall evaluation of the epidemiological evidence.

Although the exposure framework identified TRAP and other criteria for potential inclusion in the review studies considered were inconsistent in their reporting of the detailed information needed to assess the specific quantitative role of traffic sources. Therefore, rather than restrict study selection to those reporting detailed quantitative information on the role of traffic (which might bias and limit results), the Panel decided to further categorize included studies based on two characteristics. These were already part of the exposure framework but were refined to strengthen the assessment of traffic specificity: (1) the spatial resolution of the air pollution surface and subject address or location, and (2) the role of TRAP sources in the exposure contrast that drives the epidemiological associations.

In practice the assessment of traffic specificity involved consideration of a combination of the exposure metric (e.g., pollutant), the exposure assessment method, and the spatial resolutions and relied on information already collected during screening of studies according to the exposure framework. Furthermore, traffic specificity was assessed for each exposure metric included in a study because studies often used multiple exposure metrics with differing levels of traffic specificity (e.g., $PM_{2.5}$ mass and distance to the nearest road).

6.6.2 CRITERIA CONSIDERED IN THE DETERMINATION OF TRAFFIC SPECIFICITY

Criteria for high traffic specificity exposure assessment were built on the exposure framework to identify studies that were more likely traffic health studies.

6.6.2.1 Exposure Metric

Two main categories of exposure metrics were considered to have the potential to qualify for high traffic specificity: (1) those where the assessment of exposures involved a specific subset of pollutants considered in the review and (2) those where indirect approaches based on road network information (i.e., distance and traffic density measures) were used (Table 6.5). Studies based on either of these were subject to further scrutiny based on spatial resolution and source specificity to determine if they qualified as high traffic specificity.

Traffic-Related Air Pollutants Studies that used one or more of the following pollutants were considered higher in traffic specificity compared to the other pollutants that often come from a wider variety of sources: NO_2, NO_x, NO, CO, EC, BC, BS, PM_{abs} ("soot"), UFPs, particle number concentration, and PM components associated with nontailpipe emissions from traffic (e.g., trace metals from brake and tire wear such as Cu, Fe, and Zn; other nontailpipe PM; or quasi-ultrafine PM). The Panel recognized that the sources represented by these pollutants (traffic, coal, lower quality fuel oil, biomass burning, etc.) will depend on the geographic setting and time period of the study. However, these two factors were not addressed by the traffic specificity ranking because they were already considered in other sensitivity analyses (of the meta-analyses) that compared different study regions (e.g., Europe vs. North America vs. Asia) and older (pre-2008) versus newer studies.

From the outset of this review the Panel indicated that PM mass, except UFPs, would be considered as having lower traffic specificity than other pollutants because of the large number of PM sources and significant secondary formation. If concentrations of PM mass (PM_{10}, PM_{coarse}, and $PM_{2.5}$) used in a study were convincingly assessed pertinent to a TRAP-related source (e.g., tailpipe PM only) and used in meta-analyses, the Panel would have considered them high traffic specificity. However, there were very few of these studies and traffic-specific PM mass was not assessed consistently across studies so no meta-analysis and assignment of the traffic specificity variable were done for these pollutants.

PAH and benzene studies were by default considered to have moderate traffic specificity regardless of the exposure assessment method and spatial resolution because these pollutants have many sources other than traffic that generally have larger contributions to their concentrations and spatial differences.

Table 6.5. Criteria That Must Be Met for an Exposure Metric to Be Considered High Traffic Specificity[a]

Exposure Metric	Exposure Assessment Method	Spatial Resolution of Pollution Surface and Subject Location[b]
More traffic specific pollutants NO_2, NO_x, NO; CO; EC, BC, BS, PM_{abs} ("soot"); selected PM components associated with nontailpipe emissions from traffic (e.g., trace metals from brake and tire wear [e.g., Cu, Fe and Zn], other nontailpipe PM, or quasi-ultrafine PM); UFPs, particle number concentration	Dispersion model or CTM with emission from all sources; dispersion model or CTM with emissions from traffic sources alone; LUR model; hybrid model; traffic-specific source apportionment; dispersion model or CTM with emissions from traffic sources alone; traffic-specific source apportionment	≤1 km
Less traffic specific pollutants PM_{10}, PM_{coarse}, and $PM_{2.5}$ mass, including traffic exhaust PM	Dispersion model or CTM with emissions from traffic sources alone; traffic-specific source apportionment	≤1 km
Least traffic specific pollutants PAH, benzene	No high traffic specificity exposure methods	
Indirect traffic measures Distance to nearest major roadway; traffic density or intensity at a point or within a buffer	Directly measured (in a GIS)	Uses exact address and accurate road data

[a] If the high traffic specificity criteria were not met for an exposure metric in an included study, the exposure metric was classified as moderate traffic specificity.

[b] If unclear, the study was not identified as high resolution. The spatial resolution of interest is the one applied to the actual health analysis.

Indirect Measures of Traffic Exposure assessments using surrogates for traffic, such as distance to nearest major roadway and traffic density within a buffer or at a point, were often carried out with high geographic precision, thus providing the potential for high traffic specificity. In fact, studies using the distance to nearest major roadway or traffic density near a subject's exact address may, in some circumstances, provide the highest traffic specificity. However, without knowing the traffic volumes, the speed and fleet mixture on nearby roadways, and how major roads are defined, there is unavoidable ambiguity in these metrics. In particular, traffic densities are calculated using a variety of methods, which makes results hard to compare among studies. Nevertheless, the Panel deemed that studies that used indirect measures of traffic exposure should be included in the high traffic specificity category if they were performed with high spatial resolution data for roadway geometry and exact addresses for subject locations. Given the potential for high traffic specificity from these exposure assignments, meta-analyses for studies using indirect methods were considered by the Panel. However, this was ultimately not pursued, because the varying definitions across studies precluded such analyses.

6.6.2.2 Source Specificity in Exposure Assessment Methods

Studies that used dispersion models or CTMs to estimate concentrations derived solely from motor vehicle emissions and that carried those concentrations into the epidemiological studies to assess associations with health outcomes were deemed by the Panel to be highly specific to traffic. Similarly, traffic-specific source apportionment results, when used in an epidemiological study, were assumed to result in exposure estimates that were highly specific to traffic. However, very few source apportionment studies (i.e., Basagaña et al. 2016; Lubczyńska et al. 2017, both on neurodevelopment outcomes) met the inclusion criteria because these detailed source studies typically used too few monitoring sites to meet the spatial resolution criteria. These source-specific methodologies were required for the subset of air pollutants less strongly related to traffic (e.g., PM mass) to be classified as high traffic specificity in a given study.

Other exposure methodologies, such as dispersion models or CTMs using emissions from all sources, LUR or hybrid models, were only considered to potentially qualify as high traffic specificity if the pollutant used was considered by the Panel to be very closely related to traffic (e.g., NO_2 was acceptable, but PM mass was not).

Exposure assessment methods that relied exclusively on surface monitoring data were not classified as high traffic specificity because such concentration measurements reflect contributions from all sources. In most such studies the Panel was not able to determine whether a moderate or a high fraction of the spatial variation in concentrations was predominantly from traffic. In cases of ambiguity, the Panel used its discretion to identify whether there was evidence that models of exposure reflected mainly traffic or should be classified as moderate traffic specificity.

6.6.2.3 High Spatial Resolution

High spatial resolution was an essential characteristic of studies with high traffic specificity. The exposure framework's spatial resolution criterion was for spatial resolution ≤5 km. To quality as high specificity, the Panel increased this spatial resolution to ≤1 km in both the air pollution model and the participant's residence (or other location used in the study) and further stressed that the epidemiological analysis had to fully capitalize on this resolution. These refinements helped ensure that the strong spatial gradients in pollution levels from near major roadways to the urban background, and from the urban background to the surrounding rural areas were accurately resolved in a given study's exposure assessment. All else being equal, the Panel had higher confidence that an epidemiological study examined associations of health effects with TRAP if the study captured local scale differences in exposure.

The ≤1 km criterion for all pollutants was selected based on the expert judgment of the Panel and was guided by many observational studies. Examples of geographic areas meeting this 1 km criterion are provided in Table 6.6. In practice, high resolutions will often be demonstrated through use of exact addresses or city block equivalents. Several countries, including Canada, United Kingdom, and the Netherlands, have 6-digit postal codes that meet the ≤1 km criterion because they typically cover one side of a city block. Other countries may also have high resolution postal codes that meet the 1 km criterion (e.g., 9-digit ZIP codes in the United States). However, studies that used postal codes that occasionally met the 1 km criterion, such as those using 5-digit United States ZIP codes, were not considered to have high traffic specificity because most subject geolocations were not assigned with sufficient spatial resolution.

As a general rule, the Panel assumed that administrative units like detailed postcodes had ≤1 km resolution in urban areas and were therefore consistent with high traffic specificity. Small census areas (e.g., United States census block, United Kingdom census output areas, or United Kingdom enumeration district) were only accepted if the study area was predominantly within a city because administrative units tend to increase in physical size in more rural areas. Many of the spatial units typically used in regional or national studies were not considered by the Panel to qualify as high resolution for traffic specificity unless the study provided clear evidence that the spatial resolution was ≤1 km. For example, the European Union local administrative unit #2 (LAU-2) and the United States census block group represent community level scales and did not meet the Panel's criteria.

6.7 SUMMARY AND CONCLUSIONS

Building on the 2010 HEI Traffic Review, the Panel developed a novel exposure framework to transparently define which studies were eligible for inclusion in the current review. Broadly, emissions from motorized traffic may affect air quality at the local, neighborhood, urban, and regional scale. The Panel judged, however, that epidemiological studies focusing on exposure contrasts at the local and neighborhood scale offered the greatest potential in determining exposure derived from TRAP emissions.

The exposure assessment framework included three strategies to determine that a study was sufficiently traffic-specific, namely the selection of traffic-related air pollutants, the exposure assessment method, and the spatial resolution. None of the selected pollutants is fully traffic-specific and therefore the additional requirements outlined in this chapter were needed. The Panel included NO_2, EC, CO, UFPs, PM, and other pollutants and indirect traffic measures (distance and density). For PM mass studies to be selected, more stringent requirements for exposure assessment and study setting were needed (e.g., that were solely based on monitoring data. The Panel also excluded nationwide studies on any pollutant where the primary exposure contrast was due to between-cities variations, rather than within cities).

The Panel developed a traffic specificity indicator (high or moderate) based on stricter criteria for the three elements of the exposure framework. For example, all selected PM_{10} and $PM_{2.5}$ mass studies were considered as moderate traffic specificity. Furthermore, the spatial scale of the pollution surface needed to be within 1 km for high traffic specificity as opposed to only 5 km for the study to be included in the review. As noted in Chapter 7, most included studies also met the stricter high traffic specificity criteria. The Panel developed two tiers of criteria because it thought that only one tier—based on a highly strict set of criteria—would be too restrictive leading to fewer studies for assessment. The Panel concluded that the finding that most studies satisfied the stricter criteria is reassuring. It

Table 6.6. Examples of Spatial Resolution for Geographic Areas Meeting the High Traffic Specificity Criterion

Country	Geographic Area	≤1 km (pollutants)	Exact Address (indirect traffic measures)
United States	9-digit ZIP code	Yes	Yes
	5-digit ZIP code	Yes, but only in cities	No
United Kingdom	Postcode	Yes, but only in cities	Yes, but only in cities
Canada, the Netherlands	6-digit postcode	Yes, but only in cities	Yes, but only in cities

lends confidence that the exposure framework has successfully identified studies that are informative of the impact of TRAP on the selected health outcomes.

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ABBREVIATIONS

AERMOD	American Meteorological Society/ Environmental Protection Agency Regulatory Model
BC	black carbon
BS	black smoke
CO	carbon monoxide
CO_2	carbon dioxide
CMAQ	Community Multiscale Air Quality
CTM	chemical transport models
EC	elemental carbon
EPA	Environmental Protection Agency
GIS	geographic information system
LUR	land use regression
NAAQS	National Ambient Air Quality Standards
NO	nitrous oxide
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
PAH	polycyclic aromatic hydrocarbon
PM_{abs}	PM absorption

$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
PM_{10}	particulate matter ≤10 μm in aerodynamic diameter
PM_{coarse}	particulate matter between 2.5 and 10 μm in aerodynamic diameter
RLINE	Research LINE source model
SOA	secondary organic aerosol
TRAP	traffic-related air pollution
UFPs	ultrafine particles
VOC	volatile organic compound

PART C: FINDINGS FROM SYSTEMATIC LITERATURE REVIEWS OF EPIDEMIOLOGICAL STUDIES

Chapter 7

Literature Search Results

CONTENTS

CHAPTER 7

Literature Search Results

7.1 INTRODUCTION

This chapter gives a general description of the literature search results, including an overview of the number of studies by health outcome category, study design, geographical location, year of publication, exposure assessment method, and traffic specificity. The search strategy is described in Chapter 5. This chapter is followed by separate chapters describing the findings for each health outcome: birth outcomes (Chapter 8), respiratory outcomes (Chapter 9), cardiometabolic outcomes (Chapter 10), and mortality (Chapter 11). In addition, the literature reviews for neurological outcomes are described in Chapters 12 and 13 for children and adults, respectively.

7.2 NUMBER OF STUDIES IDENTIFIED

The screening results are outlined in a flow chart with reasons for exclusion documented at the full-text review level (Figure 7.1). Virtually all studies were identified using the PubMed electronic database. Only 30 and 18 additional records were identified using LUDOK and reference lists from other reviews, respectively. Of those, 24 and 3 studies were relevant to include in the systematic review.

The comprehensive search strategy identified 13,660 unique references for screening; 12,555 were excluded based on clear evidence provided in the studies' title and abstract indicating they are not relevant to the review. We aimed to be inclusive at the screening stage and discussed any uncertainties at the full-text review stage. An additional 537 studies were excluded during the full-text review, with reasons for exclusion documented. The most important reasons for exclusion were that there was insufficient spatial resolution in the exposure assessment or health outcome (N = 105 studies), the study did not include a necessary area adjustment (N = 86 studies), or the study did not meet other inclusion criteria of the exposure framework (N = 51 studies).

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* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

Highlights

- The number of studies on long-term exposure to traffic-related air pollution and health outcomes has more than tripled since the 2010 HEI Traffic Review, although a direct comparison is difficult because of the difference in scope, methods, and criteria for study inclusion.
- Respiratory effects in children (N = 118) and birth outcomes (N = 86) were the most common outcomes included in the review. Fewer studies investigated cardiometabolic effects (N = 57), respiratory effects in adults (N = 50), and mortality (N = 48).
- NO_2 was the traffic-related air pollution exposure indicator that was most widely used.
- About half of the studies reported on indirect traffic measures, such as distance and traffic density, and, although they are informative, the Panel could not combine them for use in meta-analysis.

Of the remaining 570 studies, 353 were included in the systematic review, and an additional 69 were included in the literature reviews for neurological outcomes. An additional 148 studies that satisfied the Panel's inclusion criteria were subsequently excluded due to their health outcomes. The Panel ultimately decided to focus efforts on reviewing the evidence for a selected number of clinical outcomes, rather than trying to review every possible important outcome. Therefore, the Panel opted not to review studies on, for example, lung function, atherosclerosis, hypertension, and some other outcomes initially considered and included in the comprehensive search strategy, as described in Chapter 5 and the review protocol.

The full references of the 353 included studies are listed in Additional Materials 7.1 (available on the HEI website). The list of reviews searched is given in Additional Materials 7.2. The complete list of excluded studies at the full-text review stage with the reasons is given in Additional Materials 7.3.

7.3 CHARACTERISTICS OF THE STUDIES MEETING THE INCLUSION CRITERIA

The number of studies on long-term exposure to traffic-related air pollution (TRAP*) and health outcomes has more than tripled since the 2010 HEI Traffic Review, although a direct comparison is difficult because of the difference in scope, methods, and criteria for study inclusion. Most of the studies

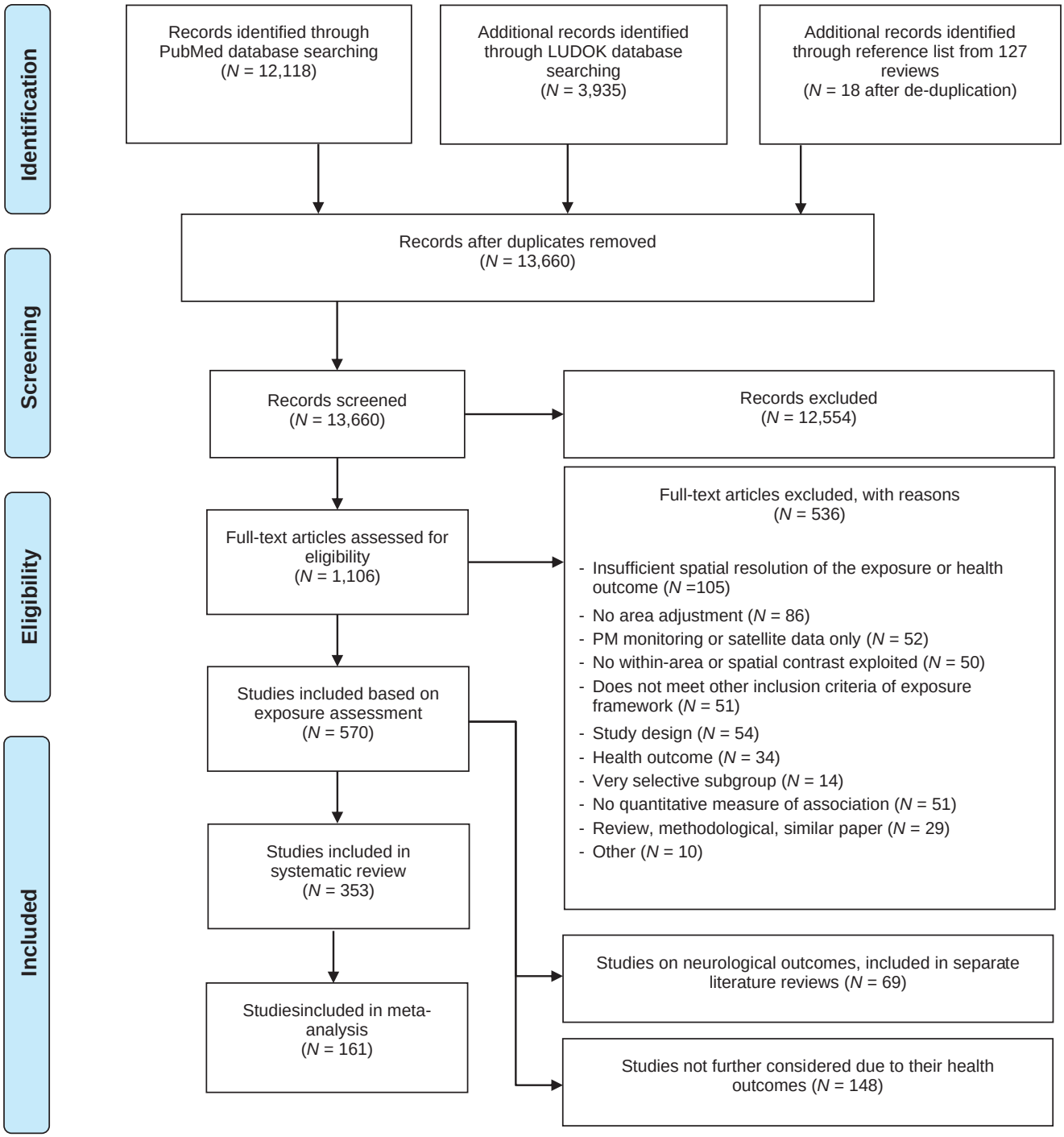

Figure 7.1. PRISMA flowchart of assessment of eligible studies.

were published after 2008 (Figure 7.2). Respiratory effects in children (N = 118 studies, 33%) and birth outcomes (N = 86 studies, 24%) were the most common outcomes included in the review. Fewer studies investigated cardiometabolic effects (N = 57 studies, 16%), respiratory effects in adults (N = 50 studies, 14%), and mortality (N = 48 studies, 13%). These numbers refer to studies fulfilling the inclusion criteria. A sizable number of studies on general air pollution (e.g., on particulate matter ≤2.5 µm in aerodynamic diameter [$PM_{2.5}$]) and mortality in nationwide cohorts were not included because across these large geographic areas it is impossible to disentangle TRAP from other sources.

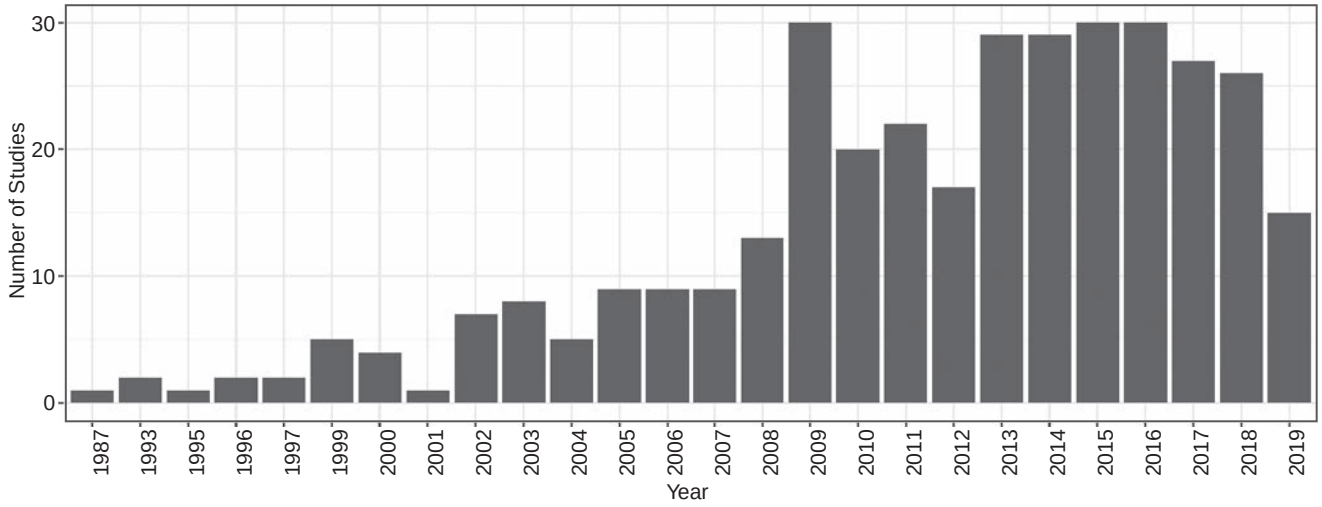

Figure 7.2. Number of studies in the systematic review per year (*N* = 353). 2019 was only half a year, hence the lower bar—until July 2019.

The majority of the available studies used a cohort design (*N* = 224 studies, 63%), and the number of case-control studies and cross-sectional studies was considerably lower (*N* = 41, 12% and *N* = 86 studies, 24%, respectively) (Table 7.1). Land use regression (LUR) was the most common exposure assessment method (*N* = 148 studies, 42%). Most studies met the Panel's criteria for high traffic specificity (*N* = 278 studies, 79%), suggesting that the exposure framework for study inclusion worked as intended. The actual exposure period of most studies happened earlier—before 2010 in the majority of studies (Table 7.2).

Studies were conducted in populations residing in a wide range of countries, although the majority were done in Europe (*N* = 163 studies, 46%) and North America (*N* = 130 studies, 37%), consistent with the systematic reviews conducted as part of the 2021 WHO Air Quality Guidelines (Chen and Hoek 2020; Huangfu and Atkinson 2020). Studies in Asia (predominantly China) emerged more recently (*N* = 41 studies, 12%) as well as studies in Australia or New Zealand (*N* = 16 studies, 4%), but the number of studies from Africa and Central and South America (*N* = 3 studies, 1%) remains limited (Figure 7.3). Beyond there being fewer air pollution studies in general, the small number of studies outside Europe and North America is due to lack of traffic-specific studies. The Panel developed strict inclusion criteria to identify studies with a clear traffic signal in the exposure contrast, which typically required high spatial resolution models.

Nearly half of the studies reported on indirect traffic measures, such as distance and traffic density (*N* = 153 studies, 43%) (Figure 7.4, Table 7.3). Many of the studies (*N* = 167 studies, 47%) included more than one exposure measure indicative of long-term exposure to TRAP, in which case each of these results was included in the Panel's assessment. Nitrogen dioxide (NO_2) was the TRAP exposure indicator most widely used (*N* = 180 studies, 51%). In addition, $PM_{2.5}$, nitrogen oxides (NO_x), and elemental carbon (EC) were commonly used as TRAP exposure indicators (*N* = 78, 67, and 65 studies, respectively, 22%, 19%, and 18%). Particulate matter ≤10 µm in aerodynamic diameter (PM_{10}) was studied less often in the context of TRAP (*N* = 55 studies, 16%) and specific particulate matter (PM) chemical components other than EC were used relatively infrequently (*N* = 30 studies, 8%). There were fewer qualifying studies for carbon monoxide (CO) (*N* = 24 studies, 7%), nitric oxide (NO) (*N* = 17 studies, 5%), coarse particulate matter (PM_{coarse}) (*N* = 16 studies, 5%), and even fewer studies for benzene (*N* = 12 studies, 3%), ultrafine particles (UFPs) (*N* = 10 studies, 3%), and polycyclic aromatic hydrocarbons (PAHs) (*N* = 2 studies, <1%). A limited number of studies adjusted for traffic noise (*N* = 24 studies, 7%), and few studies corrected for general $PM_{2.5}$ or ozone (O_3) (*N* = 46 studies, 13%) (Table 7.3).

7.4 CHARACTERISTICS OF THE STUDIES INCLUDED IN THE META-ANALYSES

The number of studies and, hence, the number of exposure–outcome pairs that were judged by the Panel to be appropriate for including in the meta-analyses was about half of the total number of studies in the systematic review. The reasons for this large reduction stem from criteria detailed in Chapter 5. For example, the Panel was not able to devise an approach to meaningfully meta-analyze exposure–outcome pairs based on road proximity and density ranges. Specifically, there were 88 studies that reported only indirect traffic measures, which were excluded from meta-analysis. From the 265 studies based on traffic-related pollutants, 161 entered a meta-analysis (61%) (Table 7.4). This difference is mainly due to exclusion of studies using

Table 7.1. Number of Studies (% of Studies for This Health Outcome) Included in the Systematic Review per Health Outcome Category and Important Study Features

Health Outcome Category	Number of Studies[a]	Cohort	Case-Control	Cross-Sectional	Publication Date before 2008	Exposure Assessment Method[c]			High Traffic Specificity
						Monitoring	LUR Modeling	Dispersion / CTM	
Birth Outcomes	86[b]	75 (86%)	9 (10%)	0[b] (0%)	10 (12%)	11 (13%)	46 (53%)	17 (20%)	61 (71%)
Respiratory Outcomes—Children	118	50 (42%)	17 (14%)	51 (43%)	35 (30%)	22 (19%)	41 (35%)	17 (14%)	89 (75%)
Respiratory Outcomes—Adults	50	19 (38%)	7 (14%)	24 (48%)	11 (22%)	2 (4%)	15 (30%)	15 (30%)	44 (88%)
Cardiometabolic Outcomes	57	34 (60%)	9 (16%)	14 (25%)	4 (7%)	5 (9%)	23 (40%)	19 (33%)	48 (84%)
Mortality	48	48 (100%)	0 (0%)	0 (0%)	7 (15%)	0 (0%)	25 (52%)	15 (31%)	38 (79%)

CTM = chemical transport model; LUR = land use regression.

[a] The total number of studies was 353, and there were 6 studies reporting more than one health outcome category; hence, the total number of studies by outcome does not add up.

[b] Two studies not displayed with a case cohort design.

[c] Numbers do not necessarily add up to total number of studies because other exposure assessment methods are not displayed.

Table 7.2. Number of Studies (% of Studies for This Health Outcome) Included in the Systematic Review per Health Outcome Category, Publication Year, and Start and End Year of the Exposure Assessment

		Publication Year			Exposure Start Year			Exposure End Year		
Health Outcome Category	Number of Studies[a]	Before 2010	2010–2015	After 2015	Before 2010	2010–2015	After 2015	Before 2010	2010–2015	After 2015
Birth Outcomes	86	16 (19%)	39 (45%)	31 (36%)	79 (92%)	7 (8%)	0 (0%)	62 (72%)	23 27%)	1 (1%)
Respiratory Outcomes—Children	118	51 (43%)	47 (40%)	23 (19%)	117 (99%)	4 (3%)	0 (0%)	94 (80%)	27 (23%)	0 (0%)
Respiratory Outcomes—Adults	50	22 (44%)	14 (28%)	17 (34%)	48 (96%)	4 (8%)	1 (2%)	42 (84%)	10 (20%)	1 (2%)
Cardiometabolic Outcomes	57	8 (14%)	28 (49%)	22 (39%)	53 (93%)	5 (9%)	0 (0%)	38 (67%)	20 35%)	0 (0%)
Mortality	48	13 (27%)	23 (48%)	14 (29%)	48 (100%)	2 (4%)	0 (0%)	34 (71%)	16 (33%)	0 (0%)

[a] The total number of studies was 353. There were 7 studies reporting different exposure start years for the same outcome, and 10 studies had different exposure end years for the same outcome; hence, the total number of studies and percentages by outcome do not add up.

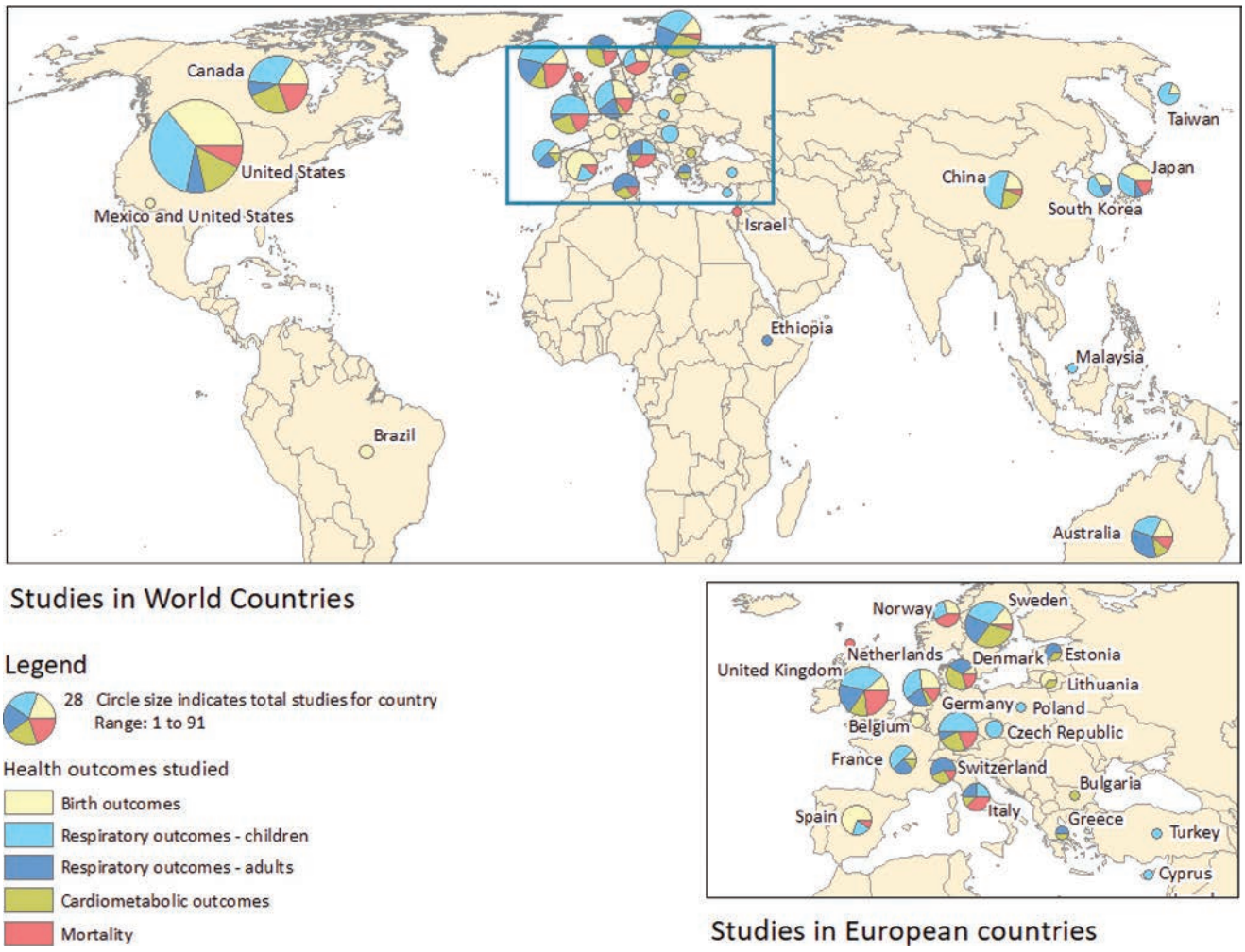

Figure 7.3. Geographical location of the studies in the systematic review (*N* = 353). Multicountry studies not shown (*N* = 21: *N* = 5 birth outcomes, *N* = 4 respiratory outcomes in children, *N* = 4 respiratory outcomes in adults, *N* = 3 cardiometabolic outcomes, *N* = 5 mortality).

an exposure metric analyzed as log-transformed terms, pollutant exposures treated as categories in the epidemiological analyses, or pollutants with less than three studies for a particular health outcome. Also, some studies were excluded from meta-analysis if the same study population and exposure assessment method were used in several publications on the same exposure–outcome pair. In this case, the exposure–outcome pair from the study considered to be the most complete analysis of this population was selected for the meta-analysis. It is important to note that exclusion from the meta-analysis did not discount such study's importance. Their results were included in summary tables and fully considered in the narrative assessments, thus informing the Panel's overall conclusions.

Most meta-analyses involved NO_2 as the TRAP exposure indicator, followed by EC and $PM_{2.5}$ (Table 7.5). Only two meta-analyses were conducted for CO, for term low birth weight and asthma prevalence ever in children, respectively (both with the minimum number of results necessary for a meta-analysis, *N* = 3 studies). Only one meta-analysis was conducted for NO (PTB, *N* = 4 studies), and for copper (Cu) and iron (Fe) (all-cause mortality, *N* = 3 studies). No meta-analyses were possible for the traffic-related pollutants of UFPs, PAH, benzene, or PM_{coarse} because of too few studies (*N* < 3) for any given outcome. Many of the studies in the meta-analysis reported associations of the same outcome with multiple exposure measures related to TRAP (e.g., NO_2, EC). Also, many studies provide results related to more than one outcome, in particular for the mortality outcomes. As such, the assessments are not fully independent.

Overall, some form of a meta-analysis (i.e., pertaining to at least one indicator of TRAP exposure) was possible for all of the broad outcome categories of interest. The fewest number of meta-analyses were conducted for respiratory outcomes in adults (Table 7.4) due to the small number of qualifying studies.

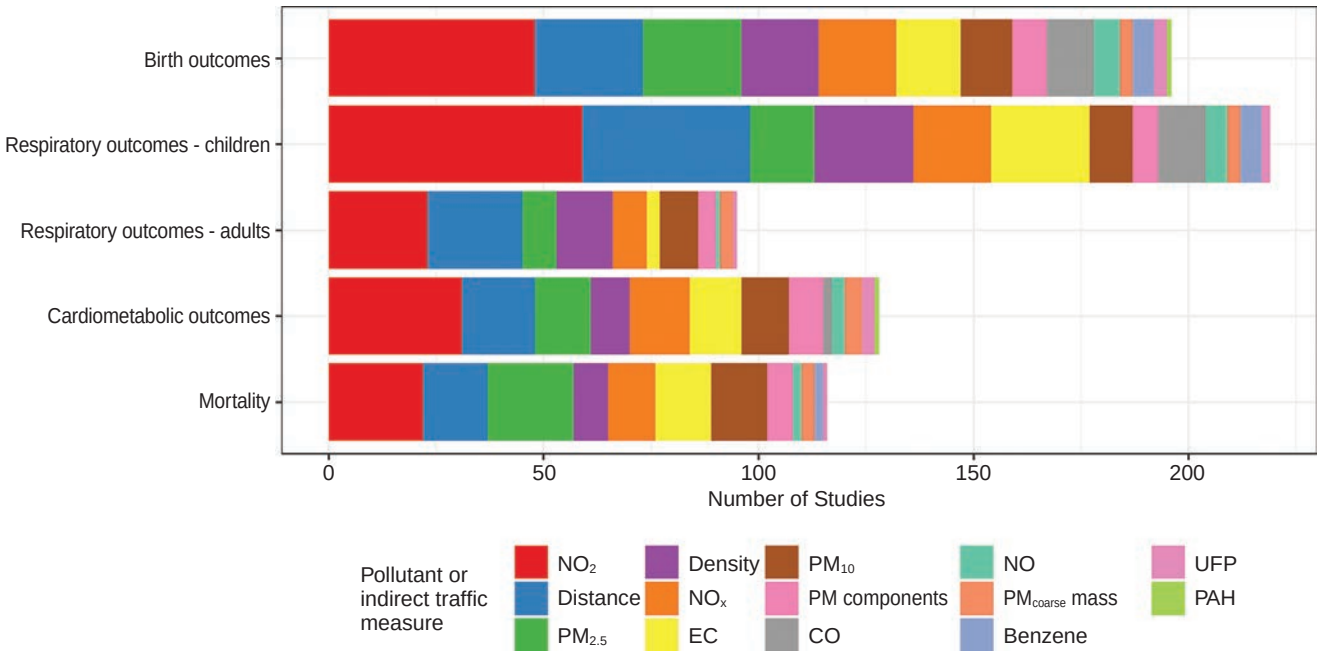

Figure 7.4. Numbers of studies included in the systematic review per health outcome category, colored by pollutant. Studies reporting multiple pollutants or health outcome categories are counted once for each pollutant and category. Pollutants are sorted by overall frequency.

Table 7.3. Number of Studies (% of Studies for This Health Outcome) Included In The Systematic Review Reporting Various Exposure Indicators per Health Outcome Category

Health Outcome Category	Number of Studies	At Least One Indirect Traffic Measure	At Least One Pollutant Measure	Indirect Measures But No Pollutants	Pollutant(s) But No Indirect Traffic Measures	Indirect Traffic Measure(s) and Pollutant(s)	More Than One Pollutant	Noise Adjusted Model
Birth Outcomes	86	33 (38%)	71 (83%)	15 (17%)	53 (62%)	18 (21%)	37 (43%)	5 (6%)
Respiratory Outcomes—Children	118	54 (46%)	80 (68%)	38 (32%)	64 (54%)	16 (14%)	35 (30%)	NA
Respiratory Outcomes—Adults	50	32 (64%)	31 (62%)	19 (38%)	18 (36%)	13 (26%)	12 (24%)	NA
Cardiometabolic Outcomes	57	20 (35%)	48 (84%)	9 (16%)	37 (65%)	11 (19%)	25 (44%)	13 (23%)
Mortality	48	18 (38%)	39 (81%)	9 (19%)	30 (63%)	9 (19%)	19 (40%)	6 (13%)

NA = not assessed.

Table 7.4. Number of Studies Available for Meta-analyses per Health Outcome Category

	N in Systematic Review[a]	*N* with at Least One Pollutant Measure[a]	*N* Contributing to at Least One Meta-analysis[a]	*N* in Meta-analysis for the Most Common Pollutants (percentage of studies for each pollutant–outcome pair that are also in meta-analysis)[a]				
Health Outcome Category				NO_2	NO_x	EC	PM_{10}	$PM_{2.5}$
Birth Outcomes	86	71	38	30 (62%)	13 (72%)	10 (67%)	5 (42%)	15 (65%)
Respiratory Outcomes—Children	118	80	50	43 (73%)	10 (56%)	11 (48%)	8 (80%)	8 (53%)
Respiratory Outcomes—Adults	50	31	13	13 (57%)	3 (38%)	Fewer than three studies	Fewer than three studies	4 (50%)
Cardiometabolic Outcomes	57	48	35	27 (87%)	12 (86%)	10 (83%)	9 (82%)	10 (77%)
Mortality	48	39	26	15 (68%)	7 (64%)	12 (92%)	10 (77%)	16 (80%)

[a] *N* = number of studies. Number of studies do not add up to total because studies may include multiple exposure–outcome pairs.

Table 7.5. Overview of Number of Meta-analyses Conducted for the Selected Health Outcomes

Health Outcome	Subcategory	Total Meta-analyses	NO_2	NO_x	EC	PM_{10}	$PM_{2.5}$
Birth Outcomes	Term low birth weight	6 (+CO)	X	X	X	X	X
	Term birth weight	4	X	X	X		X
	Small for gestational age	4	X		X	X	X
	Preterm birth	5 (+NO)	X	X	X		X
Respiratory Outcomes—Children	Asthma onset[a]	4	X	X	X		X
	Asthma ever[b]	6 (+CO)	X	X	X	X	X
	Active asthma[b]	4	X	X	X	X	
	ALRI[a]	2	X		X		
Respiratory Outcomes—Adults	Asthma onset[a]	1	X				
	ALRI[a]	1	X				
	COPD[a]	3	X	X			X
Cardiometabolic Outcomes	Ischemic heart disease events[a]	5	X	X	X	X	X
	Coronary events[a]	1	X				
	Stroke events[a]	5	X	X	X	X	X
	Diabetes[a]	4	X	X	X		X
	Diabetes[b]	3	X			X	X

Continues next page

Table 7.5 (*Continued*). Overview of Number of Meta-analyses Conducted for the Selected Health Outcomes

Health Outcome	Subcategory	Total Meta-analyses	NO_2	NO_x	EC	PM_{10}	$PM_{2.5}$
Mortality	All-cause	7 (+Cu and Fe)	X	X	X	X	X
	Circulatory	5	X	X	X	X	X
	Respiratory	5	X	X	X	X	X
	Lung cancer	4	X		X	X	X
	Ischemic heart disease	4	X	X	X		X
	Stroke	3	X	X			X
	COPD	1	X				

ALRI = acute lower respiratory infection; COPD = chronic obstructive pulmonary disease.

[a] Incidence.

[b] Prevalence.

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MATERIALS AVAILABLE ON THE HEI WEBSITE

Additional Materials 7.1 to 7.3 contain supplemental material not included in the main report. They are available on the HEI website at *www.healtheffects.org/publications.*

Appendices

7.1 List of Included Studies (*N* = 353)

7.2 List of Reviews and Other Documents Searched for Additional References (*N* = 127)

7.3 List of Excluded Studies with Reason (*N* = 536)

ABBREVIATIONS

ALRI	acute lower respiratory infection
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CTM	chemical transport model
Cu	copper
EC	elemental carbon
Fe	iron
LUR	land use regression
NO	nitric oxide
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
O_3	ozone
PAHs	polycyclic aromatic hydrocarbons
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 µm in aerodynamic diameter
PM_{10}	particulate matter ≤10 µm in aerodynamic diameter
PM_{coarse}	particulate matter between 2.5 and 10 µm in aerodynamic diameter
PTB	preterm birth
TRAP	traffic-related air pollution
UFPs	ultrafine particles

PART C: FINDINGS FROM SYSTEMATIC LITERATURE REVIEWS OF EPIDEMIOLOGICAL STUDIES

Chapter 8

Traffic-Related Air Pollution and Birth Outcomes

CONTENTS

CHAPTER 8

Traffic-Related Air Pollution and Birth Outcomes

8.1 SUMMARY

A large number of studies reported associations between traffic-related air pollution (TRAP*) and birth outcomes (N = 86); they were selected using the HEI Panel's exposure-assessment framework. The number of studies of TRAP and birth outcomes has increased greatly since the publication of the 2010 HEI Traffic Review, which included only four studies on birth outcomes. Outcomes in the current review included preterm birth and three measures of fetal growth and growth restriction—low birth weight (categorical), birth weight (continuous), and small for gestational age. The Panel restricted the analyses to studies of full term birth weight (greater than or equal to 37 weeks gestation) and full term low birth weight to disentangle the effects of TRAP on growth restriction from the effects on gestational age.

The majority of studies of TRAP and birth outcomes were conducted in North America and Europe, and most used a cohort study design; these included many that leveraged data from very large birth registry studies. Studies ranged in sample size from several hundred in the smaller birth cohorts to up to 1.2 million for the larger birth-registry-based studies. Study populations were followed for periods between 1989 and 2017, with most of the studies starting enrollment before or in 2008. Although data on individual and area-level indicators of socioeconomic status were typically available across studies, data on individual-level risk factors such as maternal prepregnancy body mass index (BMI) and smoking—both a priori deemed by the Panel to be important potential confounders for TRAP and the selected birth outcomes—were typically unavailable for studies based on birth registry data.

Across all studies, exposure assessment was largely based on land use regression (LUR) models or on dispersion or chemical transport models (dispersion/CTM). Several of the mainly older preterm birth and term low birth weight studies used only surface monitoring. Nitrogen dioxide (NO_2) was the most studied pollutant, followed by particulate matter ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$) for term birth weight, term low birth weight, and small for gestational age and nitrogen oxides (NO_x) for preterm birth. The number of studies (three or more) required to perform meta-analyses was not met for other fractions of PM, including metals and benzene. As with other outcomes, meta-analyses were also not conducted for the indirect measures of distance to roads and traffic density; their results are included in summary tables

Highlights

- This is a systematic review of 86 studies examining the effects of traffic-related air pollution on birth outcomes. Outcomes in the current review included preterm birth and three measures of fetal growth and growth restriction—low birth weight (categorical), birth weight (continuous), and small for gestational age. Studies of birth weight were restricted to births at greater than or equal to 37 weeks of gestation. The primary focus was on exposure during the entire pregnancy window, although trimester-specific associations were also included, where available.
- The majority of studies of traffic-related air pollution and birth outcomes were conducted in North America and Europe and used a cohort design. Many studies used birth registry data and therefore lacked potentially important confounder information on lifestyle factors, such as maternal smoking during pregnancy and prepregnancy body mass index.
- The most frequently studied pollutants were NO_2, followed by $PM_{2.5}$. Exposure assessment was largely based on land use regression, or dispersion or chemical transport models.
- The summary estimates showed that $PM_{2.5}$ was most clearly associated with measures of fetal growth restriction, which was also supported by consistent associations with PM_{10}. Associations for preterm birth were largely null, although the few traffic-$PM_{2.5}$ and indirect traffic measure studies supported an association.
- The Panel concluded that there was an overall moderate level of confidence in the presence of an association between traffic-related air pollution and term low birth weight (categorical outcome) and small for gestational age, and low confidence for term birth weight (continuous outcome) and preterm birth.

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* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

and are fully considered in the narrative assessment. Studies evaluating exposure over the entire pregnancy formed the main body of evidence, as fewer studies included trimester-specific results. Where available, results for trimester-specific associations were also reported in the narrative assessment.

Table 8.1 summarizes the evidence for associations between TRAP and the selected birth outcomes, including results from the meta-analyses, narrative assessments, and the Panel's confidence assessments using the modified Office of Health Assessment and Translation (OHAT) method. Based on the

Table 8.1. Summary of the Confidence in the Evidence for an Association Between TRAP and Birth Outcomes (Exposure Window: Entire Pregnancy)[a]

Pollutant	Term Low Birth Weight	Term Birth Weight[b]	Small for Gestational Age	Preterm Birth
Meta-analytic Summary Estimate and Narrative Assessment to Assess Confidence in the Presence of an Association with TRAP				
NO_2	1.01 (0.99 to 1.03)	−3.2 (−11.0 to 4.6)	1.00 (0.98 to 1.02)	1.00 (0.96 to 1.04)
	N = 12	*N* = 8	*N* = 11	*N* = 14
NO_x	1.02 (1.01 to 1.03)	−3.4 (−11.7 to 4.8)	Fewer than three studies	1.03 (0.90 to 1.17)
	N = 5	*N* = 5		*N* = 6
EC	1.01 (0.99 to 1.04)	−2.6 (−6.1 to 0.9)	1.02 (0.92 to 1.14)	1.02 (0.97 to 1.07)
	N = 5	*N* = 4	*N* = 3	*N* = 5
$PM_{2.5}$	1.11 (1.03 to 1.20)	−17.3 (−33.2 to −1.5)	1.09 (1.04 to 1.14)	0.99 (0.90 to 1.09)
	N = 7	*N* = 6	*N* = 4	*N* = 4
Narrative assessment	Sizable number of large birth cohorts, mostly in North America and Europe with high traffic specificity. Associations found for NO_X and $PM_{2.5}$; indirect traffic measures showed mostly null associations.	Modest number of large birth cohort and case-control studies, mostly in North America and Europe and with high traffic specificity. Many studies had high risk of bias (mainly birth registries). Strongest associations with $PM_{2.5}$; other pollutants, while trending in the expected direction, were much closer to the null; mostly null results for the indirect traffic measures.	Modest number of large birth cohort and case-control studies, mostly in North America and Europe. Consistent associations across $PM_{2.5}$ and PM_{10}, supported by distance to roadways studies.	Sizable number of large birth cohort and case-control studies, mostly in North America and Europe with high traffic specificity. Many studies had high risk of bias (mainly birth registries). Associations largely null for the main pollutants, though the few traffic-PM and distance to roadway studies support an association. Clear associations with NO_2 exposure in the third trimester.
	Moderate	**Low**	**Moderate**	**Low**
Modified OHAT Assessment to Assess Confidence in the Quality of the Body of Evidence				
NO_2	High	Low	Moderate	Low
NO_x	Moderate	Low	Fewer than three studies	Very low
EC	Moderate	Low	Very low	Low
$PM_{2.5}$	Moderate	Moderate	Low	Low
TRAP	**Moderate**	**Low**	**Moderate**	**Low**
Overall Assessment Combining the Narrative Assessment and Modified OHAT Assessment				
TRAP	**Moderate**	**Low**	**Moderate**	**Low**

EC = elemental carbon; *N* = number of studies; NO_2 = nitrogen dioxide; NO_x = nitrogen oxides; OHAT = Office of Health Assessment and Translation; $PM_{2.5}$ = particulate matter ≤2.5 µm in aerodynamic diameter; PM_{10} = particulate matter ≤10 µm in aerobic diameter.

[a] The table presents only the four pollutants most widely used. The individual pollutants are considered as indicators of the TRAP mixture. Relative risks (RRs) and 95% confidence intervals (CIs) are expressed per 10-, 20-, 1- and 5-µg/m^3 increments for NO_2, NO_x, EC, and $PM_{2.5}$, respectively.

[b] Term birth weight effect estimates represent the mean difference expressed in grams instead of RRs.

results of the meta-analysis, there were notably consistent associations of $PM_{2.5}$ exposure over the entire pregnancy with all three fetal growth outcomes: the summary relative risk (RR) was 1.11 (95% confidence interval [CI]: 1.03–1.20) for term low birth weight and 1.09 (1.04–1.14) for small for gestational age, and a mean difference in term birth weight of –17.3 (–33.2 to –1.5) grams per 5-μg/m^3. Meta-analysis showed null associations for pregnancy $PM_{2.5}$ with preterm birth (0.99; 0.90–1.09); however, the few traffic-PM studies available (e.g., on-road diesel or gasoline and primary PM ≤0.1 μm in aerodynamic diameter [$PM_{0.1}$]) were indicative of an association. PM ≤10 μm in aerodynamic diameter [PM_{10}] exposure during entire pregnancy was also associated with small for gestational age and suggestive for term low birth weight in meta-analysis.

Associations for the other meta-analyzed traffic-related air pollutants, including NO_2, NO_x, and elemental carbon (EC), with all four birth outcomes were mostly null, with the exception of an association of NO_x with term low birth weight (1.02; 95% CI: 1.01–1.03 per 20-μg/m^3). With the exception of $PM_{2.5}$ and PM_{10}, most studies were rated as high traffic specificity. Based on the narrative assessment, the Panel judged that there was either low or moderate confidence in the presence of an association between TRAP and the selected birth outcomes.

For the modified OHAT assessment, the confidence in the quality of the body of evidence for TRAP and birth outcomes was initially rated as moderate because studies used exclusively cohort and case-control designs. Confidence was most commonly downgraded due to imprecision and risk of bias. The decision to downgrade on imprecision was based on wide confidence intervals, which clearly included unity. Risk of bias was rated as low to moderate in the confidence assessment for most domains, with the exception of confounding. Most of the included birth outcome studies used birth registry data, which tended not to have data on lifestyle factors that the Panel determined to be important potential confounders, including maternal smoking during pregnancy and prepregnancy BMI. As a result, those studies were rated as high risk of bias for potential confounding, which reduced confidence in the quality of the body of evidence, particularly for term birth weight and preterm birth. For term low birth weight, there was also some evidence for negative confounding, where adjusting for BMI (and smoking) drove associations further from the null. Evidence was also downgraded for term birth weight and preterm birth based on unexplained inconsistency. The modified OHAT assessment resulted in a final judgement of moderate confidence for term low birth weight and small for gestational age, and low confidence for term birth weight and preterm birth.

Combining the narrative and modified OHAT assessments, the Panel concluded that there was an overall moderate level of confidence in the evidence for an association between TRAP and term low birth weight and small for gestational age, and low confidence for term birth weight and preterm birth.

INTRODUCTION

In evaluating the evidence on the relationship between TRAP exposure and birth outcomes, the Panel focused on two principal pathways—the first centered on TRAP-related effects on fetal growth and the second on effects on length of gestation. For fetal growth (Sections 8.3–8.5), the Panel included three primary outcomes: (1) term low birth weight, dichotomized as birth weight less than 2,500 grams among births greater than or equal to 37 weeks of gestation; (2) term birth weight, defined as continuous birth weight (grams) among births greater than or equal to 37 weeks of gestation and; (3) small for gestational age, defined as birth weight below the 10th percentile for gestational age and sex according to national growth curves. TRAP-related associations with these different but related measures of fetal growth have slightly different implications. Continuous birth weight, a potentially more sensitive endpoint than dichotomous low birth weight, might enable detection of more subtle TRAP-related effects than does low birth weight. However, low birth weight has more clinical significance as an endpoint, with well-recognized health outcomes resulting from growth restriction, such as a higher risk for metabolic conditions, adverse neurodevelopment, and at the extreme, infant mortality (Hack et al. 1995; McCormick 1985; Nobili et al. 2008). Because fetal growth is directly related to gestational age, restricting to term birth weight and term low birth weight is essential for disentangling TRAP-related associations with gestational age from growth restriction. Finally, small for gestational age, an outcome that, by definition, accounts for gestational age, also indicates intrauterine growth restriction that can occur across the birth weight spectrum—in other words, a baby does not have to have low birth weight (<2,500 grams) to be at a low birth weight for gestational age. This may also be considered to be a more sensitive endpoint than low birth weight, especially in studies of women from diverse locations, conditions, or racial or ethnic backgrounds that have different birth weight norms (Kierans et al. 2008).

The second pathway centered on the effects of TRAP on length of gestation and included one primary outcome: preterm birth, dichotomized as birth less than 37 weeks gestation (Section 8.6).

Studies evaluating exposure over the entire pregnancy formed the main body of evidence, as fewer studies included trimester-specific results. Where available, trimester-specific results were included as supporting evidence, providing an opportunity to assess potentially critical exposure windows with respect to the specific birth outcomes. We use the term RR to describe effect estimates as it is easier to communicate in a consistent manner, even if in some of the included studies it would be technically more correct to refer to an odds ratio.

Each section (8.3–8.6) starts with a general description and characterization of the available literature reporting on

associations of TRAP with each respective birth outcome. Results of the primary meta-analyses of associations with individual traffic-related air pollutants (primarily NO_2, NO_x, EC, and $PM_{2.5}$) follow, as well as an examination of associations with indirect measures of traffic (distance to major roadways, traffic density) and a more general narrative assessment of the literature. Finally, a modified OHAT assessment of confidence, including a risk of bias assessment on the body of evidence, is provided for each of the outcomes.

The chapter concludes with an overall discussion of the evidence, including a summary of the main findings for each endpoint, findings in relation to other assessments, strengths and limitations, and unanswered questions and future directions for research.

8.3 TERM LOW BIRTH WEIGHT

8.3.1 STUDY SELECTION AND DESCRIPTION

In total, 25 studies investigated associations between TRAP or indirect traffic measures (i.e., distance and density) and term low birth weight—a categorical measure of birth weight at gestational age greater than or equal to 37 weeks—for studies that examined exposure during the entire pregnancy (Table 8.2 and Appendix Table 8A-3 [available on the HEI website]). Of these, 22 studies reported associations of term low birth weight with individual traffic-related air pollutants, 14 studies reported associations with indirect traffic measures (traffic density, distance to roadway), and 11 studies reported associations with both. Eleven studies estimated associations with exposure during specific trimesters of pregnancy (Appendix Table 8A-1), providing an opportunity to assess a potential window of vulnerability during pregnancy to TRAP exposure.

Most of the TRAP and term low birth weight studies used a cohort study design; two studies used a case-control design, and one used a case-cohort design. Many of the studies were based on birth registry data. Studies were geographically distributed across North America (Canada, U.S.) and Europe (Denmark, France, Germany, Greece, Hungary, Italy, Lithuania, the Netherlands, Norway, Spain, Sweden, U.K.), with several also in South America (Brazil) and Asia (Japan). Studies were also distributed over time, encompassing years of birth as early as 1989 and as late as 2017. There was a wide range of study sample sizes, ranging from N = 3,292 to 1,359,284 participants. Larger samples were mainly based on birth registry data. Exposure was mainly assessed using LUR or dispersion/CTM. All studies published before 2008

SIDEBAR 8.1 SUMMARY OF CRITICAL CONSIDERATIONS REGARDING THE SELECTED BIRTH OUTCOMES AND STUDIES

- The Panel included only studies of dichotomous low birth weight and continuous birth weight that were restricted to full term births (gestational age greater than or equal to 37 weeks). This was to disentangle TRAP-related associations with growth restriction from associations with gestational age, which could also be driving associations with reduced birth weight. Associations with length of gestation are assessed in studies of preterm birth.
- Studies evaluating exposure over the entire pregnancy formed the main body of evidence, as fewer studies included trimester-specific results. When available, the Panel considered trimester-specific exposure to TRAP, providing an opportunity to assess potentially sensitive exposure windows during pregnancy.
- Many of the birth outcome studies used data from birth registries. Although these studies were not considered as prospective cohort studies (e.g., no prospective follow-up was conducted), historical data on air pollution exposure allowed for designation of these studies as retrospective cohort studies.
- The use of birth registries minimized selection bias resulting from factors that influence inclusion and participation in a study that are also associated with exposure and outcome.
- Birth registry data typically do not include (or have poor quality) data on some potentially important lifestyle factors. For this review the Panel considered two variables as important potential confounders that were not available in most registry data: maternal smoking during pregnancy and prepregnancy BMI. The absence of data on these potentially important confounders reduced confidence in the quality of the body of evidence for some birth outcomes. However, it should be noted that all studies did adjust for socioeconomic status, which is likely to be a mediator for associations of TRAP and maternal smoking during pregnancy and prepregnancy BMI; inclusion of socioeconomic status would therefore reduce confounding by these other confounders.
- Many women move during pregnancy. Not accounting for a change in exposure status over the course of pregnancy may lead to bias from the resulting exposure misclassification. The Panel considered it important to account for residential mobility in all birth outcome studies.

Table 8.2. Key Study Characteristics of Articles Included in the Systematic Review for Term Low Birth Weight—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Estimate (95% CI)[c]	Increment
Brauer 2008	BC 99/02 Birth Cohort	Cohort	Vancouver, British Columbia, Canada	1999–2002	70,249	LUR	NO_2	31.6	**0.97 (0.89–1.05)**	10 µg/m^3
							NO	30.7	1.01 (0.96–1.07)	10 µg/m^3
							$PM_{2.5\ abs}$	1.6	**1.00 (0.95–1.07)**	1 1×10^{-5}/m
							$PM_{2.5}$ mass	4.0	**1.03 (0.99–1.07)**	1 µg/m^3
Coker 2015	LA County Birth Registry 95/06	Cohort	Los Angeles County, California, United States	1995–2006	1,359,284	LUR	$PM_{2.5}$ mass	17.04	**1.05 (1.03–1.08)**	1.96 µg/m^3
Dadvand 2014	Barcelona Birth Cohort	Cohort	Barcelona, Spain	2001–2005	6,438	LUR	NO_2	55.5	**1.05 (0.94–1.17)**	16.8 µg/m^3
							NO_x	102.8	**1.05 (0.96–1.14)**	41.3 µg/m^3
							$PM_{2.5\ abs}$	3.1	**1.16 (0.97–1.39)**	1.1 1×10^{-5}/m
							PM_{10} mass	39.2	**1.16 (0.98–1.37)**	3.9 µg/m^3
							PM_{coarse} mass	22.3	1.11 (0.91–1.35)	2.3 µg/m^3
							$PM_{2.5}$ mass	16.9	**1.17 (0.98–1.39)**	3.1 µg/m^3
Dedele 2017	Kaunas Birth Outcomes 07/08	Cohort	Kaunas, Lithuania	2007–2008	3,292	Dispersion/ CTM	NO_2	16.8–24.2	**1.31 (0.81–2.10)**	10 µg/m^3
Gehring 2014	BC 99/02 Birth Cohort	Cohort	Vancouver, British Columbia, Canada	1999–2002	68,238	LUR	NO_2	33.5	0.97 (0.89–1.05)	10 µg/m^3
							NO	23.0	1.02 (0.96–1.07)	10 µg/m^3
							$PM_{2.5\ abs}$	1.6	1.03 (0.97–1.09)	1 1×10^{-5}/m
							$PM_{2.5}$ mass	5.5	1.02 (0.98–1.06)	1 µg/m^3
Ghosh 2012	LA County Birth Registry 95/06	Cohort	Los Angeles County, California, United States	1995–2006	209,843	LUR	NO_2	27.8	**1.04 (1.00–1.08)**	10 ppb
							NO	32.9	1.02 (1.01–1.04)	
							NO_x	60.4	**1.02 (1.00–1.03)**	

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Table 8.2 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Term Low Birth Weight—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Estimate (95% CI)[c]	Increment
Habermann 2014	Sao Paulo Birth Registry 06	Case-control	Sao Paulo, Brazil	2006	11,586	LUR	PM_{10} mass	39.1	0.86 (0.76–0.96)	40.4–108.2 vs. <35.3 μg/m³
									0.88 (0.79–0.98)	37.0–40.4 vs. <35.3 μg/m³
									0.93 (0.83–1.03)	35.3–37.0 vs. <35.3 μg/m³
Hjortebjerg 2016	DNBC	Cohort	Denmark	1996–2002	75,166	Dispersion/ CTM	NO_2	11.0	**0.91 (0.79–1.04)**	10 μg/m³
Kashima 2011	Shizuoka Seirei Birth Study 97/08	Cohort	Shizuoka, Japan	1997–2008	11,726	LUR	NO_2	29.2	**0.85 (0.70–1.04)**	10 μg/m³
Kingsley 2017	Rhode Island Birth Outcomes	Cohort	Providence, Rhode Island, United States	2002–2012	56,633	LUR	BC	0.52	**1.01 (0.93–1.10)**	0.11 μg/m³
							$PM_{2.5}$ mass	9.5	**1.05 (0.84–1.29)**	2.5 μg/m³
Laurent 2013	South Coast Births 97/06	Cohort	Los Angeles and Orange Counties, California, United States	1997–2006	68,303	LUR	NO_2	28.03	0.94 (0.86–1.02)	9.34 ppb
							NO_x	59.93	0.98 (0.91–1.06)	25.24 ppb
						Dispersion/ CTM	CO	0.10	**0.96 (0.90–1.04)**	0.08 ppm
							Traffic $PM_{2.5}$	4.25	0.99 (0.92–1.06)	1.36 μg/m³
Laurent 2014	LA County Birth Registry 01/08	Cohort	Los Angeles County, California, United States	2001–2008	960,945	Surface monitoring	NO_2	26.19	**1.01 (1.00–1.02)**	7.36 ppb
						Dispersion/ CTM	EC	1.2703	1.02 (1.01–1.02)	0.4380 μg/m³
							$PM_{2.5}$ mass	9.0466	1.02 (1.02–1.03)	2.8762 μg/m³
							$PM_{2.5}$ diesel	1.8911	1.02 (1.01–1.02)	0.6903 μg/m³
							$PM_{2.5}$ gasoline	0.7470	1.03 (1.02–1.04)	0.2908 μg/m³
							$PM_{2.5}$ Cu	0.0055	1.01 (1.00–1.02)	0.0023 μg/m³
							$PM_{2.5}$ Fe	0.2784	1.02 (1.01–1.03)	0.0836 μg/m³
							$PM_{0.1}$	1.1302	1.03 (1.02–1.03)	0.4271 μg/m³

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Table 8.2 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Term Low Birth Weight—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Estimate (95% CI)[c]	Increment
Laurent 2016b	California Birth Registry 01/08	Case-cohort	California, United States	2001–2008	396,720	Dispersion/CTM	NO_x	6.110	**1.00 (0.99–1.01)**	6.1 ppb
							CO	59.36	**1.00 (0.98–1.01)**	60.63 ppb
							EC	1.537	**1.01 (0.99–1.03)**	1.265 µg/m^3
							$PM_{2.5}$ mass	14.70	**0.99 (0.97–1.00)**	8.225 µg/m^3
							$PM_{2.5}$ onroad diesel	0.459	1.02 (1.00–1.05)	0.397 µg/m^3
							$PM_{2.5}$ onroad gasoline	0.356	1.04 (1.01–1.08)	0.385 µg/m^3
							$PM_{2.5}$ Zn	0.004	1.00 (0.98–1.01)	0.002 µg/m^3
							Primary $PM_{0.1}$	1.715	1.00 (0.98–1.01)	1.359 µg/m^3
							PNC <100 nm	5,994	1.00 (0.99–1.01)	6,444 particles/cm^3
Lavigne 2016	BORN Ontario	Cohort	Ontario, Canada	2005–2012	818,400	LUR	NO_2	15.89	0.99 (0.99–0.99)	9 ppb
Madsen 2010	Oslo Birth Registry 99/02	Cohort	Oslo, Norway	1999–2002	25,229	Dispersion/CTM	NO_2	32.0	0.7 (0.5–1.0)	>38.1 vs. <20.3 µg/m^3
									0.7 (0.5–1.0)	32.1–38.0 vs. <20.3 µg/m^3
									0.8 (0.6–1.1)	20.3–32.0 vs. <20.3 µg/m^3
							PM_{10} mass	13.2	0.7 (0.5–0.9)	>16.2 vs. <10.7 µg/m^3
									0.8 (0.6–1.1)	13.3–16.2 vs. <10.7 µg/m^3

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Table 8.2 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Term Low Birth Weight—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Estimate (95% CI)[c]	Increment
									0.8 (0.8–1.1)	10.7–13.2 vs. <10.7 μg/m^3
							$PM_{2.5}$ mass	11.5	0.7 (0.5–1.0)	>14.1 vs. <9.7 μg/m^3
									0.9 (0.6–1.2)	11.6–14.1 vs. <9.7 μg/m^3
									0.9 (0.7–1.2)	9.7–11.5 vs. <9.7 μg/m^3
Nieuwenhuijsen 2019	HELIX	Cohort	Multiple cities, multiple countries	1997–2017	31,458	LUR	NO_2	21.4	1.2 (1–1.4)[d]	0.4 μg/m^3
							$PM_{2.5\ abs}$	1.4	1.2 (1–1.4)[d]	0.4 1×10^{-5}/m
							PM_{10} mass	18.8	1.2 (1–1.5)[d]	0.4 μg/m^3
							$PM_{2.5}$ mass	13.4	1.2 (1–1.5)[d]	0.3 μg/m^3
Pedersen 2013	ESCAPE	Cohort	Multiple cities, multiple countries	1994–2011	61,452	LUR	NO_2	26.2	**1.09 (1.00–1.19)**	10 μg/m^3
							NO_x	45.5	**1.04 (0.97–1.11)**	20 μg/m^3
							$PM_{2.5\ abs}$	1.7	**1.17 (0.95–1.39)**	1 1×10^{-5}/m
							PM_{10} mass	25.4	**1.16 (1.00–1.35)**	10 μg/m^3
							PM_{coarse} mass	9.1	1.01 (0.88–1.15)	5 μg/m^3
							$PM_{2.5}$ mass	16.5	**1.18 (1.06–1.33)**	5 μg/m^3
Pedersen 2016	ESCAPE	Cohort	Multiple cities, multiple countries	1994–2008	31,173	LUR	$PM_{2.5}$ Cu	3.4	1.08 (0.81–1.44)	5 ng/m^3
							$PM_{2.5}$ Fe	104.0	1.14 (0.92–1.41)	100 ng/m^3
							$PM_{2.5}$ Zn	14.8	1.23 (0.98–1.54)	10 ng/m^3
Poirier 2015	Halifax Birth Outcomes	Cohort	Halifax, Canada	2008–2012	13,400	LUR	NO_2	5.0	**1.02 (0.83–1.26)**	3.3 ppb
							PM_{10} mass	3.3	1.04 (0.90–1.19)	0.4 μg/m^3
							$PM_{2.5}$ mass	1.1	0.96 (0.83–1.11)	0.1 μg/m^3
							Benzene	0.5	0.98 (0.85–1.12)	0.8 μg/m^3

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Table 8.2 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Term Low Birth Weight—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Estimate (95% CI)[c]	Increment
Smith 2017	London Birth Registry 06/10	Cohort	London, United Kingdom	2006–2010	540,365	Dispersion/ CTM	NO_2	40.6	**1.03 (1.00–1.06)**	8.6 µg/m^3
							NO_x	72.5	**1.03 (1.01–1.06)**	23.7 µg/m^3
							PM_{10} mass	23.1	**1.03 (0.99–1.07)**	3.0 µg/m^3
							$PM_{2.5}$ mass	14.4	**1.06 (1.01–1.12)**	2.2 µg/m^3
							$PM_{2.5}$ exhaust	0.60	1.04 (1.01–1.07)	0.35 µg/m^3
							Nontailpipe $PM_{2.5}$	0.70	1.02 (1.00–1.04)	0.29 µg/m^3
Wilhelm 2003	LA County Birth Registry 94/96	Case-control	Los Angeles County, California, United States	1994–1996	30,122	Surface monitoring	NO_2	4.36	**0.93 (0.79–1.08)**	1 pphm
							CO	1.74	**1.22 (1.03–1.44)**	1 ppm
Wilhelm 2012	LA County Birth Registry 04/06	Cohort	Los Angeles County, California, United States	2004–2006	76,277	LUR	NO_2	28.3	1.04 (0.98–1.11)	6.4 ppb
							NO	34.8	1.08 (1.02–1.13)	14.8 ppb
							NO_x	63.5	1.07 (1.01–1.13)	20.5 ppb

CO = carbon monoxide; $PM_{2.5\ abs}$ = $PM_{2.5}$ absorbance; PNC = particle number concentrations.

[a] All studies included male and female participants.

[b] Units are in the increment column.

[c] Effect estimates are odds ratios. **Bold** indicates the effect estimate was included in the meta-analysis.

[d] Estimate was log transformed.

assigned exposure to the surrounding study population based on surface monitoring (Ritz and Yu 1999; Wilhelm and Ritz 2003, 2005).

The Panel excluded eight studies that were initially extracted and met the exposure framework criteria but were not restricted to term births; these included five studies that assessed traffic-related air pollutants (Alderman et al. 1987; Malmqvist et al. 2011; Maroziene and Grazuleviciene 2002; Panasevich et al. 2016; van den Hooven et al. 2012) and three that assessed indirect traffic measures (Genereux et al. 2008; Hannam et al. 2013; Miranda et al. 2013). The Panel concluded that not much information was lost by excluding these studies, as they had considerable overlap with study populations in ESCAPE (Pedersen et al. 2013) and with results included in other fetal growth outcomes considered in this review.

8.3.2 PRIMARY META-ANALYSIS

Of the 22 term low birth weight studies that examined individual traffic pollutants (Table 8.2), 16 were included in the meta-analysis (Figure 8.1). Studies were excluded from meta-analysis for the following reasons: (1) the cohort was a subpopulation of a larger cohort (Gehring et al. 2014 is a subpopulation of Brauer et al. 2008; Wilhelm et al. 2012 is a subpopulation of Ghosh et al. 2012); (2) results were presented for categorical rather than continuous exposure or exposures were log-transformed, which did not lend itself to inclusion in the meta-analysis (Habermann and Gouveia 2014; Madsen et al. 2010; Nieuwenhuijsen et al. 2019); (3) there were not enough studies for the specific pollutant and exposure window to meta-analyze (Pedersen et al. 2016; Wilhelm and Ritz 2005); and (4) exposures were extremely low compared with other studies and the meta-analytical increment, limiting the range of exposure for estimating associations (e.g., Poirier et al. [2015] was excluded from meta-analysis of $PM_{2.5}$ and PM_{10} for this reason but was included in the NO_2 meta-analysis).

Of the traffic pollutants, NO_2 had the highest number of studies of term low birth weight, with 12 that reported associations with exposure during the entire pregnancy, followed by $PM_{2.5}$ with seven studies, NO_x and EC with five studies each, and PM_{10} and carbon monoxide (CO) with three studies each (Figure 8.1).

Figure 8.2 shows forest plots and random effect estimates from the meta-analysis for all six pollutants over the entire pregnancy. Trimester-specific forest plots and meta-analyses for NO_2, NO_x, EC, $PM_{2.5}$, and PM_{10} are displayed in Appendix Figures 8A-1 through 8A-5. There were no trimester-specific meta-analyses for CO because there were too few studies.

The summary estimates from the meta-analysis of NO_2 with term low birth weight, which had the highest number of studies of any of the traffic-related air pollutants, was consistent with the null (1.01; 95% CI: 0.99–1.03) for pollutant exposure averaged over the entire pregnancy as well as trimester-specific exposures. Associations also hovered at the null for the four studies of NO_2 and term low birth weight that were not included in the meta-analysis due to the study being a subpopulation of a larger cohort (Gehring et al. 2014; Wilhelm 2012) or exposure characterization that did not allow for inclusion in meta-analysis (Madsen et al. 2010; Nieuwenhuijsen et al. 2019) (Table 8.2).

NO_x was associated with term low birth weight in meta-analysis (1.02; 95% CI: 1.01–1.03 per 20-μg/m^3). Associations of NO_x and term low birth weight by trimester showed the second trimester (1.02; 1.01–1.02) and third trimester (1.01; 1.01–1.02) to be potentially more sensitive windows of exposure than the first trimester (1.00; 0.99–1.02) (Appendix Figure 8A-2). The one study not included in the meta-analysis because it was a subpopulation of larger cohort (Wilhelm 2012) reported an association for NO_x with term low birth weight that was slightly stronger (1.07; 1.01–1.13) than the studies included in the meta-analysis.

Summary estimates from the meta-analysis of EC with term low birth weight also showed mainly null associations with EC over the entire pregnancy (1.01; 95% CI: 0.99–1.04 per 1-μg/m^3 for EC), although the first trimester showed stronger combined meta-analysis associations for EC exposure (1.06; 0.98–1.14). There were suggestive associations for the second and third trimesters (1.02; 1.01–1.04 and 1.03; 1.03–1.04, respectively) (Appendix Figure 8A-3). Notably, for the trimester-specific results there was one very large and highly weighted study (weight of 87%) with null findings that drove meta-analysis estimates toward the null (Laurent et al. 2016b), while other lower-weight studies were more suggestive. Associations for studies of EC with term low birth weight not included in the meta-analysis were not materially different from those included (e.g., one study that was a subpopulation of a larger cohort [Gehring et al. 2014] and another that log-transformed exposure [Nieuwenhuijsen et al. 2019]).

The strongest summary estimate for term low birth weight for the entire pregnancy was $PM_{2.5}$ (1.11; 95% CI: 1.03–1.20 per 5-μg/m^3) with a meta-analysis of seven studies. The five studies with trimester-specific analyses reported that exposure to $PM_{2.5}$ in all three trimesters was associated with higher risk for term low birth weight, with stronger associations for the third trimester (1.07; 0.99–1.16) and smaller but more precise associations for the first trimester (1.03; 1.01–1.04) and the second trimester (1.02; 1.00–1.04) (Appendix Figure 8A-4). Effect estimates for four studies not included in the meta-analysis all hovered at the null, including those from a study that was a subpopulation of a larger cohort (Gehring et al. 2014), and two that included exposure characterization that did not allow for inclusion in the meta-analysis (Madsen et al. 2010; Nieuwenhuijsen et al. 2019).

The summary PM_{10} estimate was suggestive but imprecise and was derived from only three studies (1.14; 95% CI: 0.95–1.38 per 10-μg/m^3). The majority of the PM_{10} studies

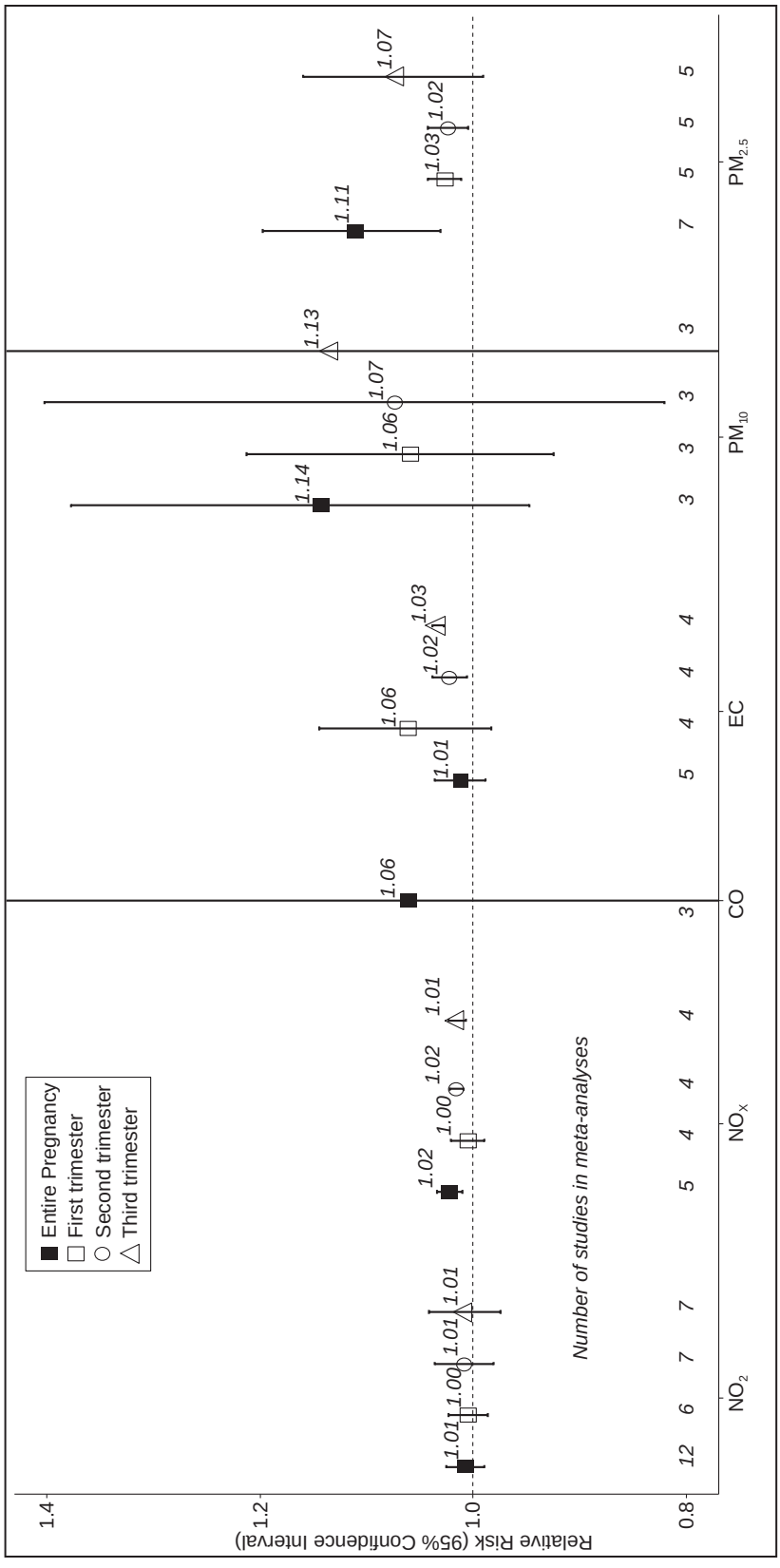

Figure 8.1. Meta-analysis of associations between traffic-related air pollutants and term low birth weight. The following increments were used: 10 µg/m^3 for NO_2, 20 µg/m^3 for NO_x, 1 mg/m^3 for CO, 1 µg/m^3 for EC, 10 µg/m^3 for PM_{10} and 5 µg/m^3 for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

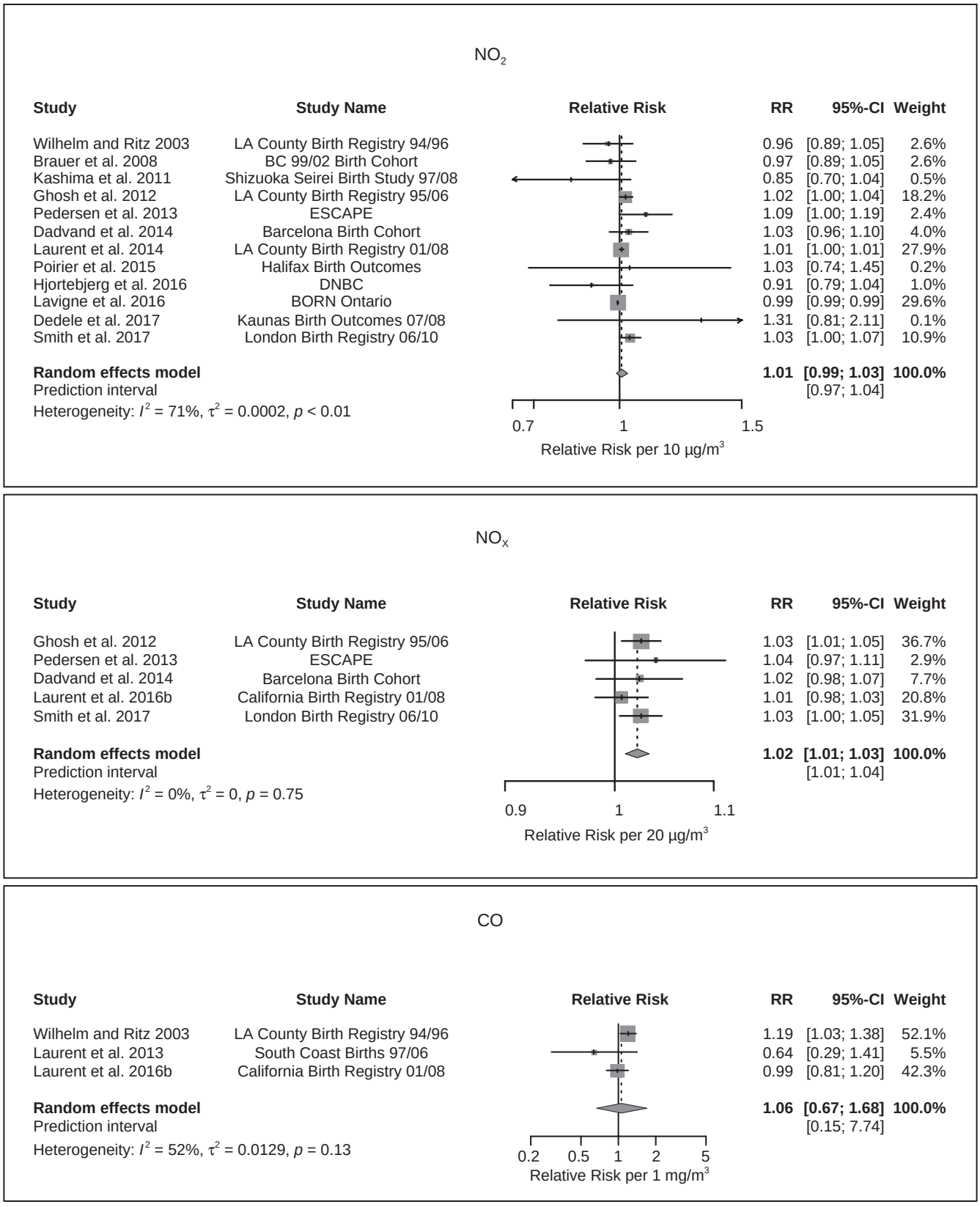

Figure 8.2. Associations of NO_2, NO_X, CO, EC, PM_{10}, and $PM_{2.5}$ with term low birth weight: meta-analysis (exposure window: entire pregnancy).

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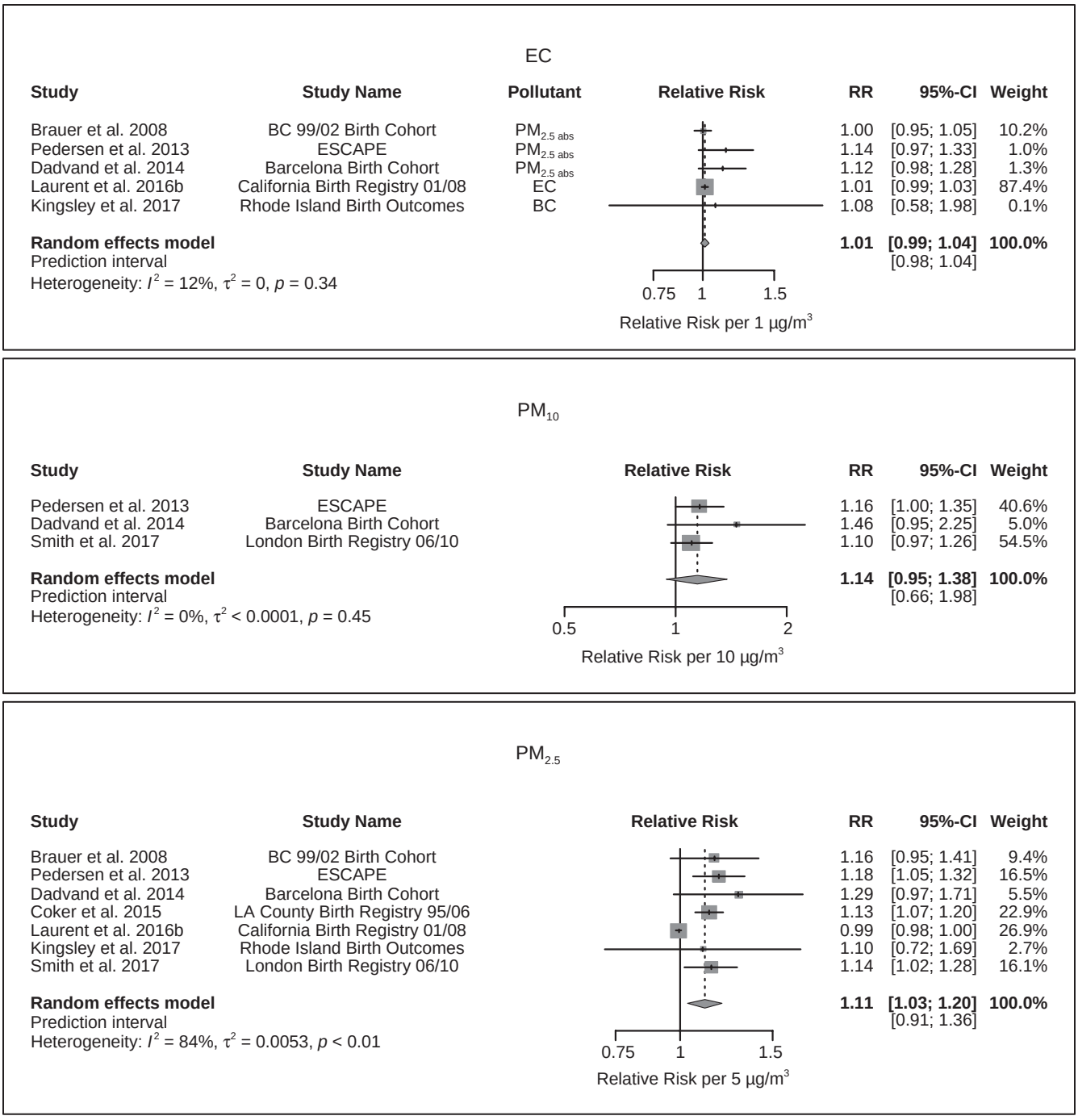

Figure 8.2 *(Continued).*

were excluded from the meta-analysis, including three studies that used log transformation or categorical exposures that did not allow for inclusion in the meta-analysis (Habermann and Gouveia 2014; Madsen et al. 2010; Nieuwenhuijsen et al. 2019). These studies reported inconsistent estimates hovering on both sides of the null.

The CO summary estimate was imprecise, was derived from only three studies, and showed essentially null associations (1.06; 95% CI: 0.67–1.68 per 1-mg/m^3). However, two additional studies conducted in California not included in the meta-analysis each reported suggestive associations for CO exposure during the third trimester. A California Birth Registry

study (Ritz and Yu 1999) reported an RR of 1.22 (1.03–1.81) for CO levels ≥5.5 versus <2.2 ppm within a 2-mile radius of the child's residence; a Los Angeles County Birth Registry study, Wilhelm and Ritz (2005), reported an RR = 1.10 (0.98–1.23) per 1-ppm of CO within a 1-mile radius of the child's residence.

8.3.3 ADDITIONAL META-ANALYSES

Figure 8.3 shows that the majority of studies of NO_2 (9 of 12) and EC (4 of 5) were rated as high traffic specificity studies. RRs were somewhat stronger for high versus moderate traffic specificity studies for NO_2 (RR_{high} = 1.02; 95% CI: 1.00–1.05 vs.

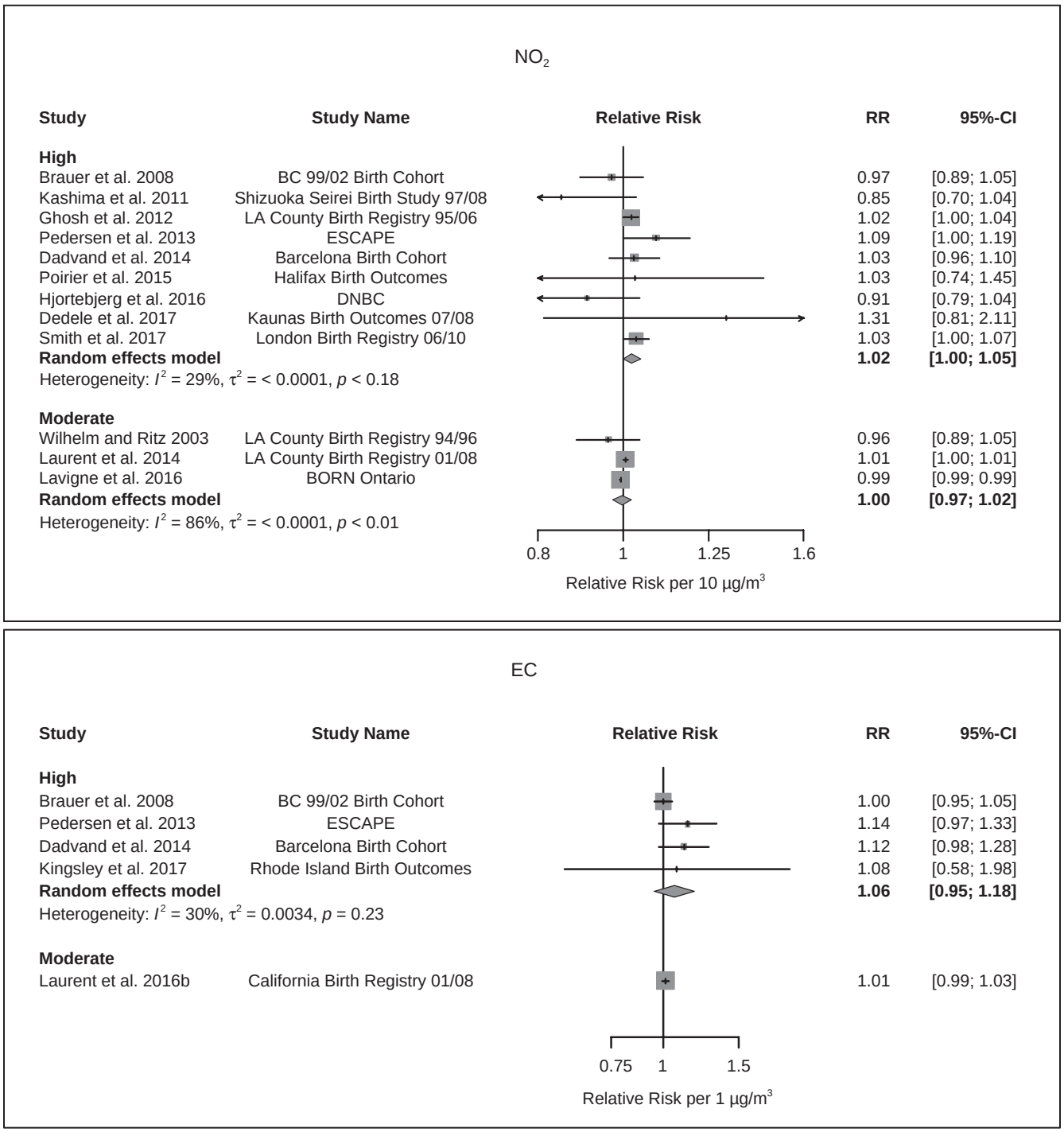

Figure 8.3. Associations of NO_2 and EC with term low birth weight: meta-analysis by traffic specificity (exposure window: entire pregnancy).

$RR_{moderate}$ = 1.00; 0.97–1.02). In addition, effect estimates for EC were also stronger (RR_{high}1.06; 0.95–1.18) compared with the main meta-analysis (1.01; 0.99–1.04), which included the single moderate traffic-specificity study (Laurent et al. 2016b). Laurent et al. 2016b drove the main meta-analysis estimate toward the null. However, differences were small and confidence intervals overlapped. All NO_x studies were rated as high traffic specificity and all $PM_{2.5}$ studies were rated as moderate traffic specificity.

Although the Panel restricted low birth weight associations with TRAP to term births, there was still a possibility that gestational age could confound or modify the association. However, additional adjustments for gestational age did not change summary TRAP and term low birth weight effect estimates, as shown in Appendix Figure 8A-6.

There were some subtle regional differences, as shown in Appendix Figure 8A-7. Associations of term low birth weight with NO_2, EC, and $PM_{2.5}$ all showed regional differences, with stronger summary estimates from meta-analysis of studies conducted in Western Europe versus other regions, such as North America. There were no notable differences in studies published before and after 2008 (the end of the search date for the 2010 HEI Traffic Review).

Meta-analyses stratified by whether studies adjusted for maternal smoking during pregnancy (Appendix Figure 8A-8) showed no differences for NO_2, NO_x, and EC. For $PM_{2.5}$, adjusting for smoking strengthened summary effect estimates (estimates were further away from the null), showing that smoking was a negative confounder and therefore could not explain associations for $PM_{2.5}$ with term low birth weight. Meta-analyses stratified by whether studies adjusted for maternal prepregnancy BMI (Appendix Figure 8A-9) showed no differences for NO_2 and NO_x. For EC and $PM_{2.5}$ adjusting for prepregnancy BMI strengthened summary effect estimates (estimates were further away from the null), showing that prepregnancy BMI was a negative confounder and therefore could not explain observed associations for EC and $PM_{2.5}$ with term low birth weight. All analyses are in Additional Materials to Chapter 8, available on the HEI website.

Three studies of TRAP and term low birth weight reported estimates additionally adjusted for traffic noise with varying results (Appendix Table 8A-2) (Dadvand et al. 2014; Gehring et al. 2014; Smith et al. 2017). Noise-adjusted effect estimates were similar to single pollutant results in one study (Smith et al. 2017), attenuated in another study (particularly the indirect traffic measure distance to roadways [Gehring et al. 2014]), and drove $PM_{2.5}$ estimates away from the null in the third study (Dadvand et al. 2014).

8.3.4 ASSOCIATIONS WITH INDIRECT TRAFFIC MEASURES

Appendix Table 8A-3 lists studies reporting associations of term low birth weight with indirect traffic measures (distance to traffic and traffic density), and Figure 8.4 shows the effect estimates for these associations. Studies showed inconsistent associations of indirect traffic measures with term low birth weight with estimates on both sides of the null. Associations of term low birth weight with distance to traffic ranged from 0.90 to 1.50, although studies with large magnitude estimates tended to be less precise (i.e., with wider confidence intervals), and studies with effect estimates closer to the null tended to be more precise. The same was true for traffic density, with effect estimates ranging from 0.90 to 1.12. Overall, evidence from these studies was inconsistent and suggested mostly null associations of indirect traffic measures with term low birth weight.

8.3.5 NARRATIVE ASSESSMENT

Studies included in the meta-analysis, as well as those not included in the meta-analysis, were conducted primarily in North America and Europe, with a smaller number in South America and Asia. Most studies of TRAP and term low birth weight used a cohort design with only a few studies using case-control and case-cohort designs. Many studies used data from birth registries.

Meta-analyses showed the strongest evidence for associations of term low birth weight with $PM_{2.5}$ exposure averaged over the entire pregnancy (1.11; 95% CI: 1.03–1.20 per 5-μg/m^3). Evidence for PM_{10} and term low birth weight was suggestive (1.14; 0.95–1.38 per 10-μg/m^3); however, it was imprecise and based on only three studies. Evidence from studies of pollutants more specific to traffic was mixed, with evidence for NO_x (1.02; 1.01–1.03 per 20-μg/m^3) and less clear evidence for NO_2 (1.01; 0.99–1.03 per 10-μg/m^3) and EC (1.01; 0.99–1.04 per 1-μg/m^3). Evidence for studies of CO with term low birth weight showed essentially null associations.

Studies not included in meta-analyses showed mostly similar associations to those that were included. Exceptions were for NO_x, where the only study not included because it was a subpopulation of a larger cohort (Wilhelm et al. 2012) found stronger associations with term low birth weight (RR = 1.07; 95% CI: 1.01–1.13) than the studies included in the meta-analysis (Ghosh et al. 2012). In addition, studies of $PM_{2.5}$ not included in the meta-analysis for a variety of reasons (Gehring et al. 2014; Madsen et al. 2010; Nieuwenhuijsen et al. 2019; Poirier et al. 2015) showed null associations with TRAP, compared with the more robust associations among those included in the meta-analysis.

Many studies included a limited set of confounders; in particular studies based on birth registries generally did not adjust for smoking during pregnancy and prepregnancy BMI. There was some evidence of negative confounding, where adjusting for BMI and maternal smoking drove $PM_{2.5}$ and EC estimates further from the null. Studies were generally at low risk of selection bias, a notable advantage of large and inclusive birth registries, which are therefore a good representation of the overall population. There were some studies that did

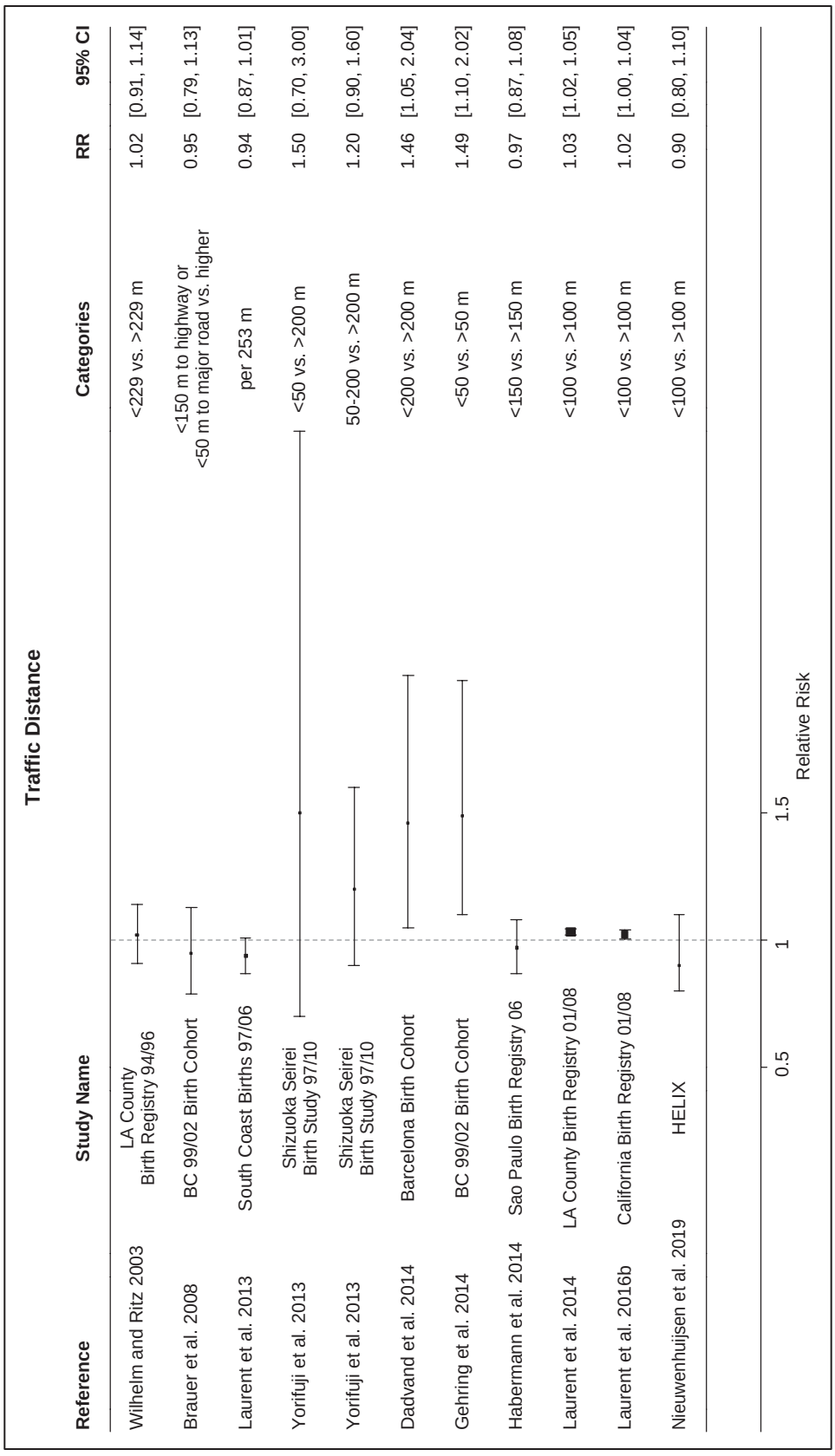

Figure 8.4. Associations of distance to major roads and traffic density with term low birth weight. *Figure continues next page.*

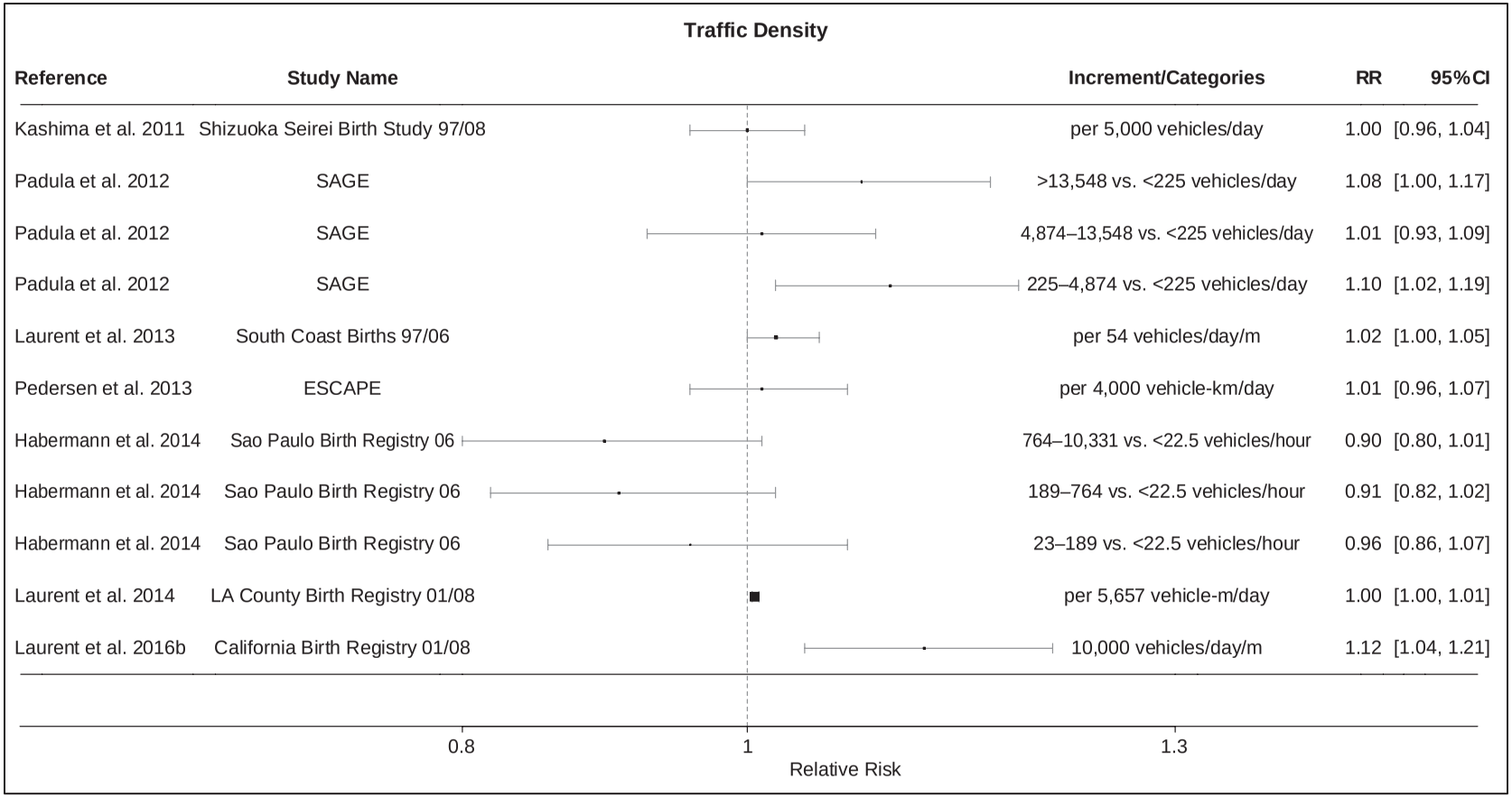

Figure 8.4 *(Continued).*

not account for residential mobility across the entire pregnancy, which could have led to exposure misclassification. A number of studies examined exposure–response functions by examining associations across categories of exposure. These studies reported evidence for a monotonic exposure–response for NO_2, NO_x, and $PM_{2.5}$, but not for PM_{10}.

Studies of indirect traffic measures were inconsistent and showed mostly null associations for larger, more precise studies. There were no notable patterns for TRAP and term low birth weight by trimester of exposure. Associations were slightly stronger for high versus moderate traffic specificity studies. Overall, the Panel rated the confidence in the presence of an association of TRAP with term low birth weight as moderate.

Summary of Narrative Assessment for TRAP and Term Low Birth Weight

The primary meta-analysis supplemented with additional analyses provided moderate confidence in the presence of an association between exposure to TRAP and term low birth weight. Studies on pollutants not included in the meta-analyses were consistent with this assessment. However, studies of indirect traffic measures showed predominantly null associations.

8.3.6 RISK OF BIAS ASSESSMENT

The Panel conducted a risk of bias assessment for term low birth weight across all pollutants per study and per pollutant–study pair, as shown in Table 8.3. Across the 16 individual studies there were a total of 35 pollutant–outcome pairs. Risk of bias was low to moderate across all domains of bias for the majority of studies, with the exception of the confounding domain. More specifically, most studies were in the high risk of bias category for confounding because they did not control for all predefined important confounders (10 of 16 studies). In most cases, this was because those studies did not control for maternal smoking during pregnancy and prepregnancy BMI; it should be noted that many of the studies of TRAP and birth outcomes relied on data from birth registries, which typically do not have this type of data. However, the Panel applied this strict assessment to err on the side of caution with respect to confounding and to be consistent with respect to important confounders across the different outcomes included in this Review.

Across other domains of bias, most noteworthy was that the majority of studies (9 of 16) fell in the moderate risk of bias category for change in exposure status because those studies did not account for residential mobility across the entire pregnancy. For example, if a participant moved to a different residence during their pregnancy, the residence at birth would only represent exposure for a portion of the pregnancy; this could result in exposure measurement error. One study was rated as high risk of bias for change in exposure status because of less-than-optimal temporal resolution of exposure, which was considered a trade-off in this study for better spatial resolution of exposure (Coker et al. 2015). All studies and pollutant–outcome pairs were rated as low risk of bias for selection bias, outcome assessment, handling of missing data, and selective reporting.

8.3.7 CONFIDENCE ASSESSMENT OF THE BODY OF EVIDENCE

Table 8.4 provides the Panel's confidence assessment for entire pregnancy exposure to pollutants for which a meta-analysis was conducted. The meta-analysis included only cohort and case-cohort studies and an initial rating of moderate was designated for all pollutants; no combined assessment across study design was needed.

The Panel discussed four factors that may reduce confidence (downgrade). For the downgrade factor indirectness, all studies addressed the research question directly, and therefore no downgrade was applied. Next, the Panel discussed factors that may increase confidence (upgrade). The Panel decided a priori not to consider large magnitude of the effect as an upgrading factor.

8.3.7.1 Factors That Reduce Confidence

Risk of bias for each study and exposure–outcome pair is presented in Table 8.3. Appendix Table 8A-4 contains the risk of bias assessment for each individual study. The Panel decided to downgrade NO_x, EC, $PM_{2.5}$, and CO for risk of bias, because for these pollutants the majority of studies were at a high risk of bias; the number of studies at low or moderate risk of bias was not sufficient for a reliable comparison across bias categories (Figure 8.5). For PM_{10} only one of the studies was rated high risk of bias, thus no downgrade was required. The only pollutant for which there were enough studies in each category to make a comparison was for NO_2. Because there was no difference across categories of risk of bias, no downgrade was made for NO_2.

No downgrade was applied for unexplained inconsistency. Heterogeneity was only high for $PM_{2.5}$ (I^2 = 84%), which had RRs ranging from 0.99 to 1.29 (Figure 8.2). Indeed, there did appear to be some inconsistency, particularly across some larger studies, including studies with null results such as the California Birth Registry 01/08 study, compared with studies showing evidence of increased risk for term low birth weight, such as the LA County Birth Registry 95/06 and the ESCAPE study. Despite this heterogeneity in magnitude of effect, most of the estimates were in the same direction (with the exception of the California Birth Registry study) and therefore did not result in a downgrade in confidence due to unexplained

Table 8.3. Summary of Risk of Bias Rating for Studies on Term Low Birth Weight (Exposure Window: Entire Pregnancy)

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	5	1	10	13	1	21
	Validity of measuring of confounding factors	11	5	0	27	8	0
	Control in analysis	16	0	0	35	0	0
	Overall	5	1	10	13	1	21
2. Selection bias	Selection of participants into the study	16	0	0	35	0	0
3. Exposure assessment	Methods used for exposure assessment	16	0	0	35	0	0
	Exposure measurement methods comparable across the range of exposure	16	0	0	35	0	0
	Change in exposure status	5	10	1	7	27	1
	Overall	5	10	1	7	27	1
4. Outcome measurements	Blinding of outcome measurements	16	0	0	35	0	0
	Validity of outcome measurements	16	0	0	35	0	0
	Outcome measurements	16	0	0	35	0	0
	Overall	16	0	0	35	0	0
5. Missing data	Missing data on outcome measures	16	0	0	35	0	0
	Missing data on exposures	16	0	0	35	0	0
	Overall	16	0	0	35	0	0
6. Selective reporting	Authors reported a priori primary and secondary study aims	16	0	0	35	0	0

inconsistency. Although the meta-analysis random effects model for NO_2 over the entire pregnancy and term low birth weight would suggest moderate heterogeneity (I^2 = 71%), close inspection of the effect estimates show that most of the associations hovered around the null, with 8 of the 12 studies ranging in estimates from 0.96 to 1.03 (Figure 8.2). The two studies with very different effect estimates (0.85 for Kashima et al. 2011 and 1.31 for Dedele et al. 2017) were very imprecise with overlapping confidence intervals, suggesting a fair amount of random error in these effect estimates. For the other pollutants, heterogeneity was low (NO_x, EC, and PM_{10}) or moderate (CO), and explained mostly by the magnitude of the estimates and not direction.

Regarding imprecision, the Panel downgraded evidence corresponding to PM_{10} and CO, because the meta-analysis confidence intervals were wide and included unity. NO_2 and EC confidence intervals were consistent with an association (both had borderline lower confidence limits of 0.99); hence, no downgrade was applied. Note that the overall sample size of all studies was much larger than the minimum sample size specified in the protocol as needed for an informative judgement for all pollutants included in the meta-analyses.

Of the pollutants, only NO_2 had at least 10 studies for evaluation of publication bias. Although the funnel plot (Figure 8.6) showed some evidence of asymmetry, the evidence for publication bias was not strong and the Egger test *P* value was not statistically significant (*P* = 0.178). It is also possible that the minor asymmetry observed was due to heterogeneity, rather than publication bias. Publication bias could not be assessed for the remaining pollutants because there were not enough studies for a formal evaluation. Based on this, the Panel did not downgrade confidence due to publication bias.

Table 8.4. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Term Low Birth Weight (Exposure Window: Entire Pregnancy)[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ (N = 12)	0	0	0	0	+	0	0	++++ (High)
	Rationale	Cohort design initially rated as moderate.	6 of 12 studies at high RoB; estimates similar across categories of RoB.	Moderate heterogeneity (I^2 = 71%), however most estimates hovered around the null.	Sample size met and narrow confidence interval with estimate consistent with an association.	Just enough studies to evaluate. No evidence found in plot and test.	Evidence of monotonic ERF in 2 influential studies (Ghosh 2012 and Smith 2017).	Confounding in both directions possible.	Insufficient evidence for consistency across populations.	
NO_X	Cohort	+++ (N = 5)	–	0	0	0	+	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	Majority of studies (3 of 5) at high RoB. Too few at low/mod RoB to compare estimates.	No heterogeneity (I^2 = 0%).	Sample size met and narrow confidence interval that does not include unity.	Too few studies, thus based on NO_2.	Evidence of monotonic ERF in 2 influential studies (Ghosh 2012 and Smith 2017).	Confounding in both directions possible.	Insufficient evidence for consistency across populations.	
CO	Cohort	+++ (N = 3)	–	0	–	0	0	0	0	+ (Very low)
	Rationale	Cohort design initially rated as moderate.	All 3 of 3 studies at high RoB.	Moderate heterogeneity (I^2 = 52%).	Sample size met but confidence interval wide and includes unity.	Too few studies, thus based on NO_2.	No evidence of plausible shape of the ERF.	Confounding in both directions possible.	Too few studies.	

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Table 8.4 (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Term Low Birth Weight (Exposure Window: Entire Pregnancy)

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
EC	Cohort	+++ (N = 5)	–	0	0	0	0	+	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	Majority of studies (3 of 5) at high RoB. Too few at low/mod RoB to compare estimates.	Low heterogeneity (I^2 = 12%).	Sample size met and narrow confidence interval with estimate consistent with an association.	Too few studies, thus based on NO_2.	Evidence for monotonic ERF in 2 studies (Dadvand 2014; Pedersen 2016), but no influential studies.	Evidence for negative residual confounding by BMI.	Insufficient evidence for consistency across populations.	
PM_{10}	Cohort	+++ (N = 3)	0	0	–	0	0	0	0	+ (Low)
	Rationale	Cohort design initially rated as moderate.	1 of 3 studies at high RoB.	No heterogeneity I^2 = 0%).	Sample size met but confidence interval wide and includes unity.	Too few studies, thus based on NO_2.	Evidence of monotonic ERF in 2 studies (Dadvand 2014, Smith 2017), but only 1 influential study (Smith 2017).	Confounding in both directions possible.	Too few studies.	
$PM_{2.5}$	Cohort	+++ (N = 7)	–	0	0	0	+	+	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	Majority of studies (5 of 7) at high RoB. Too few at low/mod RoB to compare estimates.	High heterogeneity (I^2 = 84%), but nearly all estimates in same direction.	Sample size met and narrow confidence interval that does not include unity.	Too few studies, thus based on NO_2.	Evidence for monotonic ERF in 2 influential studies (Pedersen 2013; Smith 2017).	Evidence for negative residual confounding by smoking and BMI.	Insufficient evidence for consistency across populations.	

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

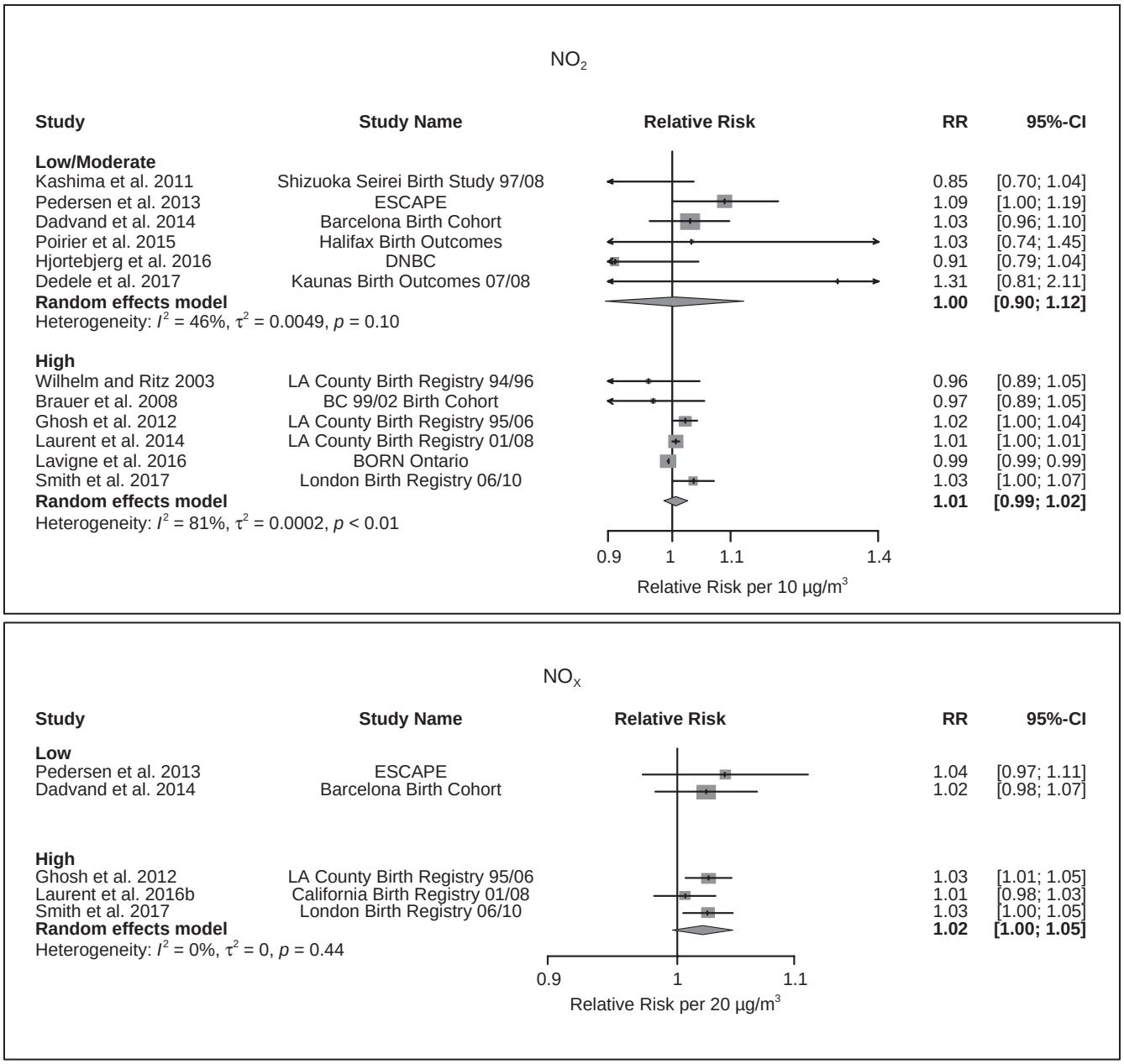

Figure 8.5. Associations of NO_2, NO_x, EC, and $PM_{2.5}$ with term low birth weight: meta-analysis by risk of bias confounding (exposure window: entire pregnancy). *Figure continues next page.*

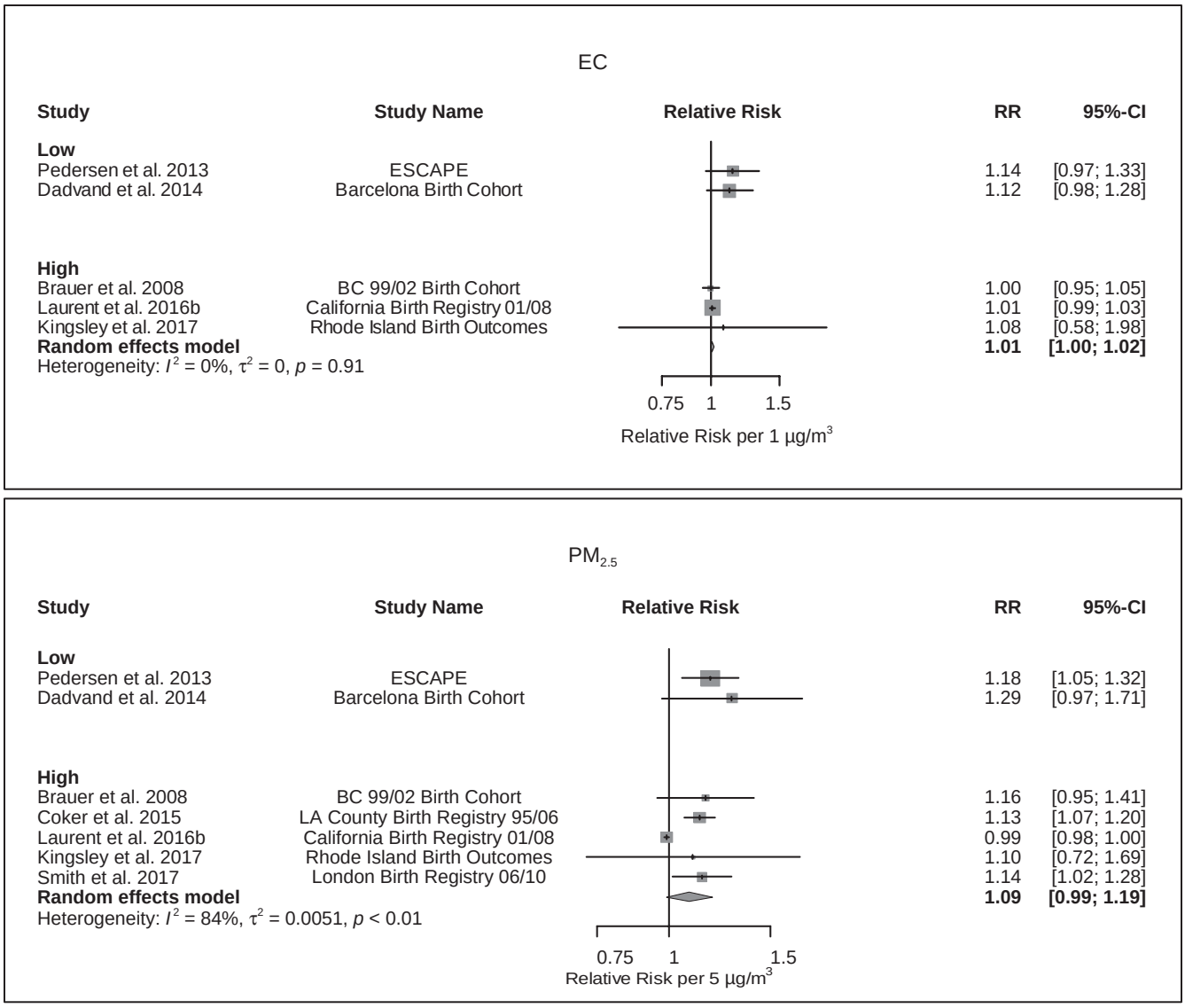

Figure 8.5 *(Continued).*

8.3.7.2 Factors That Increase Confidence

The Panel upgraded the evidence for associations of NO_2, NO_x, and $PM_{2.5}$ with term low birth weight following the demonstration of a monotonic exposure–response function in multiple influential studies. Seven of the 12 studies of NO_2 and term low birth weight assessed an exposure–response function (Dadvand et al. 2014; Dedele et al. 2017; Ghosh et al. 2012; Kashima et al. 2011; Laurent et al. 2014; Pedersen et al. 2013; Smith et al. 2017). Of the seven, three reported null results and four reported a monotonic exposure–response function for term low birth weight with exposure to NO_2, including: the LA County Birth Registry Study (Ghosh et al. 2012) (RR = 1.02; 95% CI: 1.00–1.04), the ESCAPE study (RR = 1.19; 1.00–1.19) (Pedersen et al. 2013), the London Birth Registry (Smith et al. 2017) (RR = 1.03; 1.00–1.07), and the Kaunas Birth Outcomes Study (Dedele et al. 2017) (Tertile 1 = ref, Tertile 2 RR = 1.37; 95% CI: 0.89–2.10, Tertile 3 RR = 1.53; 0.99–2.37). The Kaunas study (Dedele et al. 2017) was a very small study and not influential in the meta-analysis. Neither was the ESCAPE study (Pedersen et al. 2013), which conducted subgroup analyses to inform about the shape of the exposure–response function. The Los Angeles and London studies (Ghosh et al. 2012; Smith et al. 2017), however, contributed considerably to both the NO_2 and NO_x meta-analyses, and hence an upgrade was made. Two of the three studies of PM_{10} and term low birth weight reported a monotonic exposure–response function (Dadvand et al. 2014; Smith

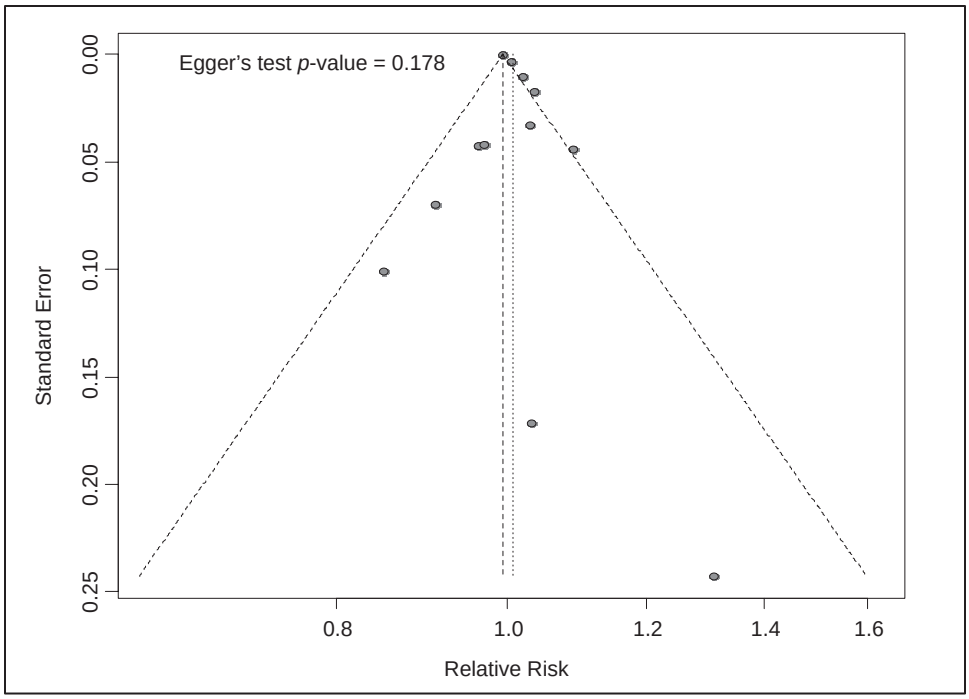

Figure 8.6. Funnel plot for NO_2 and term low birth weight (exposure window: entire pregnancy). The vertical lines in the funnel plots represent the pooled fixed and random effect estimates. The vertical dashed line in the middle of the funnel shows the fixed effect estimate. As the Panel applied a random-effects model, the funnel plot also presents the random-effects estimate with the dotted line.

et al. 2017), but only one study was influential (Smith et al. 2017) and therefore an upgrade was not applied. As for $PM_{2.5}$, three studies demonstrated a monotonic exposure–response function (Dadvand et al. 2014; Pedersen et al. 2013; Smith et al. 2017), with both Pedersen and colleagues (2013) and Smith and colleagues (2017) adding considerable weight to the meta-analysis (both 16%). No influential studies assessed the exposure–response function for EC or CO.

The Panel did upgrade the evidence for EC and $PM_{2.5}$ on the basis of residual confounding or other factors potentially biasing toward the null. Meta-analyses of $PM_{2.5}$ stratified by smoking adjustment (Appendix Figure 8A-8) showed stronger associations among studies that adjusted for smoking, indicating that residual confounding by smoking may have biased estimates toward the null. The same was true for BMI, where EC and $PM_{2.5}$ associations were stronger among studies that adjusted for BMI (Appendix Figure 8A-9). Upgrades were not made for the other pollutants because those patterns were not apparent. There was also no evidence that other factors systematically biased estimates of associations of term low birth weight with TRAP toward the null. For example, a study in Los Angeles reported that air pollution hot-spots were concentrated in health districts that were lower income and nonwhite, suggesting that these factors would drive estimates away from rather than toward the null (Coker et al. 2015). This is in contrast to a study conducted in Barcelona, which reported that participants living closer to a major road tended to experience less neighborhood deprivation that those living farther from a major road (Dadvand et al. 2014). Finally, there were not strong signs of consistency for pollutants across geographical regions, populations, or study period, in part because of the small number of studies, and therefore no upgrade was made.

8.3.7.3 Evaluation of Confidence for Combined Measures of TRAP

The Panel's final ratings of the confidence in the quality of the body of evidence was high for NO_2, moderate for NO_x, EC, and $PM_{2.5}$, low for PM_{10}, and very low for CO. The Panel thought a confidence rating of moderate would be more appropriate given the lower ratings for NO_x and EC. Studies on pollutants not included in the meta-analyses and the studies with indirect traffic measures (distance and density) were consistent with this assessment. Based on the modified OHAT assessment, the confidence in the quality of the body of evidence between exposure to TRAP and term low birth weight is moderate.

8.3.8 OVERALL CONFIDENCE ASSESSMENT

Based on the narrative assessment (moderate) and the modified OHAT assessment (moderate), the overall level of confidence in the evidence for an association between TRAP exposure and term low birth weight is moderate.

8.4 TERM BIRTH WEIGHT

8.4.1 STUDY SELECTION AND DESCRIPTION

A total of 15 studies investigated associations between TRAP or indirect traffic measures (i.e., distance and density) and term birth weight—a continuous measure of birth weight at gestational age greater than or equal to 37 weeks—for studies that examined exposure during the entire pregnancy (Table 8.5 and Appendix Table 8B-3). Of these, three included analyses of both individual pollutants and indirect traffic indicators, and one included only indirect traffic measures (Kingsley et al. 2016). Nine studies were ultimately included in meta-analyses reporting associations with exposure during the entire pregnancy, which made up the main body of evidence for this review. Four studies limited their analyses to exposure during the entire pregnancy (Laurent et al. 2013; Madsen et al. 2010; Pedersen et al. 2016; Shmool et al. 2015), and two studies reported trimester-specific findings only (Janssen et al. 2017; Keller et al. 2017).

Eighteen studies of TRAP and birth weight that initially met the exposure framework criteria were ultimately excluded because they did not restrict to term births. The Panel required this restriction to ensure that associations with low birth weight were via growth restriction, rather than shortened gestational age. The Panel concluded that relatively little information is lost restricting to term birth weight in this part of the review because many of these study populations overlapped with other studies included in the review. For example, the ESCAPE study (Pedersen et al. 2013) was included and captured the study populations of the INMA cohort (Aguilera et al. 2009; Ballester et al. 2010; Clemente et al. 2016, 2017; Estarlich et al. 2011), Generation R (van den Hooven et al. 2009, 2012), MoBA (Panasevich et al. 2016) and BiB (Schembari et al. 2015). Moreover, some studies that reported birth weight without restriction to term births also reported results for other birth outcomes in this review, such as term low birth weight from HELIX (Nieuwenhuijsen et al. 2019) and small for gestational age from the Shizuoka Seirei Birth Study (Kashima et al. 2011) and the Flanders Birth Study 99/09 (Winckelmans et al. 2015). Only six birth weight studies did not overlap with other study populations included in the review (Erickson et al. 2016; Lamichhane et al. 2018; Malmqvist et al. 2017; Wang et al. 2017; Yorifuji et al. 2012; Zeka et al. 2008).

An approximately equal number of the term birth weight studies were conducted in North America and Europe. Term birth weight studies ranged in sample size from N = 500 in prospective birth cohorts to N = 1.2 million in studies using birth registry data. Altogether, the study populations covered a period from 1994 to 2014, with most of the studies starting enrollment before or in 2008.

The traditional prospective birth cohorts had detailed recruitment and follow-up protocols with extensive information on individual lifestyle factors. Those conducted in Europe included the Amsterdam ABCD study (Gehring et al. 2011a), the Dutch PIAMA study (Gehring et al. 2011b), the multicohort European ESCAPE study (Pedersen et al. 2013, 2016), the Belgium ENVIRONAGE study (Janssen et al. 2017), and the Danish National Birth Cohort (DNBC) (Hjortebjerg et al. 2016). There was one North American prospective cohort, the Rhode Island Birth Outcomes cohort (Kingsley et al. 2016). The remaining cohorts were based in Europe or North America and used administrative data or birth registries (Gehring et al. 2014; Keller et al. 2017; Kingsley et al. 2017; Laurent et al. 2013; Li et al. 2016; Madsen et al. 2010; Savitz et al. 2014; Shmool et al. 2015; Smith et al. 2017). Although individual or area-level socioeconomic status was available for these studies, most of them did not collect data on maternal smoking and prepregnancy BMI, which were considered important potential confounders for this systematic review.

Exposure assessment in all studies was based on LUR (including hybrid models) or dispersion/CTM. Term birth weight studies were available for meta-analysis on NO_2 (N = 8 studies), NO_x (N = 5), $PM_{2.5}$ mass (N = 6), and EC (N = 4) with exposure during the entire pregnancy. Other pollutants for which fewer than three studies were available (too few to meta-analyze) included nitric oxide (NO), CO, and various fractions or components of PM (PM_{10}, PM with aerodynamic diameter between 10 μm and 2.5 μm [PM_{coarse}], exhaust, traffic or nontailpipe $PM_{2.5}$, and $PM_{2.5}$ metals). Mean or median air pollution levels were moderate to high and ranged from 11 μg/m^3 to 41 μg/m^3 for NO_2; all were at or below 20 μg/m^3 for $PM_{2.5}$ mass. Three term birth weight studies evaluated concurrent noise exposure (Gehring et al. 2014; Hjortebjerg et al. 2016; Smith et al. 2017).

Six term birth weight studies overlapped with studies included in term low birth weight (Section 8.3) (Gehring et al. 2014; Hjortebjerg et al. 2016; Kingsley et al. 2017; Laurent et al. 2013; Pedersen et al. 2013; Smith et al. 2017). The Panel describes the consistency of results of those studies between these two related birth outcomes in Section 8.4.3.1.

8.4.2 PRIMARY META-ANALYSIS

For TRAP and term birth weight, NO_2 was the most studied pollutant included in the meta-analysis (N = 8 studies of exposure during the entire pregnancy), followed by $PM_{2.5}$ (N = 6 studies), NO_x (N = 5 studies), and EC (N = 4 studies) (Figure 8.7). A sufficient number of studies were also available for evaluating associations of NO_2, NO_x, and $PM_{2.5}$ with term birth weight in meta-analysis across all three trimesters, and for EC during the first trimester.

Studies were excluded from the meta-analysis when they assessed the same study population and employed the same exposure methods as another study in the meta-analysis (Shmool et al. 2015), or when exposure was analyzed in categories (Gehring et al. 2011a; Madsen et al. 2010). The

Table 8.5. Key Study Characteristics of Articles Included in the Systematic Review for Term Birth Weight—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name[a]	Location	Study Period	Sample Size[b]	Exposure Assessment	Pollutant	Mean or Median Exposure[c]	Mean Difference (95% CI) (g)[d]	Increment
Gehring 2011a	ABCD	Amsterdam, the Netherlands	2003–2004	6,978	LUR	NO_2	38.7	21.3 (−11.1 to 53.6)	>44.8 vs. <34.6 µg/m^3
								1.2 (−31.1 to 33.5)	40.2–44.8 vs. <34.6 µg/m^3
								7.7 (−24.4 to 39.9)	37.4–40.2 vs. <34.6 µg/m^3
								−16.3 (−48.1 to 15.5)	34.6–37.4 vs. <34.6 µg/m^3
Gehring 2011b	PIAMA	Multiple cities, the Netherlands	1996–1997	3,408	LUR	NO_2	30.4	**24.7 (−4.1 to 53.4)**	11.2 µg/m^3
						$PM_{2.5\ abs}$	2.75	**20.7 (−6.8 to 48.2)**	0.94 1×10^{-5}/m
						$PM_{2.5}$ mass	20.1	**30.0 (−7.1 to 67.1)**	4.6 µg/m^3
Gehring 2014	BC 99/02 Birth Cohort	Vancouver, British Columbia, Canada	1999–2002	68,238	LUR	NO_2	33.5	**−5.2 (−9.1 to −1.4)**	10 µg/m^3
						NO	23.0	−6.5 (−9.1 to −3.9)	10 µg/m^3
						$PM_{2.5\ abs}$	1.6	**−3.4 (−6.2 to −0.6)**	1 1×10^{-5}/m
						$PM_{2.5}$ mass	5.5	**−3.1 (−5.1 to −1.1)**	1 µg/m^3
Hjortebjerg 2016	DNBC	Denmark	1996–2002	75,166	Dispersion/ CTM	NO_2	11.0	**0.21 (−5.20 to 5.62)**	10 µg/m^3
						NO_x	Not reported	**−0.62 (−4.08 to 2.85)**	20 µg/m^3
Kingsley 2017	Rhode Island Birth Outcomes	Providence, Rhode Island, United States	2002–2012	56,633	LUR	BC	0.52	**0.0 (−4.7 to 4.7)**	0.11 µg/m^3
						$PM_{2.5}$ mass	9.5	**−12.1 (−24.2 to −0.1)**	2.5 µg/m^3
Laurent 2013	South Coast Births 97/06	Los Angeles and Orange Counties, California, United States	1997–2006	68,303	LUR	NO_2	28.03	**16.59 (12.01 to 21.16)**	9.34 ppb
						NO_x	59.93	**9.42 (5.25 to 13.59)**	25.24 ppb
					Dispersion/ CTM	CO	0.10	15.09 (11.27 to 18.91)	0.08 ppm
						Traffic $PM_{2.5}$	4.25	5.94 (2.32 to 9.57)	1.36 µg/m^3

Continues next page

Table 8.5 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Term Birth Weight—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name[a]	Location	Study Period	Sample Size[b]	Exposure Assessment	Pollutant	Mean or Median Exposure[c]	Mean Difference (95% CI) (g)[d]	Increment
Li 2016	LA County Birth Registry 01/08	Los Angeles County, California, United States	2001–2008	1,203,782	LUR	NO_2	25	**−1.89 (−2.23 to −1.55)**	1 ppb
						NO_x	17.32	**−0.87 (−1.09 to −0.65)**	1 ppb
Madsen 2010	Oslo Birth Registry 99/02	Oslo, Norway	1999–2002	25,229	Dispersion/ CTM	NO_2	32.0	1.8 (−13.7 to 17.2)	>38.1 vs. <20.3 μg/m³
								19.7 (4.2 to 35.3)	32.1–38.0 vs. <20.3 μg/m³
								11.7 (−3.7 to 27.1)	20.3–32.0 vs. <20.3 μg/m³
						PM_{10} mass	13.2	15.9 (0.0 to 31.9)	>16.2 vs. <10.7 μg/m³
								21.3 (6.0 to 36.5)	13.3–16.2 vs. <10.7 μg/m³
								11.7 (−3.5 to 26.9)	10.7–13.2 vs. <10.7 μg/m³
						$PM_{2.5}$ mass	11.5	13.6 (−2.4 to 29.5)	>14.1 vs. <9.7 μg/m³
								16.3 (0.8 to 31.7)	11.6–14.1 vs. <9.7 μg/m³
								0.8 (−14.5 to 16.0)	9.7–11.5 vs. <9.7 μg/m³
Pedersen 2013	ESCAPE	Multiple cities, multiple countries	1994–2011	61,452	LUR	NO_2	26.2	**−1 (−6 to 4)**	10 μg/m³
						NO_x	45.5	**−1 (−4 to 3)**	20 μg/m³
						$PM_{2.5\ abs}$	1.7	**−3 (−13 to 7)**	1 1×10^{-5}/m
						PM_{10} mass	25.4	−8 (−19 to 3)	10 μg/m³
						PM_{coarse} mass	9.1	−3 (−11 to 6)	5 μg/m³
						$PM_{2.5}$ mass	16.5	**−7 (−17 to 2)**	5 μg/m³

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Table 8.5 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Term Birth Weight—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name[a]	Location	Study Period	Sample Size[b]	Exposure Assessment	Pollutant	Mean or Median Exposure[c]	Mean Difference (95% CI) (g)[d]	Increment
Pedersen 2016	ESCAPE	Multiple cities, multiple countries	1994–2008	31,173	LUR	$PM_{2.5}$ Cu	3.4	10 (–8 to 27)	5 ng/m^3
						$PM_{2.5}$ Fe	104.0	6 (–5 to 16)	100 ng/m^3
						$PM_{2.5}$ Zn	14.8	–4 (–21 to 12)	10 ng/m^3
Savitz 2014	NYC Birth Registry 08/10	New York City, New York, United States	2008–2010	252,967	LUR	NO_2	25	**–18.0 (SE: 2.2)**	10 ppb
						$PM_{2.5}$ mass	11	**–48.4 (SE: 7.1)**	10 µg/m^3
Shmool 2015	NYC Birth Registry 08/10	New York City, New York, United States	2008–2010	243,853	LUR	NO_2	26.8	–16.2 (–21.9 to –10.5) (least deprived)	10 ppb
								0.5 (–7.7 to 8.7) (mid-range deprived)	
								–11.0 (–22.8 to –0.9) (most deprived)	
Smith 2017	London Birth Registry 06/10	London, United Kingdom	2006–2010	540,365	Dispersion/ CTM	NO_2	40.6	**–10.97 (–12.98 to –8.96)**	8.6 µg/m^3
						NO_x	72.5	**–10.74 (–12.76 to –8.73)**	23.7 µg/m^3
						PM_{10} mass	23.1	–7.27 (–9.84 to –4.70)	3.0 µg/m^3
						$PM_{2.5}$ mass	14.4	**–12.94 (–16.41 to –9.47)**	2.2 µg/m^3
						$PM_{2.5}$ exhaust	0.60	–12.43 (–14.51 to –10.35)	0.35 µg/m^3
						Nontail-pipe $PM_{2.5}$	0.70	–7.41 (–8.96 to –5.86)	0.29 µg/m^3

$PM_{2.5\ abs}$ = $PM_{2.5}$ absorbance; SE = standard error.

[a] All were cohort studies.

[b] All studies included male and female participants.

[c] Units are in the increment column. **Bold** indicates the effect estimate was included in the meta-analysis.

[d] None of the estimates were log transformed.

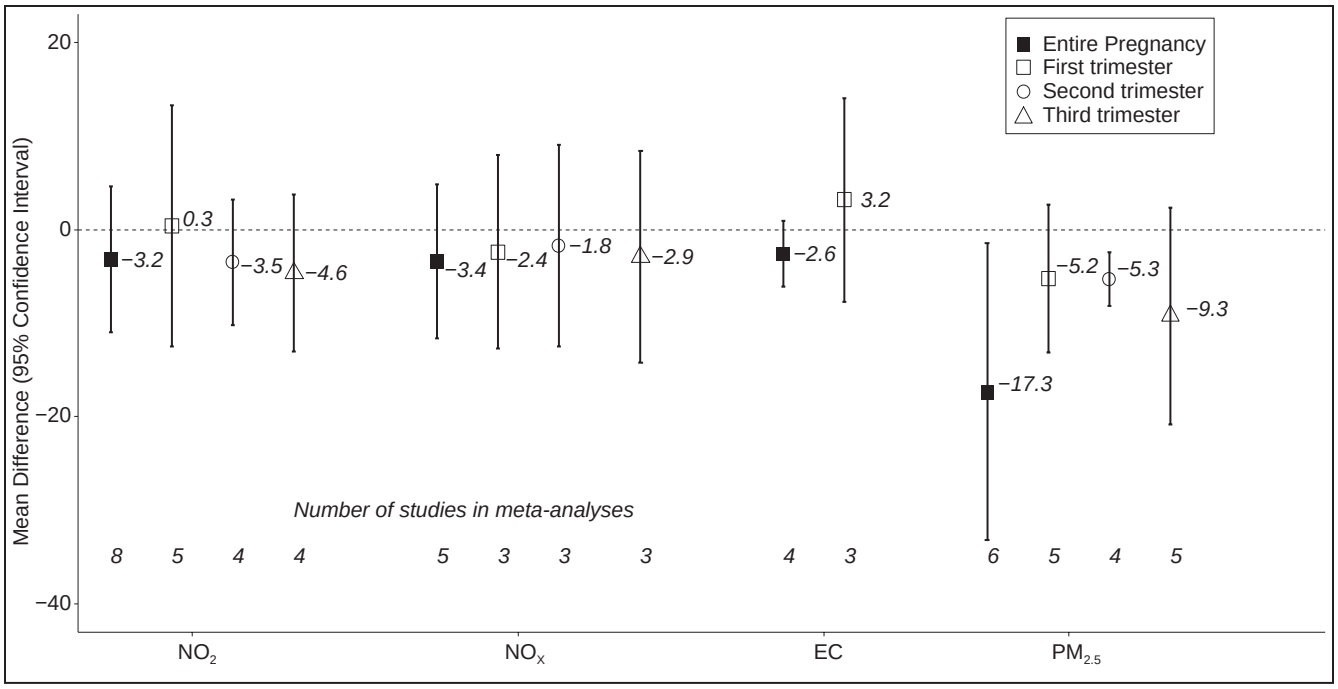

Figure 8.7. Meta-analysis of associations between traffic-related air pollutants and change in term birth weight (grams). The following increments were used: 10 μg/m³ for NO_2, 20 μg/m³ for NO_x, 1 μg/m³ for EC and 5 μg/m³ for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

Panel decided to be inclusive when there were differences in either the study population or the exposure methods. Therefore, the Dutch PIAMA study (Gehring et al. 2011b) that used a different LUR model than the ESCAPE LUR model was included in the meta-analysis, even though it was also part of the ESCAPE study (Pedersen et al. 2013, 2016). Likewise, the Danish DNBC cohort (Hjortebjerg et al. 2016) used dispersion modeling instead of the ESCAPE LUR models, and ESCAPE included only the greater Copenhagen area subset of this nationwide cohort.

Term birth weight was most strongly associated with $PM_{2.5}$. The negative mean difference for term birth weight was strongest for exposure during the entire pregnancy (−17.3; 95% CI: −33.2 to −1.5 per 5-μg/m³) but was also evident across all three trimesters (Figure 8.8 and Appendix Figure 8B-1). The association of entire pregnancy $PM_{2.5}$ exposure with term birth weight was not heavily influenced by any individual study, although heterogeneity was high (I^2 = 77%), possibly due to the small and very imprecise PIAMA study (Gehring et al. 2011b), which reported associations in the opposite direction (higher term birth weight with increased exposures to $PM_{2.5}$). The study by Gehring and colleagues (2011b) also contributed to the moderate heterogeneity in the first trimester results, while the small ENVIRONAGE study (Janssen et al. 2017) contributed to heterogeneity in the third trimester (Appendix Figure 8B-1).

Term birth weight associations with the other pollutants, while trending in the expected direction, were much closer to the null (−3.2 grams; 95% CI: −11.0 to 4.6 per 10-μg/m³ NO_2; −3.4 grams; −11.7 to 4.8 per 20-μg/m³ NO_x; and −2.6 grams; −6.1 to 0.9 per 1-μg/m³ EC). Overall, meta-analyses of NO_2 and NO_x with term birth weight were heterogeneous (both with I^2 = 97%) and were not heavily influenced by any individual study (Figure 8.8). The EC and term birth weight meta-analysis, on the other hand, were heavily dominated (92% weight) by the large BC 99/02 Birth Cohort (Gehring et al. 2014).

Of the traffic-related air pollutants included in a meta-analysis, only NO_2 had three studies excluded from the meta-analysis. Two excluded studies did not show an association in categorical analyses (Gehring et al. 2011a; Madsen et al. 2010). The NYC Birth Registry study (Shmool et al. 2015), which reported associations for the same study population as another included study (Savitz et al. 2014), stratified by area-level socioeconomic deprivation; this study reported associations with lower term birth weight for mothers living in the least and most deprived areas, but null associations in mid-range areas (Shmool et al. 2015). Studies of pollutants that numbered too few for meta-analysis showed mixed results (Table 8.5).

8.4.3 ADDITIONAL META-ANALYSES

All NO_2, NO_x, and EC studies in the meta-analyses were rated as high traffic specificity studies. Stratified by region,

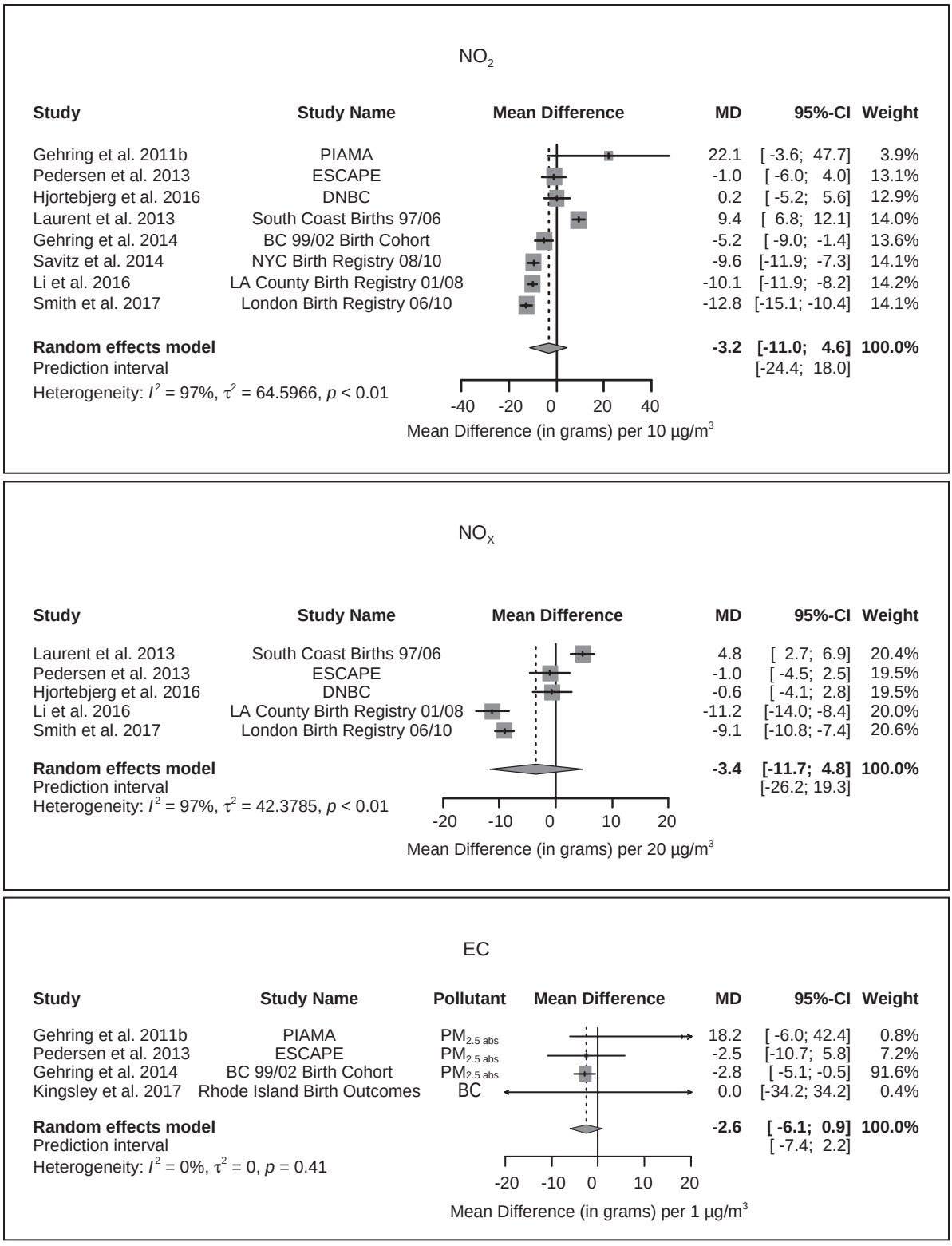

Figure 8.8. Associations of NO_2, NO_x, EC, and $PM_{2.5}$ with change in term birth weight: meta-analysis (exposure window: entire pregnancy).
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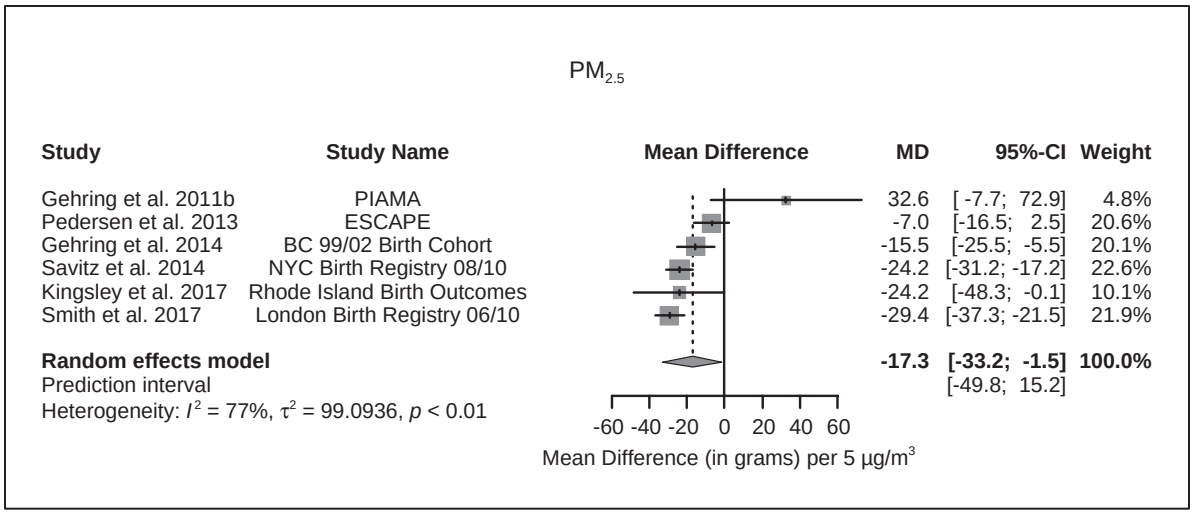

Figure 8.8 *(Continued).*

associations between NO_2, NO_x, and EC and term birth weight were null for both North America and Western Europe (Appendix Figure 8B-2). Meta-analyses of NO_2 and EC stratified by whether the epidemiological models adjusted for maternal smoking during pregnancy or for prepregnancy BMI were not different than studies that did not adjust for these covariates. For NO_x, all three studies that did not adjust for smoking showed associations further from the null compared with studies that did (Appendix Figure 8B-3); two of the studies showed associations in the expected direction, with lower term birth weight (Li et al. 2016; Smith et al. 2017), and one study showed associations in the opposite direction, with higher term birth weight (Laurent et al. 2013). The same pattern was observed for BMI (Appendix Figure 8B-4).

All $PM_{2.5}$ studies in the meta-analysis were rated as moderate traffic specificity. With three studies each in North America and Western Europe, associations between $PM_{2.5}$ and term birth weight were only found in North America (−21.1 grams; 95% CI: −33.8 to −8.4) (Additional Materials). With the exception of one study, all $PM_{2.5}$ studies were adjusted for maternal smoking during pregnancy (Appendix Figure 8B-3). The one study that did not adjust for maternal smoking, the London Birth Registry study (Smith et al. 2017), found the strongest association of $PM_{2.5}$ and term birth weight (−29.4 grams; −37.3 to −21.5), suggesting that residual confounding by smoking could be driving the association, and the overall summary estimate, away from the null. A similar trend was found for prepregnancy BMI, but in this case there were more studies that did not adjust for BMI (four studies), and summary estimates from these studies without BMI adjustment were considerably further from the null (−23.7 grams; −33.3 to −14.1) (Appendix Figure 8B-4). This suggests that residual confounding by maternal smoking and BMI could explain some of the associations of $PM_{2.5}$ with term birth weight.

Three term birth weight studies additionally corrected for noise exposure in additional models (Gehring et al. 2014; Hjortebjerg et al. 2016; Smith 2017) (Appendix Table 8B-2). Adjusting for noise did not meaningfully change associations, although they did attenuate associations of TRAP with term birth weight for one study (Gehring et al. 2014). There were no studies that reported associations corrected for general $PM_{2.5}$ or ozone.

8.4.3.1 Additional Meta-analysis of Studies Reporting Both Term Birth Weight and Term Low Birth Weight

The overall evidence for TRAP and term low birth weight was inconsistent with the evidence for TRAP and term birth weight. For example, meta-analyses showed suggestive associations for NO_x and term low birth weight (RR = 1.02; 95% CI: 1.01 to 1.03), while meta-analysis of NO_x and term birth weight resulted in null associations (mean difference = −3.4 grams; −11.7 to 4.8). To explore these differences more directly, the Panel conducted sensitivity analyses (Appendix Figure 8B-5) that were restricted to the six studies that reported associations of TRAP with both term low birth weight and term birth weight (Gehring et al. 2014; Hjortebjerg et al. 2016; Kingsley et al. 2017; Laurent et al. 2013; Pedersen et al. 2013, Smith et al. 2017). For the three NO_x studies that were common to both outcomes (Laurent et al. 2013; Pedersen et al. 2013; Smith et al. 2017), associations were null for both term low birth weight (RR = 1.02; 0.96 to 1.07) and term birth weight (mean difference = −1.8 grams; −19.2 to 15.6). The point estimate is similar as for all NO_x-TLBW studies but with wider confidence intervals, and the association is no longer statistically significant. Furthermore, this suggests that the associations between NO_x and term low birth weight in the primary meta-analysis were driven by those studies that did not also report low birth weight results, particularly the LA

County Birth Registry study (Ghosh et al. 2012), which was influential in the meta-analysis (37% weight) (Figure 8.2). Additional meta-analyses restricting to studies that reported associations of other pollutants with both term low birth weight and term birth weight did not reveal any additional insight (Appendix Figure 8B-5).

8.4.4 ASSOCIATIONS WITH INDIRECT TRAFFIC MEASURES

Only four studies included indirect traffic measures for term birth weight (Appendix Table 8B-3). For the distance measures, all three studies showed associations in the expected direction (Gehring et al. 2014; Kingsley et al. 2016; Laurent et al. 2013), although only one very small study was statistically significant (Kingsley et al. 2016). The two studies assessing traffic density measures and term birth weight reported null results (Laurent et al. 2013; Pedersen et al. 2013).

8.4.5 NARRATIVE ASSESSMENT

Studies of TRAP and term birth weight included in the meta-analyses, as well as those not included in the meta-analyses, were all conducted in North America and Europe (14 studies). All studies of TRAP and term birth weight were cohort studies, with some from prospective traditional birth cohorts and others created retrospectively from large birth registries.

Meta-analyses showed the strongest associations for $PM_{2.5}$ and term birth weight, with a reduction in mean birth weight of 17.3 grams (95% CI: −33.2 to −1.5) per 5-μg/m^3. Associations with other traffic-related air pollutants, although in the same direction, were considerably smaller (reductions of 2 to 3 grams per increment in pollutant exposure), and none were statistically significant. The three studies (all on NO_2) that were excluded from the meta-analysis because of categorical analyses or overlap in population had essentially null results. Studies of pollutants that numbered too few for meta-analysis showed mixed results.

As many studies used data from large birth registries, selection bias was minimized. However, most registry-based studies did not collect data on maternal smoking during pregnancy or prepregnancy BMI, which may have resulted in residual confounding. There were some studies that did not account for residential mobility across the entire pregnancy, which could have led to exposure misclassification. A few studies that examined exposure–response functions showed a monotonic relationship.

The four studies of indirect traffic associations with term birth weight were essentially null. Studies that examined associations of term birth weight with trimester-specific TRAP exposure showed similar associations for individual trimesters compared with those observed for the entire pregnancy, with the exception of $PM_{2.5}$ where stronger associations were observed with exposure during the entire pregnancy. All NO_2, NO_x, and EC studies in the meta-analysis were rated as high traffic specificity studies (and all $PM_{2.5}$ studies were, by definition, moderate traffic specificity studies).

Associations were more suggestive for TRAP with term low birth weight (Section 8.3) compared with term birth weight. Although there was some overlap, with several studies reporting associations with both continuous and dichotomized birth weight, stronger associations for term birth weight were likely driven by studies that did not report associations with low birth weight results. The Panel rated the level of confidence in the presence of an association between TRAP and term birth weight as low.

Summary of Narrative Assessment for TRAP and Term Birth Weight

The primary meta-analysis supplemented with additional analyses provided low confidence in the presence of an association between exposure to TRAP and term birth weight. Studies on pollutants not included in the meta-analyses and the studies with indirect traffic measures (distance and density) are consistent with this assessment.

8.4.6 RISK OF BIAS ASSESSMENT

Table 8.6 summarizes the risk of bias assessment for full pregnancy TRAP exposure and term birth weight by study and by pollutant–study pair. Nine studies were included in the risk of bias assessment and reporting of multiple pollutants per study resulted in a total of 23 pollutant–study pairs. Across most domains, the large majority of studies were rated as low to moderate risk of bias. The exception was the confounding domain where 78% of the studies were rated at high risk of bias. This was largely due to the high number of studies that used registry or administrative data without information on maternal smoking during pregnancy or maternal prepregnancy BMI, both considered important potential confounders in this systematic review.

8.4.7 CONFIDENCE ASSESSMENT OF THE BODY OF EVIDENCE

As all studies used the cohort study design, the Panel's initial rating was moderate for confidence in an association between term low birth weight and individual pollutants; no combined assessment across study designs was needed (Table 8.7). Below is a description of the factors that reduced and increased confidence. For the downgrade factor indirectness, all studies addressed the research question directly, and therefore no downgrade was applied. Because there were fewer than 10 studies for NO_2, NO_x, EC, and $PM_{2.5}$, no formal assessment or downgrade was made for publication bias. The

Table 8.6. Summary of Risk of Bias Rating for Studies on Term Birth Weight (Exposure Window: Entire Pregnancy)

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	3	0	6	9	0	14
	Validity of measuring of confounding factors	5	3	1	13	7	3
	Control in analysis	9	0	0	23	0	0
	Overall	2	0	7	6	0	17
2. Selection bias	Selection of participants into the study	9	0	0	23	0	0
3. Exposure assessment	Methods used for exposure assessment	9	0	0	23	0	0
	Exposure measurement methods comparable across the range of exposure	9	0	0	23	0	0
	Change in exposure status	2	7	0	5	18	0
	Overall	2	7	0	5	18	0
4. Outcome measurements	Blinding of outcome measurements	8	1	0	20	3	0
	Validity of outcome measurements	9	0	0	23	0	0
	Outcome measurements	9	0	0	23	0	0
	Overall	8	1	0	20	3	0
5. Missing data	Missing data on outcome measures	9	0	0	23	0	0
	Missing data on exposures	9	0	0	23	0	0
	Overall	9	0	0	23	0	0
6. Selective reporting	Authors reported a priori primary and secondary study aims	9	0	0	23	0	0

Panel decided a priori not to consider upgrading on large magnitude of the effect.

8.4.7.1 Factors That Reduce Confidence

The Panel downgraded all pollutants for risk of bias. This decision was based on the majority of term birth weight studies across all pollutants being rated at high risk of bias for confounding. Many of these studies were registry-based studies that did not collect data on maternal smoking during pregnancy and prepregnancy BMI. In addition, one study was rated high risk of bias because it did not measure potential confounders at the appropriate time, as prepregnancy BMI was based on self-report three months after birth (Gehring et al. 2011b).

Appendix Table 8B-4 contains the risk of bias assessment for each individual study included in the meta-analysis. The very small number of studies at low and moderate risk of bias due to confounding (fewer than three studies across all pollutants) precluded a formal comparison of effect estimates at high risk of bias versus low and moderate risk of bias. Of note is that the risk of bias was rated low or moderate for all other domains, including selection bias, exposure assessment, outcome measurement, missing data, and selective reporting.

The Panel downgraded NO_2 and NO_x associations for unexplained inconsistency. Heterogeneity was high for both pollutants (Figure 8.8), and effect estimates varied widely in both magnitude and direction. For EC, no heterogeneity of effect estimates across studies was found (I^2 = 0%), although this was only based on four studies. For $PM_{2.5}$, high heterogeneity of effect estimates across studies was found (I^2 = 77%), but this was likely due to heterogeneity of magnitude of associations, as all estimates from all studies—except one imprecise study—were in the same direction.

The Panel did not downgrade the confidence for imprecision for any pollutant. NO_2 and NO_x had precise confidence intervals, albeit they included unity. The estimate for EC was consistent with an association (borderline significant); hence no

Table 8.7. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Term Birth Weight (Exposure Window: Entire Pregnancy)[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ ($N = 8$)	–	–	0	0	+	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	Majority of studies (6 of 8) at high RoB. Too few at low/mod RoB to compare estimates.	High heterogeneity ($I^2 = 97\%$) due to magnitude and direction.	Sample size met and confidence interval includes unity, but confidence interval precise.	No formal evaluation possible.	Monotonic ERF reported in three influential studies (Li 2016; Savitz 2014; Smith 2017).	Confounding in both directions possible.	Too few studies across different populations.	
NO_x	Cohort	+++ ($N = 5$)	–	–	0	0	+	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	Majority of studies (3 of 5) at high RoB. Too few at low/mod RoB to compare estimates.	High heterogeneity ($I^2 = 97\%$) due to magnitude and direction.	Sample size met and confidence interval includes unity, but confidence interval precise.	No formal evaluation possible.	Monotonic ERF reported in 2 influential studies (Li 2016; Smith 2017).	Confounding in both directions possible.	Too few studies across different populations.	
EC	Cohort	+++ ($N = 4$)	–	0	0	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	Majority of studies (3 of 4) at high RoB. Too few at low/mod RoB to compare estimates.	No heterogeneity ($I^2 = 0\%$).	Sample size met and estimate consistent with an association.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies across different populations.	

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Table 8.7 (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Term Birth Weight (Exposure Window: Entire Pregnancy)

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
$PM_{2.5}$	Cohort	+++ (N = 6)	–	0	0	0	+	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	Majority of (5 of 6) studies at high RoB. Too few at low/mod RoB to compare estimates.	High heterogeneity (I^2 = 77%) primarily due to magnitude not direction.	Sample size met, and confidence interval does not include unity.	No formal evaluation possible.	Monotonic ERF reported in 2 influential studies (Savitz 2014; Smith 2017).	Confounding in both directions possible.	Too few studies across different populations.	

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

downgrade was applied, as per protocol. The $PM_{2.5}$ confidence interval did not include unity. Note that for all pollutants included in the meta-analysis, the sample size was larger than the specified needed minimum sample size in the protocol.

8.4.7.2 Factors That Increase Confidence

The Panel upgraded the evidence for associations of NO_2, NO_x, and $PM_{2.5}$ with term birth weight following the demonstration of a monotonic exposure–response function in three influential studies (Li et al. 2016; Savitz et al. 2014; Smith et al. 2017). No studies assessing EC and term birth weight evaluated an exposure–response function, and therefore no upgrade was applied.

The Panel did not upgrade the evidence on any of the associations of pollutants with term birth weight on the basis of residual confounding or other factors potentially biasing toward the null. In fact, there was some evidence of the opposite—residual confounding biasing estimates away from the null. Finally, too few studies were available to evaluate consistency across geographic regions, populations or study period.

8.4.7.3 Evaluation of Confidence for Combined Measures of TRAP

The final confidence rating across the four pollutants for which there were sufficient studies to conduct meta-analyses was moderate for $PM_{2.5}$, and low for NO_2, NO_x, and EC. Based on these ratings, the Panel's assessment for TRAP and term birth weight was low. In this assessment, the evidence from other pollutants was weighted more strongly than that from $PM_{2.5}$ because $PM_{2.5}$ is typically a poorer indicator of TRAP, and all $PM_{2.5}$ studies were rated as moderate traffic specificity. Studies on pollutants not included in the meta-analyses and the studies with indirect traffic measures (distance and density) were consistent with this assessment. In conclusion, based on the modified OHAT assessment, the confidence in the quality of the body of evidence between exposure to TRAP and term birth weight is low.

8.4.8 OVERALL CONFIDENCE ASSESSMENT

Based on the narrative assessment (low) and the modified OHAT assessment (low), the overall level of confidence in the evidence for an association between TRAP exposure and term birth weight is low.

8.5 SMALL FOR GESTATIONAL AGE

8.5.1 STUDY SELECTION AND DESCRIPTION

In total, 25 studies investigated associations between TRAP or indirect traffic measures (i.e., distance and density) and small for gestational age for studies that examined exposure during the entire pregnancy and trimesters (Table 8.8 and Appendix Table 8C-4). The most common definition of small for gestational age is birth weight below the 10th percentile for gestational age and sex according to national growth curves. Of these, 16 studies reported associations of small for gestational age with individual traffic-related air pollutants during the entire pregnancy, while a further four reported associations during specific trimesters only. Five studies reported associations solely with indirect traffic measures, and seven studies reported associations with both. Section 8.5.4 describes the indirect traffic measures.

Of the included studies reporting associations with individual pollutants assessed during the entire pregnancy, 14 studies in total assessed trimester-specific associations with small for gestational age (see Appendix Table 8C-1), four of which only reported trimester results (Malmqvist et al. 2011; Mannes et al. 2005; Olsson et al. 2015; Sathyanarayana et al. 2013). A further six studies reported associations of TRAP with small for gestational age using birth-weight-for-gestational-age Z-scores (Appendix Table 8C-2).

All were cohort studies and the majority of studies on small for gestational age were conducted in North America and Europe. BMI and smoking history were mostly derived from medical records or other administrative data. For example, Smith and colleagues (2017) reported the extraction of smoking information from administrative data at an aggregated level, making the results prone to risk of bias. In two studies, individual-level lifestyle factors were obtained from a detailed perinatal hospital database (Dadvand et al. 2014; Kashima et al. 2011). All the other studies were based on administrative databases or birth registers, with some important individual lifestyle data missing or only available at the aggregated level (Brauer et al. 2008; Gehring et al. 2014; Kingsley et al. 2017; Lavigne et al. 2016; Madsen et al. 2010; Malmqvist et al. 2011; Mannes et al. 2005; Olsson et al. 2015; Pereira et al. 2012; Poirier et al. 2015; Sathyanarayana et al. 2013; Smith et al. 2017; Winckelmans et al. 2015). One study was based on administrative data from twin pregnancies (Mariet et al. 2018).

Sample size of small-for-gestational-age studies ranged from 249 up to 818,400 newborn–mother pairs. Altogether, the study populations covered a 15-year span from 1997 to 2012, with most of the studies starting enrollment before or in 2008. Exposure assessment in almost all studies was based on LUR (including hybrid models) or dispersion/CTM. Only the Sydney Birth Study 98/00 (Mannes et al. 2005) used surface monitoring; this study only reported results for trimesters and not for the entire pregnancy. Average air pollution levels of the different studies ranged from 5.0 to 55.5 $\mu g/m^3$ for NO_2; all were below 17 $\mu g/m^3$ for $PM_{2.5}$ mass.

8.5.2 PRIMARY META-ANALYSIS

Figure 8.9 shows summary estimates by pollutant for small for gestational age based on meta-analyses. The combined estimates comprised 11 studies for NO_2, three for EC, four for PM_{10}, and four for $PM_{2.5}$. Studies were excluded from

Table 8.8. Key Study Characteristics of Articles Included in the Systematic Review for Small for Gestational Age—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name[a]	Location	Study Period	Sample Size[b]	Exposure Assessment	Pollutant	Mean or Median Exposure[c]	Effect Estimate (95% CI)[d,e]	Increment
Ballester 2010	INMA Valencia	Valencia, Spain	2003–2006	785	LUR	NO_2	36.9	**1.28 (0.94–1.74)**	10 µg/m^3
Brauer 2008	BC 99/02 Birth Cohort	Vancouver, British Columbia, Canada	1999–2002	70,249	LUR	NO_2	31.6	**0.99 (0.96–1.02)**	10 µg/m^3
						NO	30.7	1.02 (1.00–1.04)	10 µg/m^3
						$PM_{2.5\ abs}$	1.6	1.01 (0.99–1.03)	1 1×10^{-5}/m
						$PM_{2.5}$ mass	4.0	**1.02 (1.00–1.03)**	1 µg/m^3
Dadvand 2014	Barcelona Birth Cohort	Barcelona, Spain	2001–2005	6,438	LUR	NO_2	55.5	**1.03 (0.98–1.10)**	16.8 µg/m^3
						NO_x	102.8	1.02 (0.97–1.07)	41.3 µg/m^3
						$PM_{2.5\ abs}$	3.1	**1.06 (0.97–1.17)**	1.1 1×10^{-5}/m
						PM_{10} mass	39.2	**1.02 (0.93–1.11)**	3.9 µg/m^3
						PM_{coarse} mass	22.3	1.06 (0.96–1.17)	2.3 µg/m^3
						$PM_{2.5}$ mass	16.9	**1.07 (0.97–1.17)**	3.1 µg/m^3
Dedele 2017	Kaunas Birth Outcomes 07/08	Kaunas, Lithuania	2007–2008	3,292	Dispersion/ CTM	NO_2	16.8–24.2	**1.05 (0.82–1.32)**	10 µg/m^3
Gehring 2011a	ABCD	Amsterdam, the Netherlands	2003–2004	7,541	LUR	NO_2	38.7	0.88 (0.68–1.13)	>44.8 vs. <34.6 µg/m^3
								0.97 (0.76–1.24)	40.2–44.8 vs. <34.6 µg/m^3
								1.00 (0.78–1.27)	37.4–40.2 vs. <34.6 µg/m^3
								1.14 (0.90–1.43)	34.6–37.4 vs. <34.6 µg/m^3
Gehring 2014	BC 99/02 Birth Cohort	Vancouver, British Columbia, Canada	1999–2002	68,238	LUR	NO_2	33.5	0.98 (0.96–1.01)	10 µg/m^3
						NO	23.0	1.02 (1.00–1.04)	10 µg/m^3
						$PM_{2.5\ abs}$	1.6	1.02 (1.00–1.04)	1 1×10^{-5}/m
						$PM_{2.5}$ mass	5.5	1.01 (0.99–1.02)	1 µg/m^3

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Table 8.8 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Small for Gestational Age—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name[a]	Location	Study Period	Sample Size[b]	Exposure Assessment	Pollutant	Mean or Median Exposure[c]	Effect Estimate (95% CI)[d,e]	Increment
Kashima 2011	Shizuoka Seirei Birth Study 97/08	Shizuoka, Japan	1997–2008	13,005	LUR	NO_2	29.2	**0.91 (0.80–1.05)**	10 μg/m^3
Kingsley 2017	Rhode Island Birth Outcomes	Providence, Rhode Island, United States	2002–2012	56,633	LUR	BC	0.52	**1.04 (0.99–1.08)**	0.11 μg/m^3
						$PM_{2.5}$ mass	9.5	**1.09 (0.98–1.21)**	2.5 μg/m^3
Lavigne 2016	BORN Ontario	Ontario, Canada	2005–2012	818,400	LUR	NO_2	15.89	**0.98 (0.98–0.98)**	9 ppb
Madsen 2010	Oslo Birth Registry 99/02	Oslo, Norway	1999–2002	25,229	Dispersion/ CTM	NO_2	32.0	1.0 (0.8–1.1)	>38.1 vs. <20.3 μg/m^3
								1.0 (0.9–1.1)	32.1–38.0 vs. <20.3 μg/m^3
								0.6 (0.8–1.0)	20.3–32.0 vs. <20.3 μg/m^3
						PM_{10} mass	13.2	0.9 (0.8–1.0)	>16.2 vs. <10.7 μg/m^3
								0.9 (0.8–1.0)	13.3–16.2 vs. <10.7 μg/m^3
								1.0 (0.9–1.1)	10.7–13.2 vs. <10.7 μg/m^3
						$PM_{2.5}$ mass	11.5	0.9 (0.8–1.0)	>14.1 vs. <9.7 μg/m^3
								1.0 (0.8–1.1)	11.6–14.1 vs. <9.7 μg/m^3
								1.0 (0.9–1.1)	9.7–11.5 vs. <9.7 μg/m^3
Mariet 2018	PRECEE	Dijon and Besancon, France	2005–2009	249	Dispersion/ CTM	NO_2	23.1	**0.81 (0.56–1.17)**	10 μg/m^3
Pereira 2012	Perth Birth Cohort	Perth, Australia	2000–2006	23,452	LUR	NO_2	23.04	**1.02 (0.93–1.12)**	5.63 ppb

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Table 8.8 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Small for Gestational Age—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name[a]	Location	Study Period	Sample Size[b]	Exposure Assessment	Pollutant	Mean or Median Exposure[c]	Effect Estimate (95% CI)[d,e]	Increment
Poirier 2015	Halifax Birth Outcomes	Halifax, Canada	2008–2012	14,360	LUR	NO_2	5.0	**0.97 (0.80–1.19)**	3.3 ppb
						PM_{10} mass	3.3	0.93 (0.84–1.03)	0.4 μg/m^3
						$PM_{2.5}$ mass	1.1	1.00 (0.88–1.15)	0.1 μg/m^3
						Benzene	0.5	1.07 (0.95–1.20)	0.8 μg/m^3
Smith 2017	London Birth Registry 06/10	London, United Kingdom	2006–2010	471,489	Dispersion/ CTM	NO_2	40.6	**1.01 (1.00–1.03)**	8.6 μg/m^3
						NO_x	72.5	1.01 (1.00–1.03)	23.7 μg/m^3
						PM_{10} mass	23.1	**1.01 (0.99–1.03)**	3.0 μg/m^3
						$PM_{2.5}$ mass	14.4	**1.03 (1.00–1.06)**	2.2 μg/m^3
						$PM_{2.5}$ exhaust	0.60	1.02 (1.01–1.04)	0.35 μg/m^3
						Nontailpipe $PM_{2.5}$	0.70	1.01 (1.00–1.02)	0.29 μg/m^3
van den Hooven 2012	Generation R	Rotterdam, the Netherlands	2001–2005	6,997	Dispersion/ CTM	NO_2	39.8	**1.03 (0.99–1.06)**	1 μg/m^3
						PM_{10} mass	30.3	**1.03 (0.99–1.07)**	
Winckelmans 2015	Flanders Birth Study 99/09	Flanders, Belgium	1999–2009	494,653	Dispersion/ CTM	PM_{10} mass	31.24	**1.09 (1.06–1.12)** (>36 weeks)	10 μg/m^3
								1.19 (1.07–1.32) (32–36 weeks)	
								0.96 (0.70–1.34) (<32 weeks)	

$PM_{2.5\ abs}$ = $PM_{2.5}$ absorbance.

[a] All were cohort studies.

[b] All studies included male and female participants.

[c] Units are in the increment column.

[d] Effect estimates are odds ratios. **Bold** indicates the effect estimate was included in the meta-analysis.

[e] None of the estimates were log transformed.

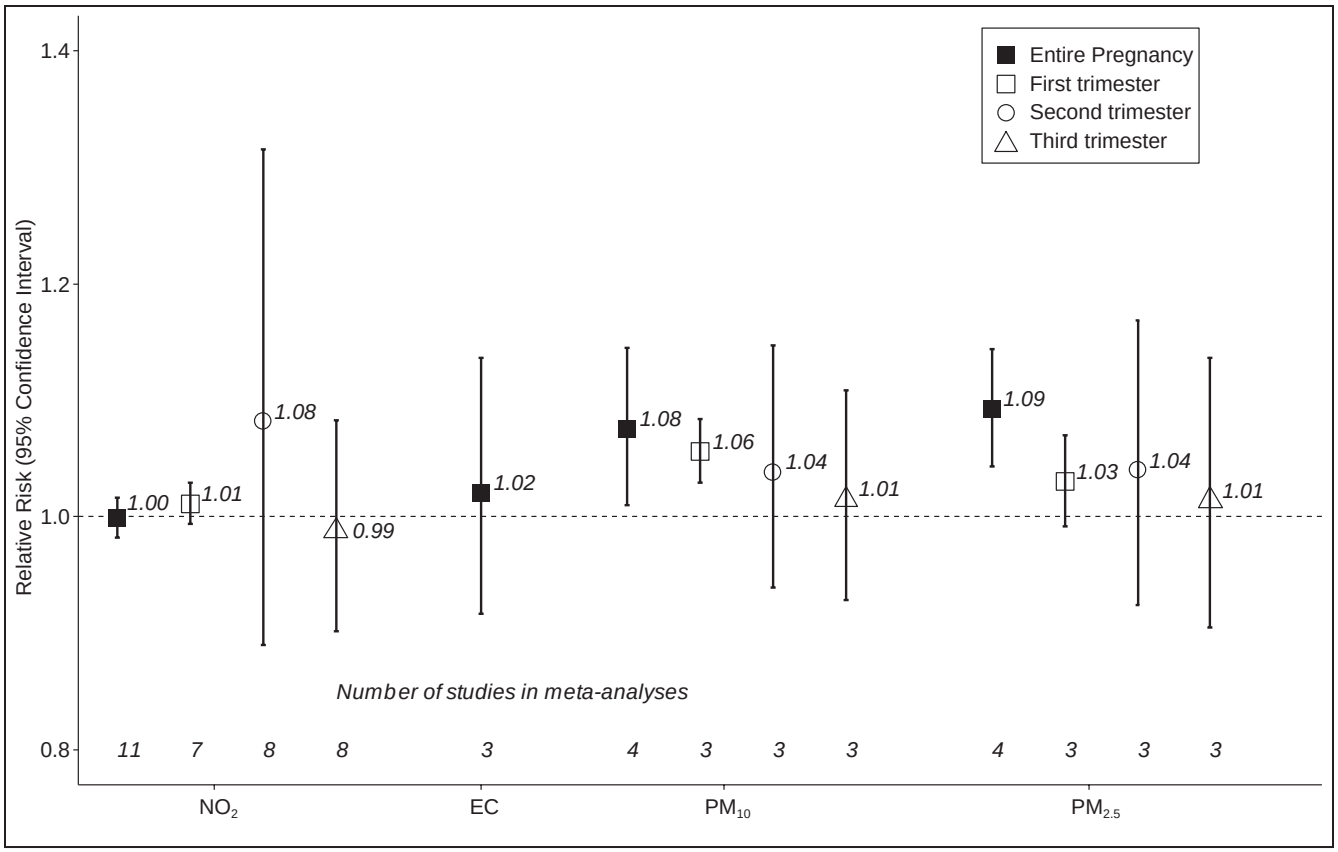

Figure 8.9. Meta-analysis of associations between traffic-related air pollutants and small for gestational age. The following increments were used: 10 µg/m³ for NO_2, 1 µg/m³ for EC, 10 µg/m³ for PM_{10} and 5 µg/m³ for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

meta-analysis when they assessed the same study population and employed the same exposure methods as another study in the meta-analysis (Gehring et al. 2014), or when exposure was analyzed in categories (Gehring et al. 2011a; Madsen et al. 2010). In addition, estimates from Poirier and colleagues (2015) for PM_{10} and $PM_{2.5}$ mass were not considered for meta-analyses due to the incredibly low exposure increment, hampering the meta-analysis. Overall, no association was found for NO_2 exposure and risk for small for gestational age, either for the exposure during the entire pregnancy or for the trimester-specific associations.

All PM studies reported positive associations, and the summary estimates for exposure during the entire pregnancy was statistically significant for both PM_{10} and $PM_{2.5}$. Figure 8.10 shows forest plots for pollutants with at least three estimates of association (NO_2, EC, PM_{10}, and $PM_{2.5}$). The summary estimate for each 10-µg/m³ increment in PM_{10} was 1.08 (95% CI: 1.01–1.14). The corresponding estimate for $PM_{2.5}$ expressed for a 5-µg/m³ increment was 1.09 (1.04–1.14). The results for entire pregnancy and PM_{10} reported overall low heterogeneity, and a large weight (67%) was given to the Flanders birth study (Winckelmans et al. 2015). Also, no heterogeneity was observed for $PM_{2.5}$ and the largest weights were given in the meta-analysis to the London Birth Registry (48%; Smith et al. 2017) and the BC 99/02 Birth Cohort (38%; Brauer et al. 2008).

The summary estimate of three studies on EC and risk of small for gestational age did not reveal a significant association for the entire pregnancy period, although all studies reported positive point estimates. The EC meta-analysis was driven by Brauer et al. 2008 (weight of 79%).

There were three small-for-gestational-age studies available for the analyses by trimester for both PM_{10} and $PM_{2.5}$. Appendix Figure 8C-1 shows the forest plots for PM_{10} and $PM_{2.5}$ across all trimesters. Almost all trimester-specific estimates were positive except for the third trimester estimates of Smith and colleagues (2017). Results indicate that the entire-pregnancy association between PM_{10} and $PM_{2.5}$ and small for gestational age was primarily driven by the exposure during the first trimester.

The Panel did not identify at least three studies to perform a meta-analysis for NO, NO_x, nontailpipe $PM_{2.5}$, $PM_{2.5}$ exhaust, and benzene. Generally, these few studies indicated a small increased risk in small for gestational age. The two

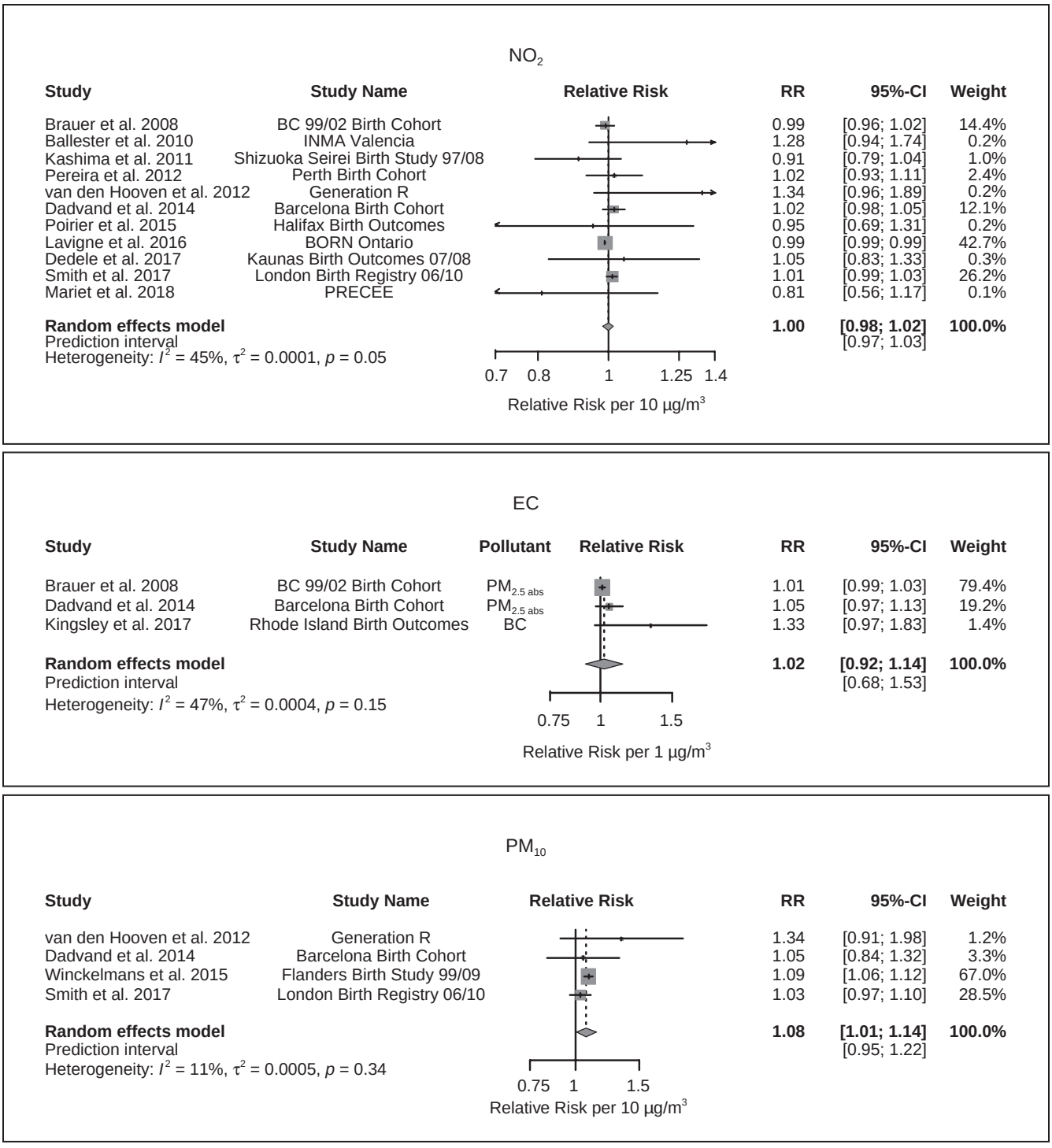

Figure 8.10. Associations of NO_2, EC, PM_{10}, and $PM_{2.5}$ with small for gestational age: meta-analysis (exposure window: entire pregnancy).
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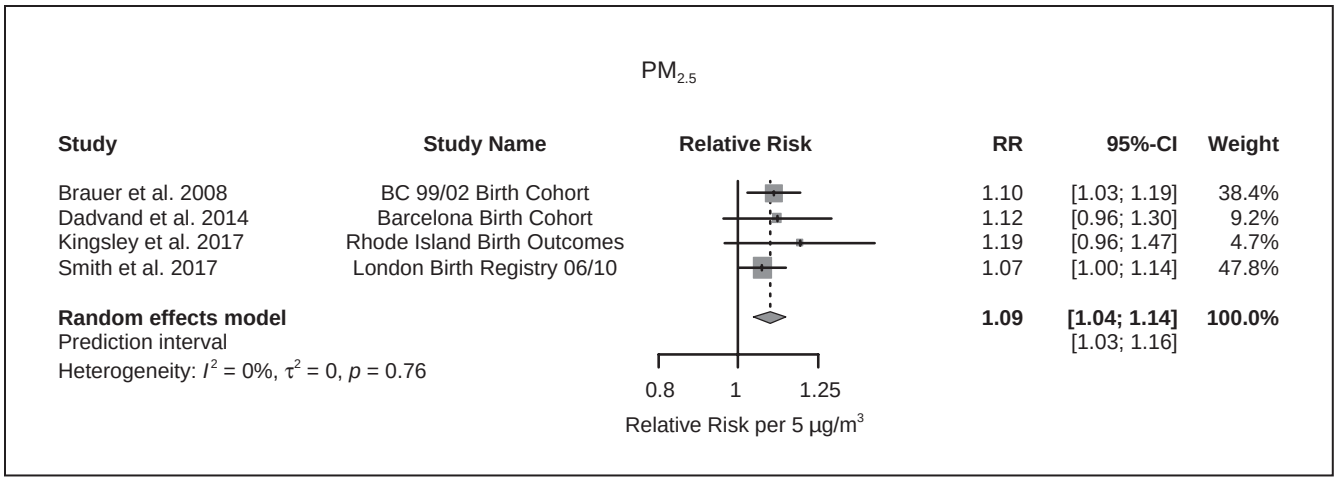

Figure 8.10. *Continued.*

NO studies, both from the BC 99/02 Birth Cohort, reported a borderline increased risk of 1.02 (95% CI: 1.00–1.04) per 10-µg/m^3 (Brauer et al. 2008, Gehring et al. 2014). From the two studies for NO_x (Dadvand et al. 2014, Smith et al. 2017), only Smith and colleagues (2017) suggested an association (1.01 [1.00–1.03] per 23.7-µg/m^3). Also, Smith and colleagues (2017) was the only study contributing nontailpipe $PM_{2.5}$ and $PM_{2.5}$ exhaust exposure during the entire pregnancy period, again reporting small increased risks. Poirier and colleagues (2015) was the only study of benzene exposure and reported a small increased risk. Likewise there were too few studies using Z-scores to perform meta-analyses. The small number of studies on Z-scores show mixed results, depending on pollutant and pregnancy window.

8.5.3 ADDITIONAL META-ANALYSES

All but one estimate in the primary meta-analysis examining NO_2 and EC were rated as high traffic-specific studies; the exception was a province-wide study in Ontario, Canada, for NO_2, which was ranked moderate traffic specificity because the study used six-digit postal codes over a large area that was mostly nonurban (Lavigne et al. 2016). A priori, and in accordance with the exposure framework method (Chapter 6) all $PM_{2.5}$ and PM_{10} studies were rated as moderate traffic specificity studies because the exposure-assessment methods did not differentiate exposures to traffic PM from exposures related to nontraffic sources and regional transport from nontraffic sources. Appendix Figure 8C-2 illustrates the included studies by region for NO_2. The combined estimates stratified by region reported similar null results in North America (N = 3) and Western Europe (N = 5). There were only single studies available in the other regions of the world.

Figure 8.11 and Appendix Figure 8C-3 show meta-analysis associations (for NO_2 and $PM_{2.5}$) stratified by studies that did and did not adjust for maternal smoking during pregnancy and prepregnancy BMI. For NO_2, one study (Smith et al. 2017) did not adjust for maternal smoking (Figure 8.11) and five did not account for maternal prepregnancy BMI (Appendix Figure 8C-3); however, the summary estimates remained null regardless of whether adjustment was made for these potential confounders. For $PM_{2.5}$, adjusting for smoking increased the summary estimate slightly, although this was based on small numbers (Figure 8.11). In addition, only one study controlled for BMI (Dadvand et al. 2014) (Appendix Figure 8C-3). For EC, three used birth registries or hospital records, and one study controlled for BMI (Dadvand et al. 2014). For PM_{10}, two of the four studies did not include smoking or prepregnancy BMI (Smith et al. 2017; Winckelmans et al. 2015). Hence, the number of studies was too small to perform sensitivity analysis for EC and PM_{10}.

Three of the small-for-gestational-age studies reported models in which the traffic-related pollutant effect estimates were adjusted for traffic noise (Appendix Table 8C-3) (Gehring et al. 2014; Smith et al. 2017; van den Hooven et al. 2012). In Smith and colleagues (2017) the effect estimates were similar, while Gehring and colleagues (2014) show the effects were attenuated after adjustment in two pollutant models. Note that van den Hooven only reported mutually adjusted results for traffic pollutants and traffic noise, hampering a comparison.

8.5.4 ASSOCIATIONS WITH INDIRECT TRAFFIC MEASURES

Appendix Table 8C-4 and Figure 8.12 summarize the findings for small for gestational age and indirect traffic measures in 10 different study populations (12 studies in total). The majority of the distance to roadway studies reported a positive association. Of note, a positive association was reported in the BC 99/02 Birth Cohort only when very close to major roads (<50 m) and not when including highway traffic further

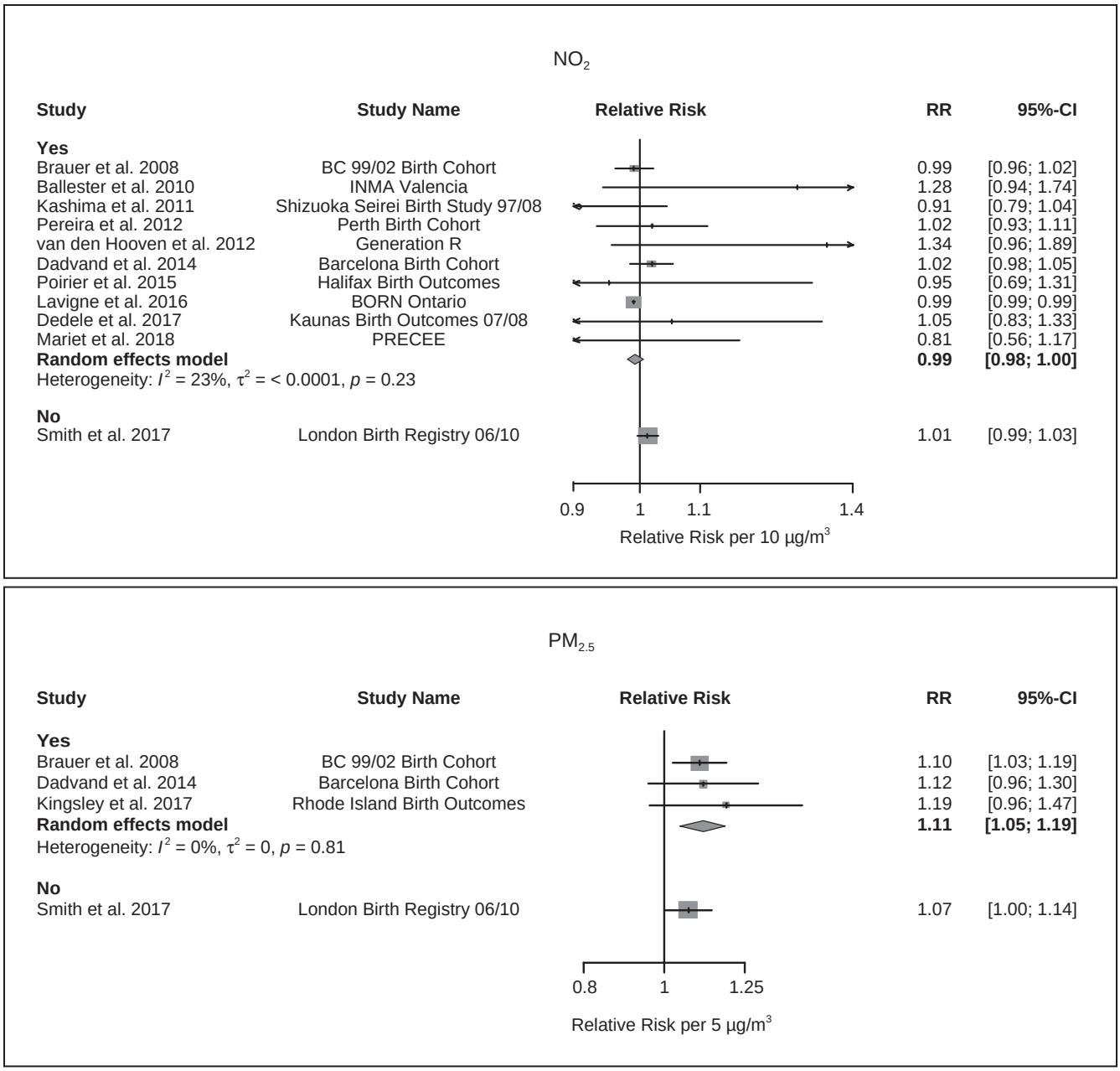

Figure 8.11. Associations of NO_2 and $PM_{2.5}$ with small for gestational age: meta-analysis by smoking adjustment (exposure window: entire pregnancy).

away (<150 m from highway) (Brauer et al. 2008; Gehring et al. 2014).

The pattern for the four studies reporting traffic density measures was less clear with half of them reporting a positive association, half of them null findings. Note that of the indirect traffic measure studies, only two reached statistical significance (Sathyanarayana et al. 2013; Zeka et al. 2008).

8.5.5 NARRATIVE ASSESSMENT

The body of evidence includes studies reporting associations between traffic-related air pollutants or indirect traffic measures and small for gestational age, with a total population base of almost 2.8 million participants. The evidence base includes small, traditional birth cohorts as well as large administrative cohorts. The most common definition of small for gestational age was birth weight below the 10th percentile

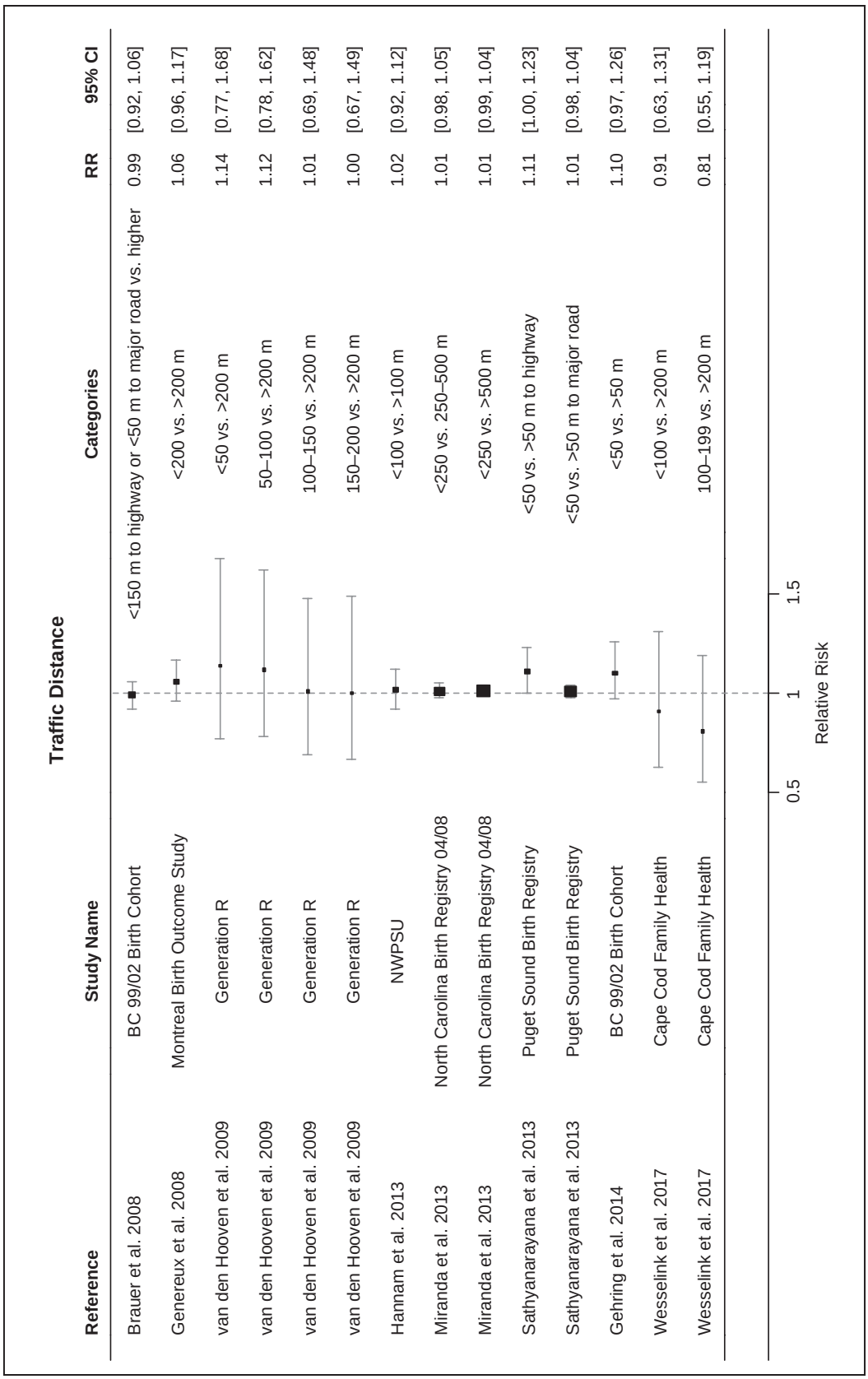

Figure 8.12. Associations of distance to major roads and traffic density with small for gestational age. *Figure continues next page.*

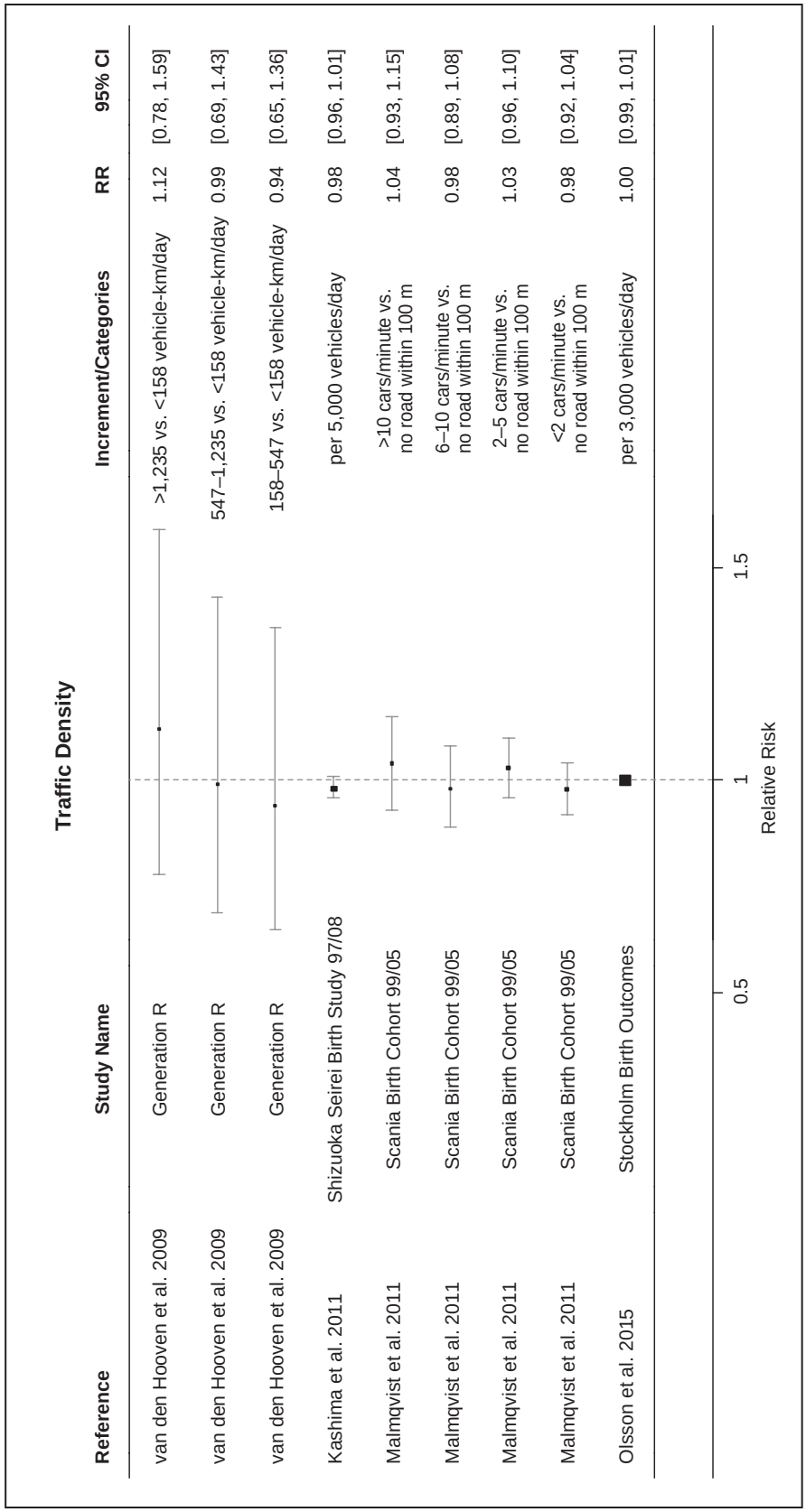

Figure 8.12. *(Continued).*

for gestational age and sex, according to the national growth curve. The majority of studies examined exposure to individual traffic-related air pollutants during the entire pregnancy. Almost all studies were conducted in North America or Europe, with only a few studies outside of these regions in Japan and Australia. Most cohorts used birth registry data allowing for large, representative populations, but these lacked some lifestyle information, making them prone to risk of bias. Six studies had extensive lifestyle information, including five prospective birth cohorts and one study using an administrative perinatal database. Exposure assessment in almost all studies on pollutants used LUR or dispersion/CTM; only one of the studies used surface monitoring, and this study was one of the earlier ones to be published. Full address history during pregnancy was not always available. Given that many women change addresses during pregnancy, studies lacking this information may be subject to increased exposure misclassification, which may introduce measurement error when exposures are assigned based on the address at delivery. Most likely, however, this leads to nondifferential misclassification leading to an underestimation of the true association (e.g., Bell et al. 2018; Hodgson et al. 2015).

The meta-analysis suggests a higher risk for small for gestational age with exposure to PM, with RR = 1.08 (95% CI: 1.01–1.14) per 10-μg/m^3 for PM_{10} and 1.09 (1.04–1.14) per 5-μg/m^3 for $PM_{2.5}$. Trimester-specific associations suggest that the PM-associated risks were mainly driven by exposure during the first trimester (1.06; 1.03–1.08) per 10-μg/m^3 for PM_{10} and 1.03 (0.99–1.07) per 5-μg/m^3 for $PM_{2.5}$, based on three studies each). There were no associations of small for gestational age with NO_2 and EC. Results from studies using distance to roadways lend some additional support to an association between TRAP and the risk for small for gestational age.

The small number of studies on Z-scores show mixed results; however, the one study on $PM_{2.5}$ exposure during the first trimester supports the findings in the main meta-analysis. The Panel rated the confidence in the presence of an association between exposure to TRAP and small for gestational age as moderate.

Summary of Narrative Assessment for TRAP and Small for Gestational Age

The primary meta-analysis supplemented with additional analyses provided moderate confidence in the presence of an association between exposure to TRAP and small for gestational age. Studies on pollutants not included in the meta-analyses are consistent with this assessment, as are studies of indirect traffic measures (distance).

8.5.6 RISK OF BIAS ASSESSMENT

Table 8.9 depicts the results of the risk of bias assessment and summarizes the risk of bias on a study level (N = 13) and for all pollutant study pairs (N = 22) for the entire pregnancy. For most domains, the vast majority of studies were ranked as a low to moderate risk of bias. One exception was within the confounding domain where approximately 54% of the studies (N = 7) were rated as high risk of bias. This was due to the risk of bias subdomains adjustment for potential important confounders and the validity of measuring potential important confounders. The confounders listed as potentially important within small-for-gestational-age meta-analyses included age, individual-level or neighborhood socioeconomic status, prepregnancy BMI, and maternal smoking.

Appendix Table 8C-5 contains the risk of bias assessment for each individual study included in the meta-analysis. Three birth cohort studies had detailed individual lifestyle factor data available from questionnaires and were rated low for confounding: the INMA cohort (Ballester et al. 2010), the Kaunas city pregnant women cohort (Dedele et al. 2017) and the Generation R cohort (van den Hooven et al. 2012). In controlling for all required potential important confounding factors, derived from the most valid measure of a self-report, these were accordingly rated as low risk of bias within the adjustment for potential confounders subdomain. Furthermore, the Barcelona Birth Cohort (Dadvand et al. 2014) and the Shizuoka Seirei Birth Study 97/08 (Kashima et al. 2011) also had detailed individual lifestyle factors available from a hospital-based birth database; hence those studies were also rated as low for risk of bias. The Rhode Island Birth Outcomes study (Kingsley et al. 2017) also used a detailed hospital-based birth database but only had maternal smoking, not prepregnancy BMI.

Seven studies were categorized as high risk for confounding, mainly because of the missing adjustment for BMI. The Flanders (Winckelmans et al. 2015) and London (Smith et al. 2017) birth registry studies did not adjust for individual maternal smoking due to the absence of this variable in the registry. In addition to controlling for maternal tobacco use, two studies (Dedele et al. 2017; Kashima et al. 2011) considered passive smoking. Four studies corrected for the gestational maternal alcohol consumption (Dadvand et al. 2014; Dedele et al. 2017; Kashima et al. 2011; van den Hooven et al. 2012).

All studies were rated as low to moderate risk of bias for exposure methods. Two main methods were adopted to assess maternal exposure to TRAP; LUR (Ballester et al. 2010; Brauer et al. 2008; Dadvand et al. 2014; Kashima et al. 2011; Kingsley et al. 2017; Lavigne et al. 2016; Pereira et al. 2012; Poirier et al. 2015) and dispersion/CTM models (Dedele et al. 2017; Mariet et al. 2018; Smith et al. 2017; van den Hooven et al. 2012; Winckelmans et al. 2015). All studies included in the main meta-analysis and risk of bias assessment estimated maternal

Table 8.9. Summary of Risk of Bias Rating for Studies on Small for Gestational Age (Exposure Window: Entire Pregnancy)

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	5	1	7	9	1	12
	Validity of measuring of confounding factors	7	6	0	13	9	0
	Control in analysis	13	0	0	22	0	0
	Overall	5	1	7	9	1	12
2. Selection bias	Selection of participants into the study	13	0	0	22	0	0
3. Exposure assessment	Methods used for exposure assessment	13	0	0	22	0	0
	Exposure measurement methods comparable across the range of exposure	13	0	0	22	0	0
	Change in exposure status	8	5	0	11	11	0
	Overall	8	5	0	11	11	0
4. Outcome measurements	Blinding of outcome measurements	13	0	0	22	0	0
	Validity of outcome measurements	13	0	0	22	0	0
	Outcome measurements	13	0	0	22	0	0
	Overall	13	0	0	22	0	0
5. Missing data	Missing data on outcome measures	13	0	0	22	0	0
	Missing data on exposures	13	0	0	22	0	0
	Overall	13	0	0	22	0	0
6. Selective reporting	Authors reported a priori primary and secondary study aims	13	0	0	22	0	0

exposure across the entire gestational period, with some studies also evaluating exposure during trimesters.

Maternal residential mobility data was lacking in some studies, particularly those that gathered data from administrative birth records or registry data. About 38% ($N = 5$) of the studies (Dadvand et al. 2014; Kingsley et al. 2017; Mariet et al. 2018; Poirier et al. 2015; Smith et al. 2017) were rated as a moderate risk of bias for the change in exposure status subdomain because they did not consider address changes during pregnancy.

8.5.7 CONFIDENCE ASSESSMENT OF THE BODY OF EVIDENCE

Table 8.10 provides the Panel's confidence assessment. The table includes the pollutants with three or more studies for which a meta-analysis was conducted. As all studies used the cohort study design, the Panel's initial rating was moderate for all pollutants. We first discuss four factors that may reduce confidence (downgrade). For the downgrade factor indirectness, all studies addressed the research question directly, and therefore no downgrade was applied. Next, factors that may increase confidence (upgrade) are discussed. The Panel decided a priori not to consider the upgrading factor large magnitude of the effect.

8.5.7.1 Factors That Reduce Confidence

Figure 8.13 shows the forest plots stratified by risk of bias for the confounding domain during the entire pregnancy for NO_2 and $PM_{2.5}$, respectively. The Panel decided to downgrade EC and $PM_{2.5}$; the majority of studies were rated high risk of bias for confounding because they did not adjust for a priori defined potential important confounders. Despite about half of the studies being rated high risk of bias for confounding, no

Table 8.10. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Small for Gestational Age (Exposure Window: Entire Pregnancy)[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ (N = 11)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	5 of 11 studies with high RoB, and no difference in summary estimates.	Low heterogeneity (I^2 = 45%). Most estimates hovered around the null.	Sample size met and confidence interval includes unity, but confidence interval precise.	Just enough studies to evaluate. No evidence found in plot and test.	No evidence of plausible shape of the ERF.	Confounding in both directions possible.	No evidence of associations in any region.	
EC	Cohort	+++ (N = 3)	–	0	–	0	0	0	0	+ (Very low)
	Rationale	Cohort design initially rated as moderate.	2 of 3 studies high RoB.	Low heterogeneity (I^2 = 47%) due to magnitude not direction.	Sample size met but confidence interval wide and clearly includes unity.	Too few studies, thus based on NO_2.	No evidence of plausible shape of the ERF.	Confounding in both directions possible.	Too few studies across different populations.	
PM_{10}	Cohort	+++ (N = 4)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	2 of 4 studies high RoB and no difference in summary estimates, though numbers of studies small.	Low heterogeneity (I^2 = 11%), due to magnitude not direction.	Sample size met, and confidence interval does not include unity.	Too few studies, thus based on NO_2.	No evidence of plausible shape of the ERF.	Confounding in both directions possible.	Too few studies across different populations.	

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Table 8.10 (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Small for Gestational Age (Exposure Window: Entire Pregnancy)

	High ++++ Moderate +++ Low ++ Very low +		Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
$PM_{2.5}$	Cohort	+++ ($N = 4$)	–	0	0	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	Majority of studies (3 of 4) at high RoB. Too few at low/mod RoB to compare estimates.	No heterogeneity ($I^2 = 0\%$).	Sample size met, and confidence interval does not include unity.	Too few studies, thus based on NO_2.	No evidence of plausible shape of the ERF.	Confounding in both directions possible.	Too few studies across different populations.	

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

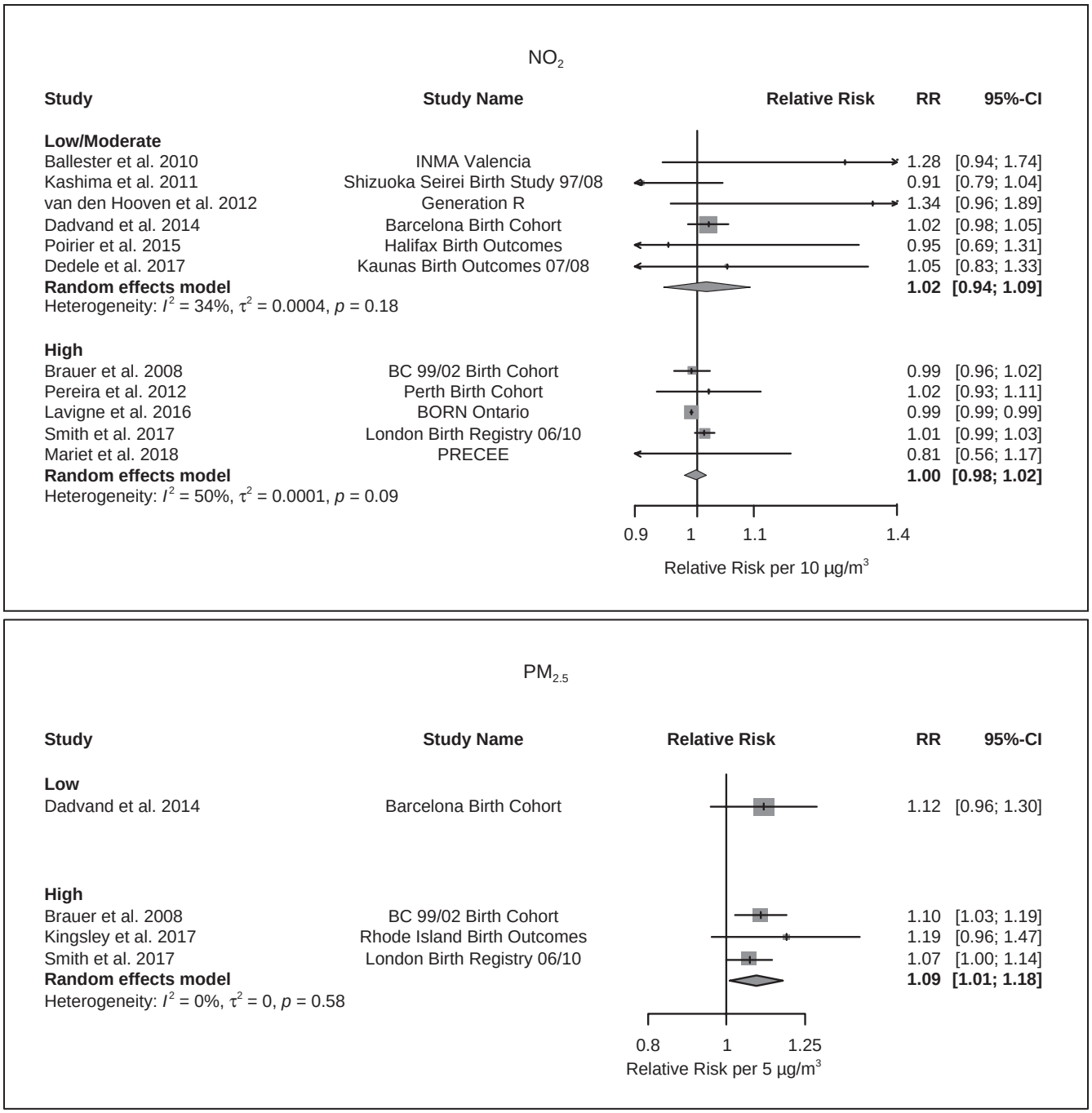

Figure 8.13 Associations of NO_2 and $PM_{2.5}$ with small for gestational age: meta-analysis by risk of bias confounding (exposure window: entire pregnancy).

downgrade was applied for NO_2 and PM_{10} because the summary effect estimates were comparable in meta-analyses stratified by risk of bias. Although, for PM_{10} a formal comparison was not possible given the small number of studies.

No downgrade was applied for unexplained inconsistency. Heterogeneity was low for all pollutants. This was entirely due to magnitude not direction for EC, PM_{10}, and $PM_{2.5}$. For NO_2, results from most individual studies hovered around the null, with effect estimates from seven of the 11 studies in the range of 0.91 to 1.02 (Figure 8.10). The four studies with very different NO_2 results (Ballester et al. 2010; Mariet et al. 2018; Poirier et al. 2015; van den Hooven 2012) had very imprecise

effect estimates and had low weight in the meta-analysis (<1% in total).

The Panel downgraded the confidence for imprecision for EC because the confidence intervals were wide and clearly included unity. NO_2 was not downgraded for imprecision because confidence intervals were narrow, albeit including unity. For particulate matter ($PM_{2.5}$ and PM_{10}), the confidence intervals did not included unity, therefore the Panel did not downgrade. Note that for all pollutants included in the meta-analysis, the sample size was larger than the specified needed minimum sample size in the protocol.

Of the pollutants, only NO_2 had a sufficient number of studies ($N > 10$) for an evaluation of publication bias. The funnel plot did not show evidence of asymmetry and the Egger test P value was not statistically significant ($P = 0.17$) (Appendix Figure 8C-4). Publication bias could not be assessed for the remaining pollutants because there were not enough studies for a formal evaluation. Based on this, the Panel did not downgrade confidence due to publication bias.

8.5.7.2 Factors That Increase Confidence

Upgrade for a monotonic exposure–response was only applied if the linear association was at least borderline significant to avoid upgrading null findings. As only one study characterized the shape of the exposure–response function for other pollutants (Winckelmans et al. 2015), no upgrade was considered. The study of Winckelmans and colleagues (2015) on small-for-gestational-age and gestational PM_{10} exposure, with the largest weight (67%) in the meta-analysis, suggested the existence of an inflection point in the shape of the association with relatively linear slopes before and after the inflection point of about 27 $\mu g/m^3$.

The Panel did not upgrade the evidence on any of the associations of pollutant and small for gestational age on the basis of residual confounding or other factors potentially biasing toward the null, because confounding can work in either direction and can differ in specific populations. Also, the Panel did not upgrade the evidence for consistency across geographic regions, populations or study period. Too few studies were available to evaluate consistency across geographic regions, populations or study period for pollutants other than NO_2. The Panel found generally consistent null associations between small for gestational age and exposure to NO_2 overall and across geographic regions. Given the absence of any evidence of associations, the Panel decided not to upgrade the evidence for NO_2.

8.5.7.3 Evaluation of Confidence for Combined Measures of TRAP

The Panel conducted separate assessments of the four pollutants for which there were sufficient studies to conduct meta-analyses. The assessment of confidence was moderate for NO_2 and PM_{10}, low for $PM_{2.5}$, and very low for EC. Based on the modified OHAT assessment, the confidence in the quality of the body of evidence between TRAP and small for gestational age is moderate.

8.5.8 OVERALL CONFIDENCE ASSESSMENT

Combining the narrative (moderate) and modified OHAT assessment (moderate), the Panel concluded that there was an overall moderate level of confidence in the evidence for an association between TRAP exposure and small for gestational age.

8.6 PRETERM BIRTH

8.6.1 STUDY SELECTION AND DESCRIPTION

Thirty studies reported associations between TRAP and preterm birth, dichotomized as birth less than 37 weeks gestation. The majority of the studies report on exposure windows of the entire pregnancy (often in addition to trimesters) (Table 8.11), while five studies included only trimester-specific results (Jalaludin et al. 2007; Lavigne et al. 2016; Leem et al. 2006; Malmqvist et al. 2011; Wilhelm and Ritz 2005) (Appendix Table 8D-1 for trimester-specific information). Seven of the studies also included indirect traffic measures (Gehring et al. 2014; Giorgis-Allemand et al. 2017; Laurent et al. 2016a; Malmqvist et al. 2011; Olsson et al. 2015; Wilhelm and Ritz 2003; Wu et al. 2011), while 11 additional studies reported associations only for traffic density or distance measures but not pollutants (see Section 8.6.4).

Although the Panel decided a priori to focus on preterm birth studies with births at less than 37 weeks gestation—the most frequently studied endpoint—estimates from the selected preterm birth studies reporting moderately or very preterm birth were also extracted (Gehring et al. 2014; Padula et al. 2014a; 2014b). Most studies were conducted in North America and Europe (almost equally represented), two in Asia (Ji et al. 2019; Leem et al. 2006), and one each in Australia (Jalaludin et al. 2007) and Brazil (Saldiva et al. 2018). Most studies ($N = 22$) used the cohort design, while Wilhelm and colleagues (2005) used a case-cohort design, and the remaining seven were case-control studies (Laurent et al. 2016a; Ritz et al. 2007; Saldiva et al. 2018; Wilhelm et al. 2011; Wilhelm and Ritz 2003; Wu et al. 2011 [LA and OC]).

The studies differed in sample size, ranging from 700 to a few thousand in smaller cohorts to much larger numbers in some birth registries with a maximum of 0.8 million participants in the BORN Ontario study (Lavigne et al. 2016) and 1.1 million participants in the California Birth Registry 01/08 (Wu et al. 2016). Across all studies, the population base included almost 6 million participants. Most studies were based on large and inclusive birth registries, which are therefore a good representation of the overall population. Those registry-based

Table 8.11. Key Study Characteristics of Articles Included in the Systematic Review for Preterm Birth—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Effect Estimate (95% CI)[b,c]	Increment
Brauer 2008	BC 99/02 Birth Cohort	Cohort	Vancouver, British Columbia, Canada	1999–2002	70,249	LUR	NO_2	31.6	1.08 (0.91–1.29)	10 μg/m^3
							NO	30.7	1.05 (0.94–1.18)	10 μg/m^3
							$PM_{2.5\ abs}$	1.6	0.99 (0.87–1.13)	1 1×10^{-5}/m
							$PM_{2.5}$ mass	4.0	1.07 (0.98–1.16)	1 μg/m^3
Dedele 2017	Kaunas Birth Outcomes 07/08	Cohort	Kaunas, Lithuania	2007–2008	3,013	Dispersion/ CTM	NO_2	16.8–24.2	**1.22 (0.94–1.56)**	10 μg/m^3
Estarlich 2016	INMA	Cohort	Multiple cities, Spain	2004–2008	2,409	LUR	NO_2	28.8	**1.11 (0.86–1.45)**	10 μg/m^3
							Benzene	1.3	1.38 (1.03–1.84)	1 μg/m^3
Gehring 2011a	ABCD	Cohort	Amsterdam, the Netherlands	2003–2004	7,541	LUR	NO_2	38.7	0.93 (0.68–1.27)	>44.8 vs. <34.6 μg/m^3
									0.95 (0.69–1.29)	40.2–44.8 vs. <34.6 μg/m^3
									0.69 (0.49–0.96)	37.4–40.2 vs. <34.6 μg/m^3
									0.76 (0.55–1.05)	34.6–37.4 vs. <34.6 μg/m^3
Gehring 2011b	PIAMA	Cohort	Multiple cities, the Netherlands	1996–1997	3,853	LUR	NO_2	30.4	**1.08 (0.80–1.47)**	11.2 μg/m^3
							$PM_{2.5\ abs}$	2.75	**1.27 (0.96–1.67)**	0.94 1×10^{-5}/m
							$PM_{2.5}$ mass	20.1	**1.22 (0.83–1.80)**	4.6 μg/m^3
Gehring 2014	BC 99/02 Birth Cohort	Cohort	Vancouver, British Columbia, Canada	1999–2002	68,238	LUR	NO_2	33.5	**1.02 (0.98–1.06)** [30–<37 weeks gestation]	10 μg/m^3
									1.06 (0.91–1.22) [<30 weeks gestation]	

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Table 8.11 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Preterm Birth—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Effect Estimate (95% CI)[b,c]	Increment
							NO	23.0	**1.01 (0.99–1.04)** [30–<37 weeks gestation]	10 µg/m^3
									1.00 (0.91–1.11) [< 30 weeks gestation]	
							$PM_{2.5\ abs}$	1.6	**1.01 (0.98–1.04)** [30–<37 weeks gestation]	1 1×10^{-5}/m
									0.97 (0.87–1.08) [<30 weeks gestation]	
							$PM_{2.5}$ mass	5.5	**1.00 (0.98–1.03)** [30–<37 weeks gestation]	1 µg/m^3
									1.07 (1.00–1.15) [<30 weeks gestation]	
Giorgis-Allemand 2017	ESCAPE	Cohort	Multiple cities, multiple countries	1994–2011	71,493	LUR	NO_2	25	**0.96 (0.91–1.01)**	10 µg/m^3
							NO_x	Not reported	**0.96 (0.92–1.00)**	20 µg/m^3
							$PM_{2.5\ abs}$	Not reported	**0.92 (0.82–1.02)**	1 1×10^{-5}/m
							PM_{10} mass	25	0.97 (0.87–1.07)	10 µg/m^3
							PM_{coarse} mass	Not reported	1.00 (0.92–1.08)	5 µg/m^3
							$PM_{2.5}$ mass	15	**0.96 (0.87–1.04)**	5 µg/m^3

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Table 8.11 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Preterm Birth—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Effect Estimate (95% CI)[b,c]	Increment
Ji 2019	Shanghai PTB Study	Cohort	Shanghai, China	2014–2015	25,493	LUR	NO_2	48.2	**1.03 (0.96–1.10)**	10 μg/m³
Kingsley 2017	Rhode Island Birth Outcomes	Cohort	Providence, Rhode Island, United States	2002–2012	61,640	LUR	BC	0.52	**1.00 (0.97–1.05)**	0.11 μg/m³
							$PM_{2.5}$ mass	9.5	**1.04 (0.94–1.15)**	2.5 μg/m³
Laurent 2016a	California Birth Registry 01/08	Case-control	California, United States	2001–2008	1,138,070	Dispersion/ CTM	NO_x	6.1	**1.00 (1.00–1.01)**	5.97 ppb
							CO	58.75	1.00 (1.00–1.01)	58.79 ppb
							EC	1.55	**1.04 (1.03–1.05)**	1.258 μg/m³
							$PM_{2.5}$ onroad diesel	0.45	1.06 (1.05–1.07)	0.397 μg/m³
							$PM_{2.5}$ onroad gasoline	0.35	1.09 (1.08–1.11)	0.386 μg/m³
							$PM_{2.5}$ Fe	0.238	0.98 (0.97–0.99)	0.190 μg/m³
							$PM_{2.5}$ Zn	0.004	0.98 (0.98–0.99)	0.002 μg/m³
							Primary $PM_{0.1}$	1.74	1.02 (1.01–1.03)	1.389 μg/m³
							PNC <100 nm	6,111	0.99 (0.99–1.00)	6,480 particles/cm³
Lavigne 2016	BORN Ontario	Cohort	Ontario, Canada	2005–2012	818,400	LUR	NO_2	15.89	**1.08 (1.05–1.10)**	9 ppb
Llop 2010	INMA Valencia	Cohort	Valencia, Spain	2003–2005	738	LUR	NO_2	36.9	1.29 (1.13–1.46) [>46.2 μg/m³]	1 μg/m³
									0.96 (0.91–1.01) [<46.2 μg/m³]	

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Table 8.11 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Preterm Birth—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Effect Estimate (95% CI)[b,c]	Increment
							Benzene	2.2	6.46 (1.58–26.35) [>2.7 µg/m^3] 0.67 (0.28–1.60) [<2.7 µg/m^3]	1 µg/m^3
Maroziene 2002	Kaunas Birth Outcomes 98	Cohort	Kaunas, Lithuania	1998	3,988	Surface monitoring	NO_2	11.69	**1.25 (1.07–1.46)**	10 µg/m^3
Olsson 2015	Stockholm Birth Outcomes	Cohort	Stockholm, Sweden	1997–2006	74,991	Dispersion/ CTM	NO_x	15.1	**1.17 (1.10–1.26)**	10 µg/m^3
Padula 2014b	SAGE	Cohort	Fresno, California, United States	2001–2006	42,904	LUR	PAH	3.55	0.99 (0.92–1.07) [34–36 weeks gestation] 0.93 (0.79–1.11) [32–33 weeks gestation] 0.76 (0.62–0.93) [28–31 weeks gestation] 0.51 (0.39–0.67) [20–27 weeks gestation]	Q4 vs. Q1–Q3 ng/m^3
Panasevich 2016	MoBa	Cohort	Oslo and Bergen, Norway	1999–2008	16,283	LUR	NO_2	13.6	0.96 (0.82–1.13)	10 µg/m^3
Poirier 2015	Halifax Birth Outcomes	Cohort	Halifax, Canada	2008–2012	14,415	LUR	NO_2	5.0	**0.94 (0.85–1.04)**	3.3 ppb
							PM_{10} mass	3.3	0.93 (0.88–0.98)	0.4 µg/m^3
							$PM_{2.5}$ mass	1.1	0.95 (0.89–1.02)	0.1 µg/m^3
							Benzene	0.5	0.99 (0.92–1.06)	0.8 µg/m^3

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Table 8.11 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Preterm Birth—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Effect Estimate (95% CI)[b,c]	Increment
Ritz 2007	Los Angeles Birth Cohort	Case-control	Los Angeles County, California, United States	2003	58,316	Surface monitoring	CO	0.92	1.03 (0.91–1.17)	>1.25 vs. <0.58 ppm
									0.84 (0.77–0.91)	0.92–1.25 vs. <0.58 ppm
									0.76 (0.7–0.82)	0.59–0.91 vs. <0.58 ppm
Saldiva 2018	Sao Paulo Birth Registry 12/13	Case-control	Sao Paulo, Brazil	2012–2013	1,414	Surface monitoring	NO_2	20	0.86 (0.63–1.16)	<16.4 vs. >16.4 μg/m^3
van den Hooven 2012	Generation R	Cohort	Rotterdam, the Netherlands	2001–2005	7,045	Dispersion/ CTM	NO_2	39.8	**1.01 (0.98–1.04)**	1 μg/m^3
							PM_{10} mass	30.3	1.03 (1.00–1.07)	
Wilhelm 2003	LA County Birth Registry 94/96	Case-control	Los Angeles County, California, United States	1994–1996	34,588	Surface monitoring	NO_2	4.36	**0.94 (0.85–1.03)**	1 pphm
							CO	1.74	1.11 (1.00–1.23)	1 ppm
Wilhelm 2011	LA County Birth Registry 04/06	Case-control	Los Angeles County, California, United States	2004–2006	66,619	LUR	NO_2	26.7	**0.97 (0.94–1.00)**	5.6 ppb
							NO	29.4	**0.99 (0.96–1.02)**	14.5 ppb
							NO_x	56.7	**0.98 (0.95–1.01)**	19.8 ppb
Wu 2009	South Coast Births 97/06	Cohort	Los Angeles and Orange Counties, California, United States	1997–2006	81,186	Dispersion/ CTM	NO_x	7.23	1.06 (1.03–1.09)	5.65 ppb
							Traffic $PM_{2.5}$	1.82	1.03 (1.01–1.06)	1.35 μg/m^3
Wu 2011	South Coast Births 97/06 LA	Case-control	Los Angeles County, California, United States	1997–2006	38,709	LUR	NO_2	28.0	**0.92 (0.85–0.98)**	5.1 ppb
							NO	30.9	**1.02 (0.98–1.07)**	11.6 ppb
							NO_x	59.9	**1.02 (0.95–1.08)**	15.6 ppb
						Dispersion/ CTM	Traffic $PM_{2.5}$	1.8	1.04 (1.00–1.08)	1.4 μg/m^3

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Table 8.11 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Preterm Birth—Pollutants (Exposure Window: Entire Pregnancy)

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Effect Estimate (95% CI)[b,c]	Increment
	South Coast Births 97/06 OC	Case-control	Orange County, California, United States	1997–2006	42,477	LUR	NO_2	28.0	**0.95 (0.89–1.01)**	5.1 ppb
							NO	30.9	**0.98 (0.94–1.02)**	11.6 ppb
							NO_x	59.9	**0.95 (0.90–1.00)**	15.6 ppb
						Dispersion/ CTM	Traffic $PM_{2.5}$	1.8	1.02 (0.97–1.07)	1.4 µg/m^3

PAH = polycyclic aromatic hydrocarbon; $PM_{2.5\ abs}$ = $PM_{2.5}$ absorbance; PNC = particle number concentrations.

[a] Units are in the increment column.

[b] Effect estimates are odds ratios. **Bold** indicates the effect estimate was included in the meta-analysis.

[c] None of the estimates were log transformed.

studies covering representative populations included nine studies in the United States (Johnson et al. 2016; Laurent et al. 2016a; Miranda et al. 2013; Padula et al. 2014b; Wu et al. 2009, 2011, 2016; Zeka et al. 2008), five studies from Canada (Brauer et al. 2008; Gehring et al. 2014; Genereux et al. 2008; Lavigne et al. 2016; Poirier et al. 2015), four studies from Europe (Hannam et al. 2013; Malmqvist et al. 2011; Maroziene et al. 2002; Olsson et al. 2015), and a single study from Asia (Leem et al. 2006). An additional nine registry-based studies, mainly using surface monitoring for exposure, restricted the study sample to those residing near monitoring stations (Jalaludin et al. 2007; Padula et al. 2014a; Ritz et al. 2007; Saldiva et al. 2018; Wilhelm and Ritz 2003; 2005; 2011; Yang et al. 2003), or to major highways (Yang et al. 2003). Many of the cohorts that were birth registry-based lacked individual lifestyle data (maternal BMI, smoking or both). Typically, detailed data were available, however, on individual and area-level socioeconomic status.

Traditional, prospective birth cohorts with specific recruitment and more detailed data collection included the Kaunas Birth Outcomes study, ABCD, PIAMA, IMNA, MoBA, Generation R, plus several in ESCAPE (Dedele et al. 2017; Estarlich et al. 2016; Gehring et al. 2011a; 2011b; Giorgis-Allemand et al. 2017; Llop et al. 2010; Panasevich et al. 2016; van den Hooven 2009, 2012). The few hospital-based cohorts included the Rhode Island Birth Outcomes study (Kingsley et al. 2017), Shanghai PTB Study (Ji et al. 2019), and the Shizuoka Seirei Birth Studies (Yorifuji et al. 2011, 2013, 2015). Individual lifestyle data were available in these Asian studies.

All the studies that were published before 2008 were based on surface monitoring, in addition to one recent study from Brazil (Jalaludin et al. 2007; Leem et al. 2006; Maroziene and Grazuleviciene 2002; Ritz et al. 2007; Saldiva et al. 2018; Wilhelm and Ritz 2003, 2005). The majority of exposure assessments were by LUR or dispersion/CTM. Together the study populations covered a span of 20 years, from the mid-1990s until 2015.

Mean or median air pollution levels were mostly moderate (e.g., NO_2 less than 40 μg/m^3), although levels varied across studies, with higher levels in Sydney, Shanghai, New York City and Los Angeles (Jalaludin et al. 2007; Ji et al. 2019; Johnson et al. 2016; Ritz et al. 2007; Wilhelm and Ritz 2003; Wilhelm et al. 2011; Wu et al. 2011). Overall, the identified studies differed substantially in population, outcome determination, study design methods, and approach to exposure assessment.

8.6.2 PRIMARY META-ANALYSIS

NO_2 was the most studied pollutant with 14 estimates available for the entire pregnancy window (Figure 8.14). Other pollutants with three or more studies included NO ($N = 4$), NO_x ($N = 6$), EC ($N = 5$) and $PM_{2.5}$ ($N = 4$). Although the Panel tended toward inclusivity in selecting studies for meta-analysis, some studies were excluded because they reported only categorical results (e.g., Gehring, 2011a), or contained both the same population and the same exposure assessment as multicity studies. In contrast to the meta-analysis for term low birth weight and small for gestational age, the estimate of Gehring and colleagues (2014) on moderately preterm births (from 30 to <37 weeks) was chosen for meta-analysis because the original study (Brauer et al. 2008) reported effect estimates only on very preterm births (<30 weeks); hence the estimate of Gehring and colleagues (2014) was more comparable to the preterm birth outcome in the other studies. Furthermore, despite some overlap in population, several studies contributed multiple estimates as different exposure models were used: INMA (Estarlich et al. 2016), PIAMA (Gehring et al. 2011b), and Generation R (van den Hooven et al. 2012) were included both as stand-alone and in the pooled ESCAPE analyses (Giorgis-Allemand et al. 2017). The MoBa cohort was not included separately in the meta-analysis because they used the same ESCAPE exposure model and the same population as included in the pooled ESCAPE study (Panasevich et al. 2016). Also INMA Valencia (Llop et al. 2010) was not included, because it was a subpopulation from the larger INMA cohort (Estarlich et al. 2016), and it used the same exposure-assessment methods.

The Panel did not identify at least three studies to perform a meta-analysis for CO, traffic $PM_{2.5}$ (the increase in PM from primary traffic emissions as opposed to ambient PM), or other fractions of PM including metals, polycyclic aromatic hydrocarbons, and benzene. Notably, while there were six studies for CO, most reported results in categories or only for specific trimesters and were therefore not available for meta-analysis. Estimates from Poirier and colleagues (2015) for PM_{10} and $PM_{2.5}$ mass were not considered for meta-analyses due to the incredibly low exposure increment.

The meta-analytic summary estimates showed null associations between exposure to all traffic-related air pollutants during the entire pregnancy and preterm birth, with RR = 1.00 (95% CI: 0.96–1.04) per 10-μg/m^3 for NO_2, 1.00 (0.98–1.03) per 10-μg/m^3 for NO, and 0.99 (0.90–1.09) per 5-μg/m^3 in $PM_{2.5}$ (Figure 8.15 and Appendix Figure 8D-1). NO_x and EC—which typically have a higher traffic specificity—were also null, although more suggestive of an association, with 1.03 (0.90–1.17) per 20-μg/m^3 for NO_x and 1.02 (0.97–1.07) per 1-μg/m^3 for EC. The confidence intervals were relatively narrow for NO_2, NO, and EC compared with the other pollutants. Forest plots for entire pregnancy exposure generally show individual studies with effect estimates above and below unity. Heterogeneity of included studies was high for NO_2 (I^2 = 79%) and NO_x (I^2 = 85%), and the results were not dominated by a single study; heterogeneity was moderate for EC (I^2 = 56%) and heavily influenced by two of the large birth registry studies (Gehring et al. 2014; Laurent et al. 2016a). The smaller number of studies included for NO and $PM_{2.5}$ did not exhibit heterogeneity (I^2 values of 0%), and all contributing studies reported null results. Results of excluded studies for NO_2, NO, EC, and $PM_{2.5}$ were also largely null. The few

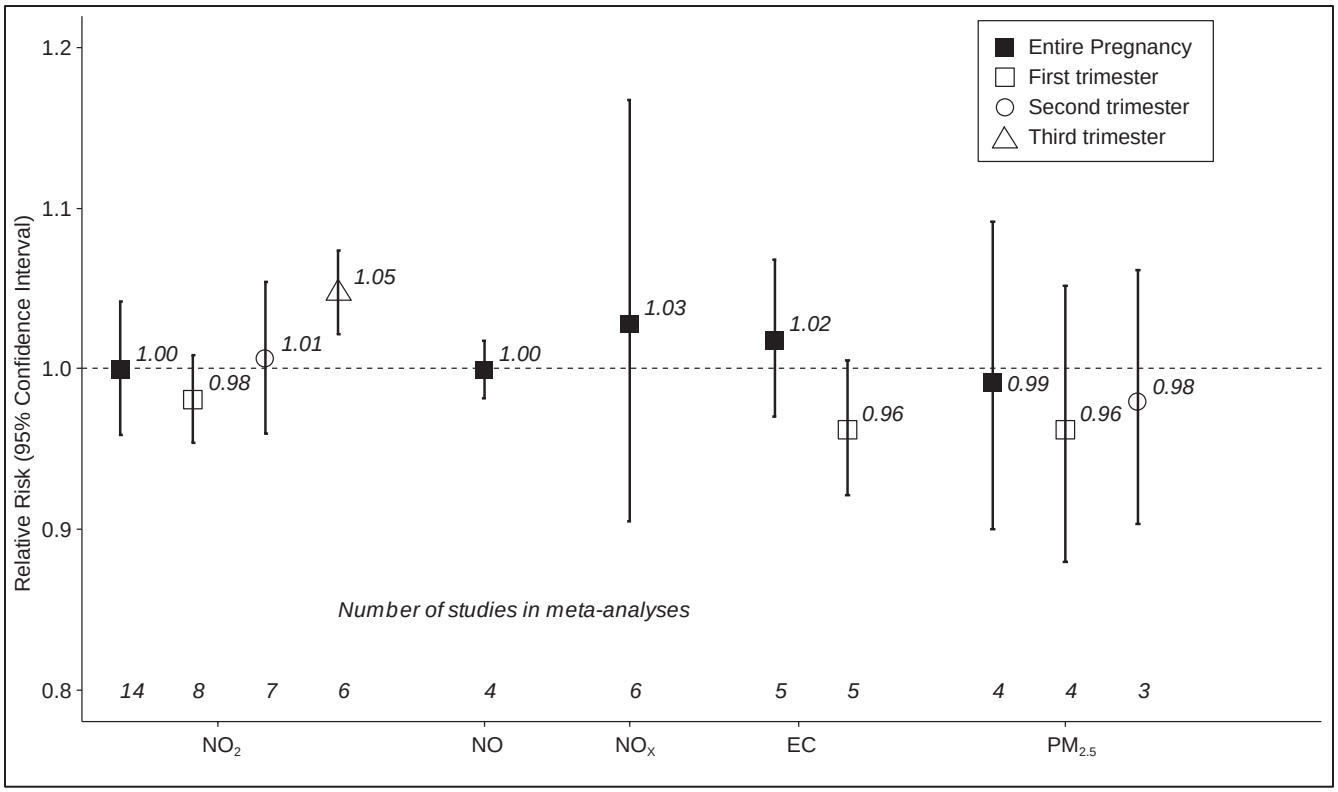

Figure 8.14. Meta-analysis of associations between traffic-related air pollutants and preterm birth. The following increments were used: 10 µg/m³ for NO_2, 10 µg/m³ for NO, 20 µg/m³ for NO_x, 1 µg/m³ for EC and 5 µg/m³ for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

exceptions reported associations of preterm birth with NO_2 (Llop et al. 2010) and NO_x (Wu et al. 2009) and an association of very preterm birth with $PM_{2.5}$ (Gehring et al. 2014).

Other pollutants with an insufficient number of studies for meta-analyses (e.g., CO) also largely indicated null associations with preterm birth (Table 8.11). The exceptions were the three studies on traffic-$PM_{2.5}$ in several California studies, where specific fractions of fine and ultrafine PM were studied, and the Spanish INMA study that considered benzene. Laurent and colleagues (2016a) reported associations for $PM_{2.5}$ from on-road diesel (1.06; 95% CI: 1.05–1.07 per 0.4-µg/m³), $PM_{2.5}$ from on-road gasoline (1.09; 1.08–1.11 per 0.4-µg/m³), and primary $PM_{0.1}$ (1.02; 1.01–1.03 per 1.4-µg/m³); an association for traffic-$PM_{2.5}$ was reported in Wu and colleagues (2009) (1.03; 1.01–1.06] per 1.4-µg/m³). Wu and colleagues (2011) reported an association with traffic-$PM_{2.5}$ and preterm birth in Los Angeles County, California but not Orange County, California.

Regarding benzene, the INMA study by Estarlich and colleagues (2016) reported an association with exposure over the entire pregnancy and preterm birth (1.38; 1.03–1.84 per 1-µg/m³), while INMA Valencia found participants exposed to benzene levels >2.7 µg/m³ had a significantly increased risk of preterm birth (Llop et al. 2010).

Similar to the entire pregnancy window, the trimester-specific meta-analyses mainly showed null associations (Figure 8.14). The exception was an association of 1.05 (95% CI: 1.02–1.08) per 10-µg/m³ for NO_2 in the third trimester that was likely masked when looking at the entire pregnancy window. The studies included in the third trimester analysis include five of the eight with a positive association in the entire pregnancy (Figure 8.15 for entire pregnancy, Appendix Figure 8D-2 trimester specific), plus Jalaludin and colleagues (2007), which contributed a very small weight. A late pregnancy or third trimester association is consistent with a triggering effect of air pollution on preterm birth, with the hypothesized mechanisms related to a direct decrease of in utero oxygen supply or indirectly via inflammation (see Chapter 3). This could not be confirmed by meta-analysis for other pollutants due to the lack of sufficient studies for the third trimester.

8.6.3 ADDITIONAL META-ANALYSES

There was little diversity in preterm birth studies by region and by publication year. Most were conducted in North America or Western Europe and were published after 2008. A few studies from Eastern Europe and Asia were also available

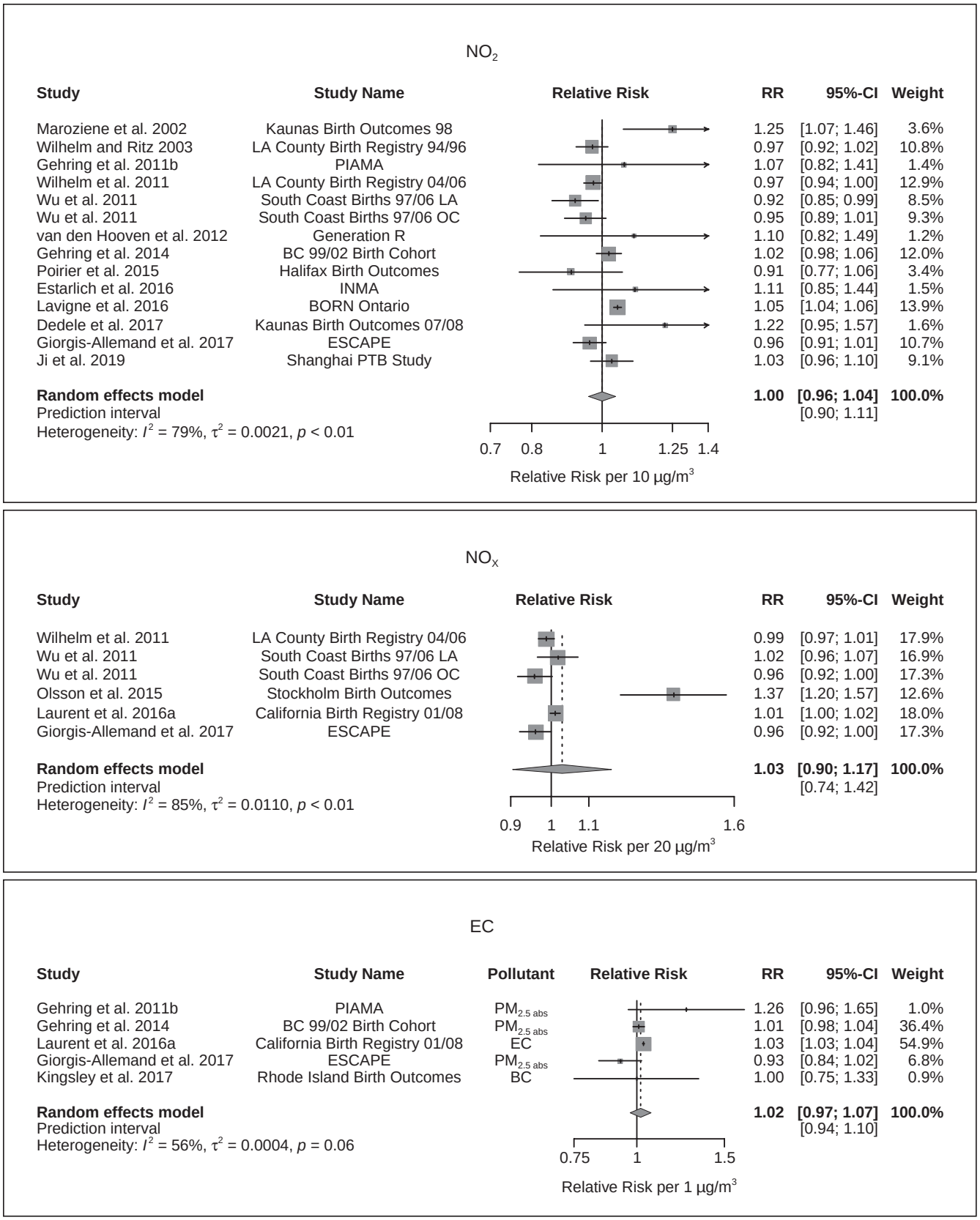

Figure 8.15. Associations of NO_2, NO_x, and EC with preterm birth: primary meta-analysis (exposure window: entire pregnancy).

for NO_2 exposure during the entire pregnancy. Stratification by region indicated mainly null associations across strata for all pollutants.

The majority of studies in the meta-analysis had high traffic specificity for exposure windows of the entire pregnancy for all pollutants. All studies for NO_x and NO were high traffic specificity and all $PM_{2.5}$ studies were rated moderate traffic specificity. The high heterogeneity in the overall summary estimate for NO_2 and the entire pregnancy was partly explained by the three studies reporting moderate traffic specificity (Lavigne et al. 2016; Maroziene et al. 2002; Wilhelm and Ritz 2003). Heterogeneity was reduced from an I^2 of 79% to an I^2 of 40% when only the NO_2 studies with high traffic specificity were retained. In general, compared with the smaller number of moderately traffic-specific studies, and across all exposure windows, those considered highly traffic specific led to slighter higher precision in the summary estimate—although associations remained null to negative for all except NO_2 in the third trimester (Appendix Figure 8D-3). Although the full study population was included in the meta-analyses, the importance of sufficiently high resolution was highlighted in Laurent and colleagues (2016a), which showed associations for multiple indicators of TRAP only in the subset of the population where residences could be resolved with the highest spatial resolution.

For NO_2 exposure during the entire pregnancy, the summary estimate with preterm birth was stronger in the subgroup of studies adjusting for maternal smoking, although still overlapping with those not adjusting for smoking. Five of the 10 NO_2 studies adjusting for smoking also adjusted for BMI (Dedele et al. 2017; Gehring et al. 2011b; Giorgis-Allemand et al. 2017; Ji et al. 2019; van den Hooven et al. 2012); there was no difference in meta-analyses stratified by adjustment for BMI (Appendix Figure 8D-4).

Only one preterm birth study corrected pollutant effect estimates for traffic noise (van den Hooven et al. 2012); however, only mutually adjusted results for traffic pollutants and traffic noise were reported, thus hampering a comparison (Appendix Table 8D-2). Four studies corrected traffic pollutant associations for general $PM_{2.5}$ or ozone, but again a comparison was not possible because only the mutually adjusted results were reported (Olsson et al. 2015; Saldiva et al. 2018) or the associations were largely null (Ji et al. 2019; Wilhelm et al. 2011).

8.6.4 ASSOCIATIONS WITH INDIRECT TRAFFIC MEASURES

The studies on indirect traffic measures provide some support for an association of TRAP and preterm birth (Figure 8.16, Appendix Table 8D-3), especially for studies using distance to roadways. As a whole, the studies showed an increased risk of preterm birth with proximity to roads. Traffic distance studies from North America, Europe, and Asia were approximately equally represented, although three of the four Asian studies were from the Shizuoka Seirei Birth Study.

There was no consistent evidence for an association of preterm birth with traffic density, with both positive and negative effect estimates. In total, there were nine studies available with four from Europe, including the multicohort ESCAPE study, and five from North America.

8.6.5 NARRATIVE ASSESSMENT

The current review includes 30 studies reporting associations between TRAP and preterm birth dichotomized as birth less than 37 weeks gestation, with a total population base of almost 6 million participants. The majority of studies (N = 25) considered an exposure window of the entire pregnancy (often in addition to trimesters, N = 13), while five studies included only trimester-specific results. Most studies were conducted in North America and Europe, with a small number also representing populations in Asia, Australia, and Brazil. The majority of studies used a cohort design followed by case-control and a single case-cohort study. Many studies leveraged birth registry data allowing for large, representative populations at the expense of risk of bias from missing detailed information on important confounders related to lifestyle. Additionally, the body of evidence included seven prospective birth cohorts from Europe—including the large multicenter ESCAPE study—and three hospital-based cohorts from North America and Asia. Older studies tended to use simple measures of exposure, such as surface monitoring or proximity to roads or traffic, while the exposure-assessment approaches in more recent studies were predominately LUR or dispersion/CTM. Full address history during pregnancy was not always available, which may contribute to potential exposure misclassification in some studies because residential mobility of pregnant women is typically high.

The meta-analyses did not suggest an association of preterm birth with any of the traffic-related air pollutants averaged over the entire pregnancy. Associations were null for all pollutants, with RR = 1.00 (95% CI: 0.96–1.04) per 10-μg/m^3 for NO_2, 1.00 (0.98–1.03) per 10-μg/m^3 for NO, and 0.99 (0.90–1.09) per 5-μg/m^3 for $PM_{2.5}$. The summary estimates for the typically more traffic-specific NO_x and EC were also null, although more suggestive of an association with 1.03 (0.90–1.17) per 20-μg/m^3 for NO_x and 1.02 (0.97–1.07) per 1-μg/m^3 for EC. These results are against a background where the majority of studies in each meta-analysis were rated as high traffic specificity, except for the $PM_{2.5}$ studies, which were rated as moderate traffic specificity.

Despite this lack of clear evidence from the overall body of literature, a few well conducted studies provided some suggestive evidence for an association. The three available studies specifically on traffic-PM (e.g., on-road diesel, on-road gasoline, and primary $PM_{0.1}$) showed clear associations of preterm birth with exposure averaged over the entire

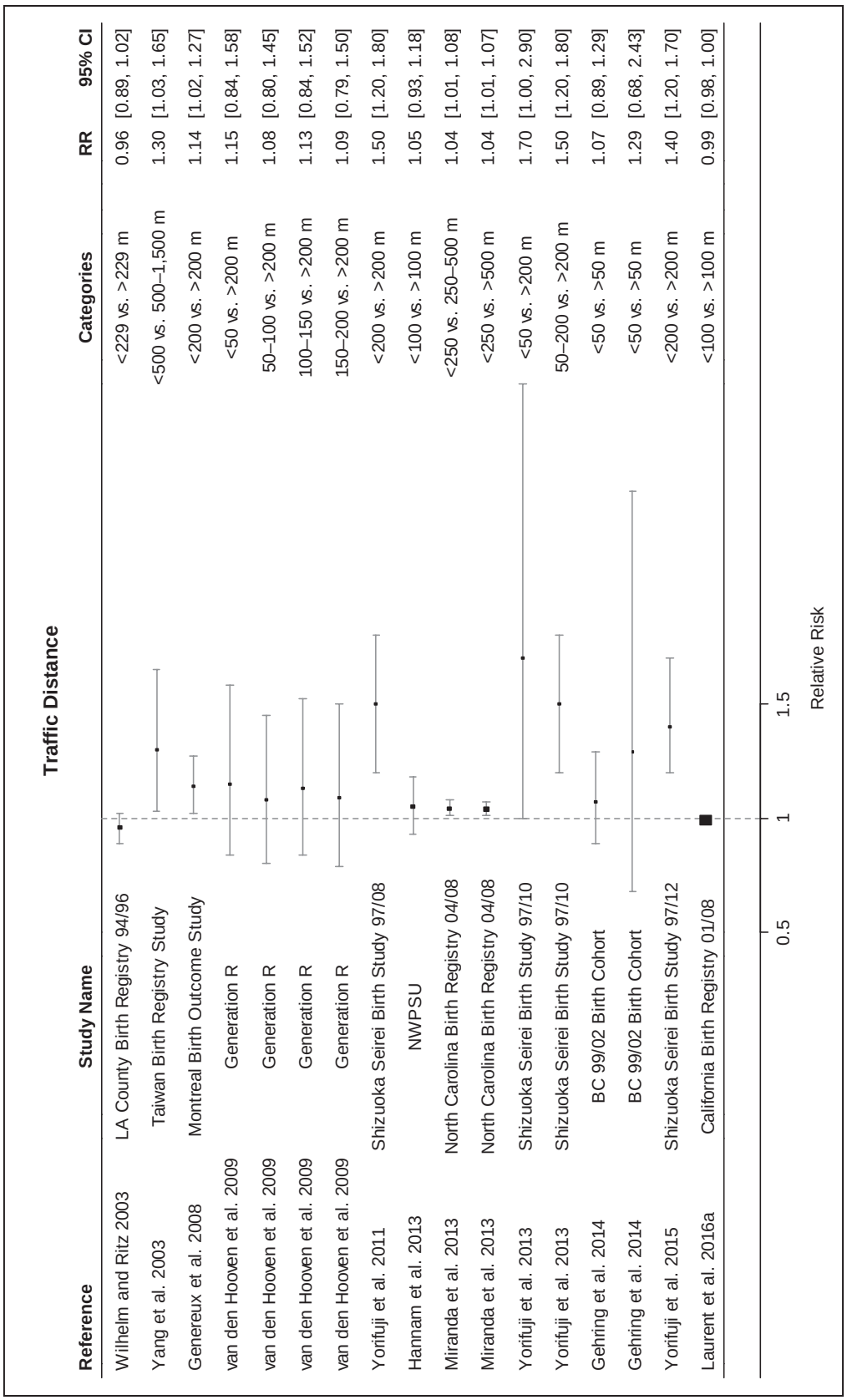

Figure 8.16. Associations of distance to major roads and traffic density with preterm birth. Gehring et al. 2014, first estimate is moderate-preterm birth; second estimate is very preterm birth. Padula et al. 2014a, estimates respectively relate to the following gestational weeks 34–36, 32–33, 28–31, 24–27, and 20–23. *Figure continues next page.*

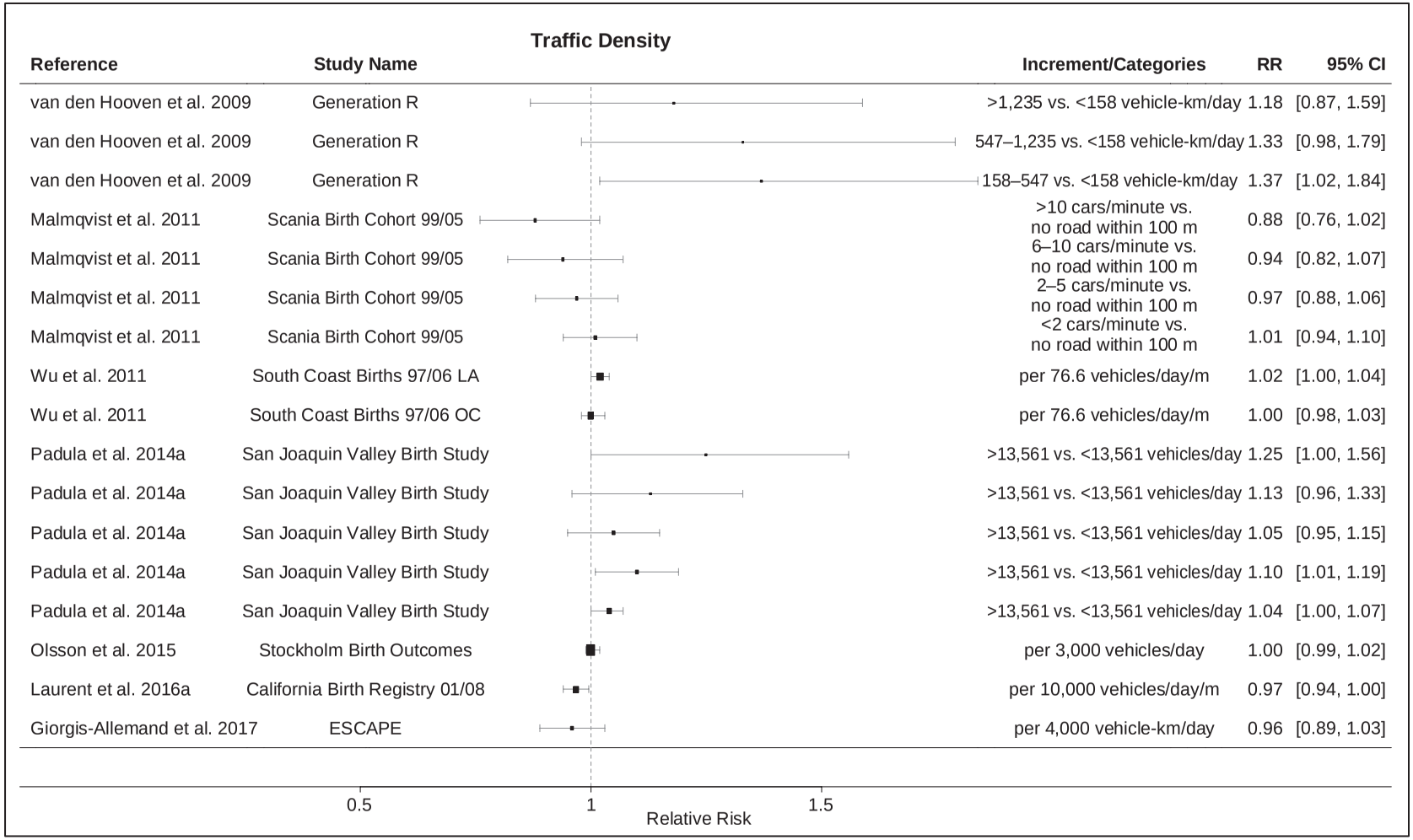

Figure 8.16. *(Continued).*

pregnancy (Laurent et al. 2016a; Wu et al. 2009, 2011), as did two of the three studies on benzene (Estarlich et al. 2016; Llop et al. 2010). However, while those studies on traffic-PM and benzene report suggestive evidence, chance and confounding could not be reasonably ruled out. Restricting studies to low risk of bias that considered residential history throughout pregnancy (N = 6), thus reducing exposure measurement error, also points to an association between preterm birth and NO_2 exposure during entire pregnancy (1.04; 95% CI: 1.00–1.08 per 10-µg/m^3 for NO_2). The trimester-specific meta-analysis also clearly shows an association between preterm birth and NO_2 exposure in the third trimester (1.05; 1.02–1.08 per 10-µg/m^3 for NO_2 based on the six available studies, and 1.07; 1.04–1.10 per 10-µg/m^3 NO_2 for the three third trimester studies designated as high traffic specificity). This is consistent with a triggering effect of air pollution on preterm birth, with the hypothesized mechanisms related to a direct decrease of in utero oxygen supply or indirectly via inflammation. Further support for an association of TRAP and preterm birth derives from the studies based on the indirect traffic measures, in particular distance to roadways. Despite the presence of some indications of a positive association, the Panel rates the confidence in the presence of an association between TRAP and preterm birth as low.

Summary of Narrative Assessment for TRAP and Preterm Birth

The primary meta-analysis supplemented with additional analyses provided low confidence in the presence of an association between exposure to TRAP and preterm birth. The few traffic-PM and distance to roadway studies, however, support an association.

8.6.6 RISK OF BIAS ASSESSMENT

Table 8.12 presents a summary of the risk of bias assessment for studies included in the meta-analysis for the entire pregnancy, summarized on a study level and for all pollutant–study pairs. In total, 16 studies were identified generally with multiple pollutants per study, for a total of 33 pollutant–outcome pairs. The risk of bias ratings for the individual studies are presented in Appendix Table 8D-4.

For most domains, the large majority of studies were rated as low to moderate risk of bias. The exception was the confounding domain where 63% of the studies were rated as high risk of bias. This was largely due to the subdomain on adjustment for potential important confounders. Most of the birth registry-based studies (Gehring et al. 2014; Kingsley et al. 2017; Laurent et al. 2016a; Lavigne et al. 2016; Maroziene and Grazuleviciene 2002; Wilhelm and Ritz 2003; Wu et al. 2011) and one birth cohort (Estarlich et al. 2016) were rated as high risk of bias because of missing adjustment for prepregnancy maternal BMI. Gehring and colleagues (2011b) was also rated as high risk of bias because prepregnancy BMI was based on a self-report three months after birth. Several of these birth registry-based studies also lacked adjustment for maternal smoking (Laurent et al. 2016a; Wilhelm and Ritz 2003; Wu et al. 2011).

8.6.7 CONFIDENCE ASSESSMENT OF THE BODY OF EVIDENCE

Table 8.13 provides the Panel's confidence assessment based on the entire pregnancy window. It includes only the pollutants with three or more studies, for which a meta-analysis was conducted. As all studies used the cohort or case-control design, the Panel's initial rating was moderate for all pollutants. Also, as cohort and case-control studies are considered together as one group, no combined assessment across study design was needed. The factors that reduce confidence and that increase confidence are described in the sections that follow. For the downgrade factor indirectness, all studies addressed the research question directly, and therefore no downgrade was applied. The Panel decided a priori not to consider the upgrading factor large magnitude of the effect.

8.6.7.1 Factors That Reduce Confidence

A downgrade based on risk of bias was applied for NO and EC. All studies on NO exposure were in the high risk of bias stratum, thus no comparison was possible. Effect estimates for EC were slightly stronger (1.03; 95% CI: 0.99–1.06), based on four studies when the single study with low risk of bias was excluded (Giorgis-Allemand et al. 2017). Although the majority of studies for NO_2, NO_x and $PM_{2.5}$ were in the high risk of bias strata, and there were few NO_x and $PM_{2.5}$ studies in the low and moderate risk of bias category (Figure 8.17 and Appendix Figure 8D-5), no downgrade was applied because most individual study estimates were null or close to null and the summary estimates were null for both high and low risk of bias studies.

The Panel downgraded associations for unexplained inconsistency for both NO_2 and NO_x because heterogeneity of magnitude and direction of effect estimates was high and could not be easily explained. The meta-analysis for preterm birth and NO_2 exposure during entire pregnancy suggests a high degree of heterogeneity (I^2 = 79%), with most of the individual effect estimates around the null (Figure 8.15). This may be due in part to differences in traffic specificity (Appendix Figure 8D-3), confounder adjustment (Appendix Figure 8D-4), or exposure assessment (Appendix Figure 8D-6); while heterogeneity was reduced in the stratified analyses accounting for these factors, the change in summary estimate was not always in the expected direction.

Regarding unexplained inconsistency, the meta-analysis for preterm birth and NO_x exposure during entire pregnancy also suggests a high degree of heterogeneity (I^2 = 85%, Figure 8.15). This seems to be driven by the strong positive

Table 8.12. Summary of Risk of Bias Rating for Studies on Preterm Birth (Exposure Window: Entire Pregnancy)

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	6	1	9	11	1	21
	Validity of measuring of confounding factors	10	5	1	21	9	3
	Control in analysis	16	0	0	33	0	0
	Overall	4	2	10	7	2	24
2. Selection bias	Selection of participants into the study	16	0	0	33	0	0
3. Exposure assessment	Methods used for exposure assessment	16	0	0	33	0	0
	Exposure measurement methods comparable across the range of exposure	16	0	0	33	0	0
	Change in exposure status	6	10	0	9	24	0
	Overall	6	10	0	9	24	0
4. Outcome measurements	Blinding of outcome measurements	15	1	0	30	3	0
	Validity of outcome measurements	16	0	0	33	0	0
	Outcome measurements	16	0	0	33	0	0
	Overall	15	1	0	30	3	0
5. Missing data	Missing data on outcome measures	16	0	0	33	0	0
	Missing data on exposures	16	0	0	33	0	0
	Overall	16	0	0	33	0	0
6. Selective reporting	Authors reported a priori primary and secondary study aims	16	0	0	33	0	0

association in the Stockholm Birth Outcomes study (Olsson et al. 2015), in contrast to the null or negative findings of the other studies. Notably Olsson and colleagues (2015) was the only study of the six that was assigned low risk of bias for exposure assessment by accounting for moving history. Heterogeneity was reduced to moderate in the risk of bias group not containing Olsson and colleagues (2015) (I^2 = 67%, Appendix Figure 8D-6), but the Panel still thought a downgrade, although perhaps conservative, was prudent.

No heterogeneity (I^2 = 0%) was found in the meta-analysis of preterm birth with NO and $PM_{2.5}$ (Appendix Figure 8D-1), and the moderate heterogeneity of EC (I^2 = 56%) was primarily due to magnitude not direction. The single study reporting a negative association (Giorgis-Allemand et al. 2017) had relatively low weight (7%) (Figure 8.15).

The overall population sample size of all studies was much larger than the minimum sample size specified in the protocol for all pollutants. However, the Panel downgraded evidence for NO_x and $PM_{2.5}$ for imprecision because confidence intervals were wide and clearly indicated unity. For the other pollutants (NO_2, NO, and EC), a downgrade was not applied because the confidence interval was considered precise, albeit including unity.

Of the pollutants, only NO_2 had a sufficient number of studies (N > 10) for evaluation of publication bias. The funnel plot for NO_2 showed some evidence of asymmetry (Appendix Figure 8D-7); however, the evidence was not strong and the Egger test P value was not statistically significant (P = 0.841). The Panel interprets this pattern as due to heterogeneity rather than publication bias. Publication bias could not be assessed with funnel plots for the remaining pollutants because there were not enough studies for a formal evaluation. The Panel did not downgrade confidence due to publication bias.

Table 8.13. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Preterm Birth (Exposure Window: Entire Pregnancy)[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort/CC	+++ (N = 14)	0	–	0	0	0	0	0	++ (Low)
	Rationale	Cohort/CC design initially rated as moderate.	9 of 14 studies with high RoB, but no difference in summary estimates.	High heterogeneity (I^2 = 79%) due to magnitude and direction.	Sample size met and confidence interval includes unity, but precise.	No evidence found in plot and test.	No evidence of plausible shape of the ERF.	Confounding in both directions possible.	No evidence of associations in any region.	
NO	Cohort/CC	+++ (N = 4)	–	0	0	0	0	0	0	++ (Low)
	Rationale	Cohort/CC design initially rated as moderate.	4 of 4 studies high RoB.	No heterogeneity (I^2 = 0%).	Sample size met and confidence interval includes unity, but precise.	Too few studies, thus based on NO_2.	No evidence of plausible shape of the ERF.	Confounding in both directions possible.	Too few studies across different populations.	
NO_x	Cohort/CC	+++ (N = 6)	0	–	–	0	0	0	0	+ (Very low)
	Rationale	Cohort/CC design initially rated as moderate.	4 of 6 studies high RoB, but no difference in summary estimates, though based on small number of studies.	High heterogeneity (I^2 = 85%), due to magnitude and direction.	Sample size met but confidence interval wide and clearly includes unity.	Too few studies, thus based on NO_2.	No evidence of plausible shape of the ERF.	Confounding in both directions possible.	Too few studies across different populations.	

Continues next page

Table 8.13 (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Preterm Birth (Exposure Window: Entire Pregnancy)

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
EC	Cohort/CC	+++ (N = 5)	–	0	0	0	0	0	0	+ (Low)
	Rationale	Cohort/CC design initially rated as moderate.	4 of 5 studies high RoB, and tendency for estimates biases away from null in high RoB studies, though based on small number of studies.	Moderate heterogeneity (I^2 = 56%), primarily due to magnitude not direction.	Sample size met and confidence interval includes unity, but precise.	Too few studies, thus based on NO_2.	No evidence of plausible shape of the ERF.	Confounding in both directions possible.	Too few studies across different populations.	
$PM_{2.5}$	Cohort	+++ (N = 4)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	3 of 4 studies high RoB, but no difference in summary estimates, though based on small number of studies.	No heterogeneity (I^2 = 0%).	Sample size met but confidence interval wide and clearly includes unity.	Too few studies, thus based on NO_2.	No evidence of plausible shape of the ERF.	Confounding in both directions possible.	Too few studies across different populations.	

CC = case-control; ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

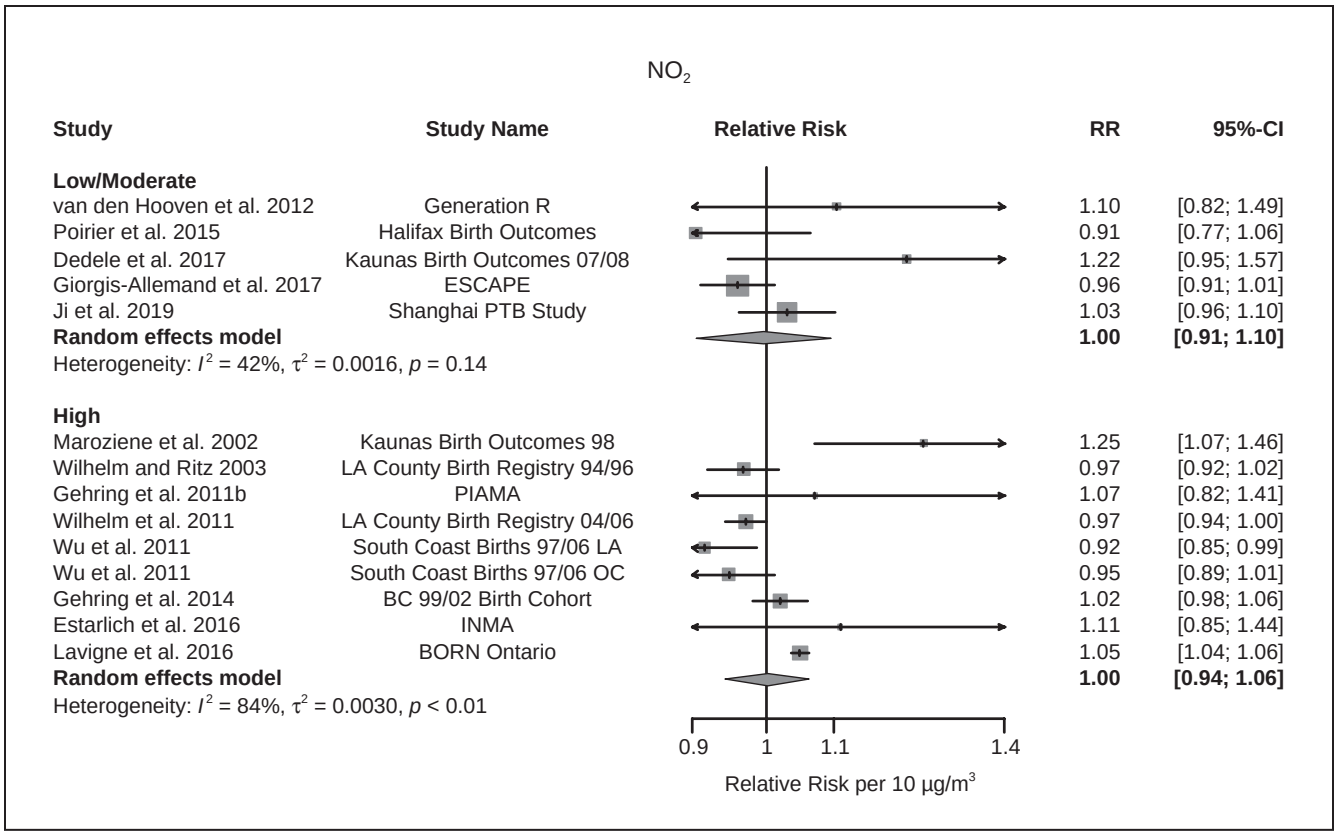

Figure 8.17 Association of NO_2 with preterm birth: meta-analysis by risk of bias confounding (exposure window: entire pregnancy).

8.6.7.2 Factors That Increase Confidence

As the pollutants had only one to two small studies supporting a monotonic exposure–response (Gehring et al. 2011b; Laurent et al. 2016a; Maroziene and Grazuleviciene 2002; Olsson et al. 2015), and the summary estimates were null, no upgrade was applied. Regarding potential bias toward the null, an upgrade was not considered appropriate given the number of studies based on birth registry data where the direction of residual confounding is difficult to evaluate. Overall, there were not strong signs of consistency across geographic regions, populations, or study period, in part because of the small number of studies. Thus, no upgrade was applied.

8.6.7.3 Evaluation of Confidence for Combined Measures of TRAP

The Panel's final ratings of the confidence in the quality of the body of evidence was low (NO_2, NO, EC, $PM_{2.5}$) or very low (NO_x). Based on the modified OHAT assessment, the Panel thought a confidence rating of low would be most appropriate, also because summary estimates between studies with high versus moderate traffic specificity were similar.

8.6.8 OVERALL CONFIDENCE ASSESSMENT

Based on the narrative assessment (low) and the modified OHAT assessment (low), the overall level of confidence in the evidence for an association between TRAP exposure and preterm birth is low.

8.7 OVERALL DISCUSSION

8.7.1 SUMMARY OF MAIN FINDINGS

The number of studies of TRAP and birth outcomes has increased greatly since the publication of the 2010 HEI Traffic Review, which included only four studies on birth outcomes. The results of the meta-analysis and other studies showed moderate confidence in evidence for associations between long-term exposure to TRAP and term low birth weight, based on associations with NO_x and $PM_{2.5}$; associations with NO_2 and EC were suggestive. Associations of $PM_{2.5}$ with fetal growth were also apparent for term birth weight and small for gestational age. Although associations for other pollutants with term birth weight and small for gestational age were in the hypothesized direction, the meta-analysis estimates

contained unity, as did associations for studies excluded from meta-analyses. All TRAP and preterm birth associations in the meta-analysis were null although a few traffic-PM and distance-to-roadway studies supported an association. For the confidence assessment in the body of evidence, using the modified OHAT methods, term low birth weight and small for gestational age were rated as moderate confidence, and term birth weight and preterm birth were rated as low confidence. Based on these findings the Panel judged that overall there was low to moderate evidence of an association between TRAP and the four selected birth outcomes.

There was some discord in the review findings across fetal growth and gestational length, and also within the three different fetal growth outcomes. This was notable for term low birth weight and term birth weight, where associations across pollutants were generally smaller for term birth weight. This was surprising, as continuously measured outcomes (i.e., term birth weight) are typically considered a more sensitive endpoint than dichotomously defined outcomes (i.e., term low birth weight) (Donner and Eliasziw 1994). Upon closer examination, restricting to studies that examined TRAP in relation to both term low birth weight and term birth weight resulted in similar associations across endpoints, suggesting that influential studies that drove positive associations for some pollutants (NO_x specifically) for term low birth weight did not also examine term birth weight.

There are a number of potential mechanisms by which TRAP exposure may impact pregnancy leading to poorer birth outcomes, as discussed in detail in Chapter 3. Briefly, these mechanisms can be defined by TRAP effects on the mother, the placenta, and directly on the fetus. These include, but are not limited, to (1) alterations in growth and development; (2) increased oxidative stress and mitochondrial alterations; (3) increased inflammatory response and maternal C-reactive protein concentrations; and (4) modification of epigenetic mechanism, such as DNA methylation. These mechanisms could lie on a pathway to reduced fetal growth as well as shorter gestational length.

8.7.2 FINDINGS IN RELATION TO OTHER ASSESSMENTS AND STUDIES

Evidence from other reviews and studies not included in this review provides support for the Panel's conclusions; however, direct comparisons are difficult due to the selection of studies and estimates that were deemed to best reflect traffic-related exposure differences.

The U.S. Environmental Protection Agency (U.S. EPA) Integrated Science Assessment (ISA) of particulate air pollution (U.S. EPA 2019) has considered $PM_{2.5}$, PM_{coarse}, and ultrafine particles (UFPs), irrespective of the source. The evidence for $PM_{2.5}$ was considered suggestive for birth outcomes, and inadequate for PM_{coarse} and UFPs. Similar to our review, the evidence was strongest for fetal growth restriction, in particular low birth weight, and weaker for preterm birth, with many associations very close to the null value. A similar determination was reached in the U.S. EPA ISA of NO_2 (U.S. EPA 2016).

A recent systematic review, restricted to European cohorts, focused on ambient NO_2, PM_{10}, and $PM_{2.5}$ in relation to the same birth outcomes included in the current systematic review, although without restricting birth weight and low birth weight to term births (Simoncic et al. 2020). Fourteen studies were included in that systematic review, and nine of them were included in the meta-analysis. In a meta-analysis of four studies, associations of NO_2 with birth weight were found in the first trimester only (mean difference = −13.63 grams; 95% CI: −28.03 to 0.77 per 10-μg/m^3). The four studies of birth weight and NO_2 that were included in that review (Aguilera et al. 2009; Ballester et al. 2010; Clemente et al. 2016; Rahmalia et al. 2012) did not overlap with any of the studies from the current review because they did not restrict to term births. In the Simoncic and colleagues (2020) review, associations for preterm birth with NO_2 exposure during the entire pregnancy were null (RR = 1.07; 0.90 to 1.28 per 10-μg/m^3), similar to what was found for the current review. Of the four studies included in the Simoncic and colleagues (2020) meta-analysis, three were included in the current review (Estarlich et al. 2016; Giorgis-Allemand et al. 2017; Maroziene and Grazuleviciene 2002). Although Simoncic and colleagues (2020) did not conduct meta-analyses for the remaining exposure–outcome pairs, the review showed other findings that were similar to the current review, including associations of low birth weight with entire pregnancy exposure to $PM_{2.5}$, PM_{10}, and NO_2.

Another recent systematic review evaluated the relationship between NO_2, $PM_{2.5}$, PM_{10}, and low birth weight (also not restricted to term births) and found slightly elevated associations for NO_2 and associations similar to the $PM_{2.5}$ results reported here (Li et al. 2020). The study reported a pooled effect for the entire pregnancy exposure window of RR = 1.03 (95% CI: 1.01–1.05) and RR = 1.08 (1.04–1.12) for 10-ppb NO_2 and 10-μg/m^3 $PM_{2.5}$, respectively. The review also reported associations for NO_2 in the first trimester (RR = 1.02; 1.01–1.04 per 10-ppb), as well as for $PM_{2.5}$ in the third trimester (RR = 1.05; 1.01–1.10 per 10-μg/m^3). There were several studies that overlapped between the Li and colleagues (2020) review and the current review.

With a broader perspective in the context of the Global Burden of Disease, and allowing for inclusion of large-area studies that do not specifically exploit $PM_{2.5}$ contrast at local to neighborhood scale and are not limited to TRAP, a review and meta-regression by Ghosh and colleagues (2021) reported associations similar to the current review of birth weight and low birth weight with ambient $PM_{2.5}$ and additionally reported a clear signal for preterm birth that was not identified in the current review. Specifically, after including 40 to 44 studies per outcome, Ghosh and colleagues (2021) reported

a 22 grams (95% uncertainty interval: 12–32) lower birth weight, 11% (95% uncertainty interval: 1.07–1.16) increased risk of low birth weight, and 12% (95% uncertainty interval: 1.06–1.19) increased risk of preterm birth per 10-μg/m^3 $PM_{2.5}$ during the entire pregnancy. The associations, however, were no longer statistically significant after adjustment for exposure-assessment method.

A systematic review of indirect traffic measures and birth outcomes (Wang et al. 2020) found largely null associations of distance to traffic and traffic density in relation to adverse birth outcomes including term low birth weight, small for gestational age, and preterm birth. However, very few studies were included in each analysis after grouping into similar distance or density cutoffs, many with less than three studies; these were reported but acknowledged as noncredible pooled estimates. Generally, the largely null findings in Wang and colleagues (2020) concur with the Panel's evaluation of the indirect traffic indicators in this review.

8.7.3 STRENGTHS AND LIMITATIONS

Major strengths of this review, which apply to all outcomes, include the systematic approach to study selection and evaluation using an a priori specified framework method for exposure assessment and for a systematic evaluation of the epidemiological evidence. The use of several indicators of TRAP allowed the evaluation of consistency across pollutants and enabled the Panel to base its conclusions on a larger number of studies with diverse exposure metrics, in contrast to focusing on only a few meta-analyzed pollutants. The application of both a narrative assessment and a confidence assessment of the body of evidence, enhances the informativeness of the findings, and may advance the field given the ongoing discussions related to confidence assessments (see Chapter 14).

Birth outcomes included three measures of fetal growth restriction (i.e., low birth weight, continuous birth weight, and small for gestational age), and length of gestation (preterm birth) allowing for a more detailed evaluation of the impact of TRAP on birth outcomes. In particular, the three measures of fetal growth restriction each represent fetal growth slightly differently, and as each measure has its own caveats, including all three permitted a deeper look into this important outcome. Indeed, there were slightly different associations of TRAP with these three outcomes, with stronger associations and more confidence for term low birth weight and small for gestational age compared with continuous term birth weight.

There were several limitations in this systematic review. Many of the studies included in the review used birth registry data to estimate associations of TRAP with birth outcomes. Registry data are typically inexpensive to access and allow for large population-based samples. However, birth records typically do not collect or collect poor quality data on potentially important lifestyle factors, such as maternal smoking during pregnancy or prepregnancy BMI. In particular, the Panel discussed whether BMI should be considered an important confounder for TRAP and birth outcomes. Confounding by prepregnancy BMI is likely to result primarily via socioeconomic status. Because socioeconomic status is already included as a potential important confounder for this review, adjusting for prepregnancy BMI was a conservative choice for this outcome. In addition, some would argue that BMI should be viewed as a mediator and on the causal pathway between TRAP and birth outcomes, which would suggest that adjusting for BMI is inappropriate. As a result of not adjusting for BMI (and smoking), many registry-based studies were classified in the high risk of bias category. This reduced confidence in the quality of the body of evidence for some outcomes, in particular for term birth weight and preterm birth. For term low birth weight, there was some evidence for negative confounding, where adjusting for BMI (and smoking) drove $PM_{2.5}$ and EC estimates further from the null.

For the current review, registry-based studies were classified as cohort studies because modeled exposures could be retrospectively assessed during pregnancy. A limitation of these registry studies, as well as of prospective birth cohorts, is that early and late fetal loss would not be captured. This survival bias, a type of selection bias also referred to as collider bias (Neophytou et al. 2021; Tchetgen et al. 2012), where only fetuses that make it to a live birth are counted, could attenuate findings if TRAP was associated with fetal loss.

The Panel focused primarily on evidence from exposure during the entire pregnancy, as this was assessed in the majority of the studies reviewed. However, this may have masked associations with exposure during particular critical windows. For example, if TRAP impacts fetal growth during a specific week or trimester of pregnancy, focusing on the entire pregnancy would likely attenuate estimated associations toward the null. The Panel did conduct ancillary analyses looking at trimesters of exposure; however, fewer studies were available and therefore the body of evidence was less reliable. In addition, a limitation of trimester-specific analyses is that the boundaries of trimesters are somewhat arbitrary, and they may confound each other. This could lead to identification of incorrect critical exposure windows when the true window does not match trimester boundaries.

On a related note, the systematic review focused on long-term TRAP exposure. Although this may indeed be the more relevant period of exposure for some outcomes, it may not be for others. More specifically, studies have shown that there may be a triggering effect of air pollution on preterm birth (Schifano et al. 2016). If this triggering effect is indeed the most relevant mechanism for preterm birth, the focus on long-term exposure may miss this potentially important pathway.

8.7.4 UNANSWERED QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

This systematic review helped to identify some unanswered questions that should be considered in future research. First, for many pollutant–outcome pairs, there are still too few studies to show convincingly whether there is an association of TRAP with birth outcomes in meta-analysis, particularly for pollutants that are considered highly specific to TRAP (e.g., NO_2, NO_x, and EC). The scant number of studies was particularly problematic in the confidence assessment of the body of evidence and when probing associations in sensitivity analyses. More studies would help to better inform a future systematic review.

Second, the question of whether maternal smoking during pregnancy and prepregnancy BMI truly confound associations of TRAP with birth outcome remains unresolved. This can only be addressed with further research into whether these are indeed confounders or perhaps mediators of these associations.

Third, few studies adjusted for factors such as transportation or community noise, aspects of the built environment (e.g., green space, walkability), and copollutants. These are all factors that could confound associations of TRAP with birth outcomes. In addition, accounting for residential mobility, time–activity patterns, and other factors that contribute to exposure measurement error could help to reduce statistical heterogeneity and improve detection of any apparent associations. Novel TRAP biomarker methods (e.g., measuring black carbon in placenta (Bové et al. 2019), cord blood, or other biological matrixes) could also be useful for quantifying gestational exposure and better characterizing exposure–response.

Fourth, future studies examining the critical window for TRAP exposure on birth outcomes are needed to better parse out the most vulnerable period during pregnancy and avoid diluting or masking the effect of TRAP on birth outcomes. For example, compared with the more conventional approach of averaging exposures over relatively large time windows, distributed lag models allow for a more detailed investigation of prenatal exposure windows and may be worthwhile to further explore (Neophytou et al. 2021; Stieb et al. 2019; Yuan et al. 2020).

Finally, the mechanisms whereby TRAP influences pregnancy outcomes require further study. Research is needed to gain a clearer understanding of how TRAP impacts growth restriction and preterm birth. This includes examining which pollutants are most important and when during the pregnancy (early vs. later in pregnancy) these exposures might have the greatest impact. Identifying changes more proximal to exposure via fetal ultrasound or other gestational testing may provide insights that could help guide future research.

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MATERIALS AVAILABLE ON THE HEI WEBSITE

Appendices 8A to 8E and Additional Materials 8.1 to 8.5 contain supplemental material not included in the main report. They are available on the HEI website at *www.healtheffects.org/publications.*

Appendices

8A Term Low Birth Weight

8B Term Birth Weight

8C Small for Gestational Age

8D Preterm Birth

8E References for Studies Included in the Systematic Review of Birth Outcomes

Additional Materials

8.1 Term Low Birth Weight

8.2 Term Birth Weight

8.3 Small for Gestational Age

8.4 Preterm Birth

8.5 Risk of Bias Rationales for Studies Included in Meta-analyses

ABBREVIATIONS

BMI	body mass index
CC	case control
CI	confidence interval
CO	carbon monoxide
CTM	chemical transport model
EC	elemental carbon
ERF	exposure–response function
ISA	Integrated Science Assessment
LUR	land use regression
NO	nitric oxide
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
OHAT	Office of Health Assessment and Translation
PAH	polycyclic aromatic hydrocarbon
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
$PM_{2.5\ abs}$	$PM_{2.5}$ absorbance
$PM_{0.1}$	particulate matter ≤0.1 μm in aerodynamic diameter
PM_{10}	particulate matter ≤10 μm in aerodynamic diameter
PM_{coarse}	particulate matter with aerodynamic diameter between 10 μm and 2.5 μm
PNC	particle number concentrations
RR	relative risk
RoB	risk of bias
TRAP	traffic-related air pollution
UFPs	ultrafine particles
U.S. EPA	U.S. Environmental Protection Agency

PART C: FINDINGS FROM SYSTEMATIC LITERATURE REVIEWS OF EPIDEMIOLOGICAL STUDIES

Chapter 9

Traffic-Related Air Pollution and Respiratory Outcomes

CONTENTS

CHAPTER 9

Traffic-Related Air Pollution and Respiratory Outcomes

9.1 SUMMARY

A large body of literature reports associations between exposure to traffic-related air pollution (TRAP*) and incidence or prevalence of respiratory outcomes both in children and in adults. The Panel considered asthma onset (incidence) as well as prevalence of an asthma diagnosis at any point in time (asthma ever), prevalence of active asthma (ongoing symptoms) and exacerbation of asthma symptoms. In addition, prevalence of wheeze ever and active wheeze were evaluated. These respiratory outcomes were assessed separately for children (<18 years) and adults (18+ years). Incidence of acute lower respiratory infections (ALRI) in children and adults, and incidence, prevalence, and exacerbation of chronic obstructive pulmonary disease (COPD) in adults were also assessed. Most studies were conducted in North America and Europe, but studies in Asia and Australia were also included. The evidence base has increased substantially, from ~75 to 168 studies, compared with the 2010 HEI Traffic Review (HEI 2010). More research has been published, and this new review also takes a more inclusive approach to the search strategy and the inclusion criteria. In most cases, cohort studies (mainly birth cohorts in children) were employed to assess associations with incidence measures, whereas cross-sectional studies were employed more often to consider prevalence of the various conditions. As defined in the protocol, included studies used general population samples, with the exception of studies on the exacerbation of pre-existing asthma and COPD. Of the traffic pollutants considered, nitrogen dioxide (NO_2), nitrogen oxides (NO_x), elemental carbon (EC), and particulate matter ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$) were studied most widely.

Respiratory outcomes were defined using standardized questionnaires and clinical or administrative records (e.g., emergency room visits or hospital admissions). Included study populations varied substantially in size and age. Most studies controlled for individual lifestyle characteristics, such as parental or individual smoking. Typically, lifestyle data were missing in administrative cohorts, but detailed data on individual and area-level socioeconomic status (SES) partially alleviate the concern for residual confounding.

Highlights

- The Panel conducted a comprehensive systematic review of the available literature examining traffic-related air pollution and selected respiratory outcomes in adults and children. Several health outcomes were considered in relation to asthma (incidence, prevalence of asthma ever, prevalence of active asthma, exacerbation), wheeze (prevalence of wheeze ever, and prevalence of active wheeze), acute lower respiratory infections (ALRI) (incidence), and chronic obstructive pulmonary disease (COPD) (incidence, prevalence, and exacerbation; only in adults).
- The Panel reviewed studies that met strict inclusion criteria, performed meta-analyses and risk of bias assessments, and completed both a narrative assessment and a confidence assessment of the body of evidence.
- A total of 118 and 50 published studies were selected for children and adults, respectively, on all the respiratory outcomes; 80 and 31 studies (children and adults, respectively) considered at least one pollutant, whereas all other studies were based on indirect measures of traffic exposure. 63% (*N* = 50) of children's studies and 42% (*N* = 13) of adult studies, that had at least one pollutant, were included in the meta-analyses, whereas the results of the others (insufficient number for meta-analyses) were summarized qualitatively.
- The overall confidence in the evidence for an association between exposure to TRAP and asthma onset (both children and adults) and ALRI (children) was considered to be moderate to high. Most of the studies had a cohort design, were conducted in different populations, were at a relatively low or moderate risk of bias, and observed associations with multiple pollutants, either in meta-analyses or in single, large studies. Studies examining exposure to NO_2 have made the greatest contribution to this overall evaluation.
- For most of the other respiratory outcomes investigated, including incidence of COPD, ALRI in adults, wheeze outcomes as well as exacerbation of asthma and COPD in adults, the confidence was very low or low for an association with traffic-related air pollution, hampered in part by the small number of qualifying studies.

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* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

Exposure assessment was based mainly on land use regression (LUR) or dispersion models, although some studies used monitoring data or road proximity measures. Follow-up periods for the cohort studies differed across studies, but many had follow-up extending until 2010–2015.

A total of 118 and 50 studies were selected for children and adults, respectively; 80 and 31 studies (children and adults, respectively) considered at least one pollutant, whereas all other studies were based on indirect measures of traffic exposure. 63% ($N = 50$) of studies in children and 42% ($N = 13$) of studies in adults with at least one pollutant were included in meta-analyses, whereas the results of the others (insufficient number for meta-analyses) were summarized qualitatively. Table 9.1 summarizes the evidence for associations between TRAP and a selection of the respiratory outcomes, including results of the meta-analyses, narrative assessment of the confidence in the presence of an association, the Panel's modified Office of Health Assessment and Translation (OHAT) assessment of the confidence in the quality of the body of evidence, and the final overall evaluation.

The overall evaluation of the association between TRAP exposure and asthma onset in children, based on the narrative and modified OHAT assessment, was moderate to high. The meta-analytic summary estimate—relative risk (RR) and 95% confidence interval (CI)—for NO_2 was 1.05 (0.99–1.12) per 10-μg/m^3 and based on 12 studies. For other pollutants—NO_x, EC, and $PM_{2.5}$—the summary estimate was positive, although the confidence interval included unity. These positive results found in some large cohorts and incidence-based case-control studies, conducted in different populations, provide confidence in the presence of an association. In addition, the majority of estimates of associations with pollutants not meta-analyzed, like PM ≤10 μm in aerodynamic diameter (PM_{10}), PM with aerodynamic diameter between 10 μm and 2.5 μm (PM_{coarse}), ultrafine particles (UFPs), and $PM_{2.5}$ from traffic emissions, were also positive, providing additional support. Results from indirect traffic measure studies, however, provided mixed findings. Given that the summary estimates were heterogeneous and confidence intervals of all the meta-analytic estimates included unity, uncertainties remain regarding the association between TRAP and asthma onset in children. Thus, the Panel judged that there was moderate evidence of an association between TRAP and onset of asthma in children based on the narrative assessment. The confidence in the body of evidence using a modified OHAT method was considered high, as incidence-based studies were involved and there was a sufficient number of studies showing a monotonic exposure–response function.

The overall confidence assessment between TRAP and prevalence of asthma ever in children was moderate. These studies were mainly cross-sectional. All meta-analytic summary estimates for TRAP and asthma ever in children were above unity except for PM_{10}. Additionally, confidence intervals clearly included unity except for NO_2, NO_x, and carbon monoxide (CO). Furthermore, associations with indirect traffic measures were highly variable. Overall, the positive meta-analytic summary estimates between most traffic pollutants and the prevalence of asthma ever in children in different locations and populations provided confidence in the presence of an association. However, uncertainties remain due to the cross-sectional nature of most studies assessed, the potential bias in outcome reporting, and the heterogeneity of the estimates (with both positive and negative effect estimates). The confidence level was thus moderate in both the narrative and the modified OHAT assessments. A similar assessment (moderate) was obtained between TRAP and active asthma in children. The summary estimates between NO_2, NO_x, and EC and active asthma in children were all positive, although with confidence intervals that included unity in all cases except for NO_2. The association with PM_{10} was close to unity (RR = 0.99). For NO_2 and PM_{10}, both positive and negative associations in individual studies were reported, while all EC and NO_x estimates were positive, although these were based on few studies. Contradictory or imprecise estimates were reported for pollutants not meta-analyzed, namely CO, $PM_{2.5}$, benzene, and PM_{coarse}, and for indirect traffic measures.

The Panel concluded that the overall confidence in the evidence for an association between exposure to TRAP and ALRI in children was moderate to high. The evidence on TRAP and ALRI in children was based mainly on cohort studies examining NO_2. Based on 11 studies, a positive and statistically significant association with NO_2 was observed. Positive associations for EC were also found in meta-analysis, although with large confidence intervals that included unity. Overall, the dominance of positive results strongly points toward an association between TRAP and ALRI. The evidence consistently suggested there is an association includes NO_2 and EC, but also a range of different indicators of TRAP (e.g., NO_x, CO) that had too few studies for meta-analysis—and multiple studies reporting an association based on indirect traffic measures. The narrative evaluation was considered high, and the modified OHAT assessment was moderate.

The overall confidence assessment was moderate to high for studies addressing asthma onset in adults. The evidence on TRAP and asthma onset in adults was mainly based on seven incidence-based studies examining NO_2 that entered the meta-analysis and a large cohort where the exposure to NO_2 was analyzed in categories. The summary estimate for NO_2 and asthma onset was positive with confidence intervals that excluded unity. NO_2 associations were reported in different populations, which provides a clear indication for an association. The findings are also supported by the fact that most estimates of association with pollutants not meta-analyzed, like NO_x, PM_{10}, $PM_{2.5}$, and EC, were also positive, albeit with wide confidence intervals. The Panel concluded that the evidence of an association between exposure to TRAP and asthma onset in adults was high based on the narrative assessment and the confidence in the body of evidence was considered moderate.

Table 9.1. Summary of the Confidence in the Evidence for an Association Between TRAP and Respiratory Outcomes in Children and Adults[a]

	Children				Adults	
Pollutant	Asthma Onset	Asthma Ever	Active Asthma	ALRI	Asthma Onset	COPD Incidence
Meta-analytic Summary Estimate and Narrative Assessment to Assess Confidence in the Presence of an Association with TRAP						
NO_2	1.05 (0.99–1.12) *N* = 12	1.09 (1.01–1.18) *N* = 21	1.12 (1.02–1.23) *N* = 12	1.09 (1.03–1.16) *N* = 11	1.10 (1.01–1.21) *N* = 7	1.03 (0.94–1.13) *N* = 7
NO_x	1.25 (0.52–3.01) *N* = 3	1.02 (0.99–1.05) *N* = 6	1.03 (0.97–1.09) *N* = 3	Fewer than three studies	Fewer than three studies	1.03 (0.88–1.20) *N* = 3
EC	1.11 (0.94–1.31) *N* = 5	1.30 (0.56–3.04) *N* = 3	1.25 (0.98–1.59) *N* = 3	1.30 (0.78–2.18) *N* = 4	Fewer than three studies	Fewer than three studies
$PM_{2.5}$	1.33 (0.90–1.98) *N* = 5	1.29 (0.58–2.87) *N* = 3	Fewer than three studies	Fewer than three studies	Fewer than three studies	0.91 (0.62–1.36) *N* = 4
Narrative	NO_2 estimate consistent with an association and positive but imprecise summary estimate for the other pollutants. Sizable number of well-designed large cohort studies in a variety of locations, with associations found for some pollutants and indirect traffic measures.	Positive summary estimate for NO_2; NO_x estimate consistent with an association; largely positive but imprecise summary estimate for most other pollutants. Sizable number of well-designed large cross-sectional studies and some cohort studies in a variety of locations, with associations found for some pollutants and indirect traffic measures.	Positive summary estimate for NO_2 and positive but imprecise summary estimate for the other pollutants. Sizable number of well-designed cross-sectional studies and some cohort studies in a variety of locations, with associations found for some pollutants and indirect traffic measures.	Positive summary estimate for NO_2 and positive but imprecise summary estimate for EC. Sizable number of well-designed large cohort and case control studies along with a smaller number of cross-sectional studies in a variety of locations, supporting associations for multiple pollutants and indirect traffic measures.	Positive summary estimate for NO_2. Sizable number of well-designed large cohort studies in a variety of locations, supporting associations for multiple pollutants.	Positive but imprecise summary estimate for NO_2 and NO_x. Small number of well-designed large cohort studies, inconsistent associations across pollutants and indirect traffic measures.
	Moderate	**Moderate**	**Moderate**	**High**	**High**	**Low**
Modified OHAT Assessment to Assess Confidence in the Quality of the Body of Evidence						
NO_2	High	Moderate	Moderate	Moderate	Moderate	Very low
NO_x	Very low	Low	Very low	Fewer than three studies[b]	Fewer than three studies[b]	Low
EC	Low	Very low	Very low	Low	Fewer than three studies[b]	Fewer than three studies
$PM_{2.5}$	Very low	Very low	Fewer than three studies	Fewer than three studies[b]	Fewer than three studies[b]	Very low
TRAP	**High**	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Low**
Overall Assessment Combining the Narrative Assessment and Modified OHAT Assessment						
TRAP	**Moderate to high**	**Moderate**	**Moderate**	**Moderate to high**	**Moderate to high**	**Low**

COPD = chronic obstructive pulmonary disease; ALRI = acute lower respiratory infection; *N* = number of studies; OHAT = Office of Health Assessment and Translation.

[a] The table presents only the four pollutants most widely used. The individual pollutants are considered as indicators of the TRAP mixture. Relative risks (RR) and 95% confidence intervals are expressed per 10-, 20-, 1- and 5-μg/m³ increments for NO_2, NO_x, EC, and $PM_{2.5}$, respectively.

[b] The studies provided some support for an association.

For most of the other respiratory outcomes investigated, including incidence of COPD, ALRI in adults, wheeze outcomes as well as exacerbation of asthma and COPD in adults, the confidence was very low or low for an association with TRAP, hampered in part by the small number of qualifying studies.

9.2 OVERVIEW OF THE DIFFERENT RESPIRATORY OUTCOMES

This introductory section describes the respiratory health outcomes that the Panel evaluated in relation to TRAP exposure in children and in adults. Next, Sections 9.3 and 9.4 summarize findings and assessments for studies among children and adults, respectively. Each section follows the same format: (1) a description of the available literature; (2) results of the primary meta-analyses; (3) stratified meta-analyses (e.g., by geographical region, year of publication, traffic specificity in the exposure methods); (4) a summary of indirect measures of traffic exposure (i.e., distance from major roads and density of traffic on nearby roads); (5) a narrative assessment of the level of confidence in the evidence; (6) a summary of the risk of bias assessment on this body of evidence; and (7) an assessment of confidence in the body of evidence of the associations between exposure to TRAP and respiratory outcomes. Section 9.5 concludes the chapter with an overall discussion of key findings, and strengths and limitations of this review.

The definition of respiratory diseases in both children and adults is complicated, especially for asthma and COPD. The definition and ascertainment of respiratory disease endpoints has been problematic in epidemiological studies as well as in clinical settings. The reason for such difficulties lies in the essence of the diseases with distinct physiopathological mechanisms, namely, subtle and progressive onset, presentation via a wide range of potentially transient symptoms (especially in children), persistent or chronic course, and objective measures (like lung function tests) that are not uniformly available and sometimes not entirely informative (Bakke et al. 2011; Kemp et al. 1996; Pekkanen et al. 2005; Subbarao et al. 2009). Several considerations regarding the main issues and difficulties in assessing the role of TRAP for the selected respiratory outcomes are summarized in Sidebar 9.1.

It is well known that asthma is a complex syndrome characterized by several potential phenotypes arising from different etiologies, especially in children (Martinez et al. 1995). There are recent suggestions for using the term asthma solely as a descriptive label for a collection of symptoms, with no assumptions about the physiopathology (Pavord et al. 2018). In fact, the previously widespread belief that asthma is an allergic or atopic disease caused by allergen exposure has been questioned (Pearce et al. 1999); it is clear now that nonatopic asthma is more important than has been recognized until recently (Pavord et al. 2018). Because childhood asthma and adult asthma might represent distinct phenotypes with different etiological patterns, the Panel has distinguished between traffic studies conducted in children (<18 years) and those conducted in adults (18+ years).

Most previous studies have used self-administered questionnaires to define asthma and asthma-like symptoms, with parents responding on behalf of their children (Kemp et al. 1996). For studies on children, the development of standardized instruments extends back to the American Thoracic Society (ATS) questionnaire (Ferris 1978) and then the International Study on Asthma and Allergy in Children (ISAAC) questionnaire (Asher et al. 1995), both of which seek to document the presence of physician-diagnosed asthma and to define wheezing more consistently, a characteristic symptom of asthma. The reproducibility of responses to these instruments has been well assessed (e.g., Brunekreef et al. 1992). For adults, the questionnaire used most has been developed under an International Union Against Tuberculosis and Lung Diseases initiative (Burney et al. 1989), followed by the questionnaire used in the European Community Respiratory Health Survey (Burney et al. 1994).

Questionnaires are useful in epidemiological studies because of low costs, permitting larger sample sizes compared with intensive and expensive data collection methods, including bronchial challenge tests and reversibility tests. Bias in the associations depends on the sensitivity (probability that a person who truly has the outcome will be identified as such) and, more importantly, on the specificity (probability that a person who does not have the outcome will be identified as such). Early validation studies have indicated a sensitivity of 80% to 85% for asthma-like symptoms and a specificity ranging from 81% to 97% (Pekkanen and Pearce 1999).

A subsequent study in Canada indicated that information about an asthma diagnosis obtained from participant responses in a questionnaire had a relatively low sensitivity (59%) but specificity was high (96%) (Yang et al. 2011). However, the appropriateness of using self-reported data to assess asthma in etiological studies has been debated, mainly due to problems associated with participants' recall of events and individual differences in symptom perception. This aspect is especially relevant to studies related to potential exposures to air pollution because knowledge of exposure could favor increased reporting of symptoms, that is, reporting bias. In many countries, there is also the possibility of using population-based registry data to obtain information about asthma diagnoses, or to use administrative data like emergency room visits or hospitalizations, or prescriptions for specific drugs (e.g., bronchodilators). These instruments can be useful as they do not depend on participants' recall, but the potential remains in these cases for disease misclassification.

There is large variability between outcome definitions for incident asthma among studies using medical records or

SIDEBAR 9.1 SUMMARY OF CRITICAL CONSIDERATIONS REGARDING THE SELECTED RESPIRATORY OUTCOMES

Several considerations regarding the main issues and difficulties in assessing the role of TRAP for the selected respiratory outcomes are summarized below as they help in the interpretation of the results. Some of these aspects have been discussed in the 2010 HEI Traffic Review (HEI 2010) and should be considered to be issues that go beyond air pollution research, as they reflect the complexity of assessing respiratory outcomes within epidemiological studies.

- The epidemiological definitions of the conditions under study have limitations, and misclassification of the outcomes is likely, especially in the case of COPD. Nondifferential misclassification of a dichotomous outcome will generally bias toward the null with the result of a decreased possibility to detect an association. Bias in the associations depends on the sensitivity (probability that a person who truly has the outcome will be identified as such) and, more importantly, on the specificity (probability that a person who does not have the outcome will be identified as such). For most of the respiratory outcomes the Panel has reviewed, the specificity tends to be high, and the studies tend to provide an unbiased association even if sensitivity is imperfect. In some situations, misclassification may be differential and may lead to bias in either direction because it is related to the exposure status, for instance when SES is a predictor of exposure and of the quality of disease classification (Chen et al. 2013).
- Although for each outcome the Panel considered specific study designs for the confidence assessment (e.g., cohort studies for incidence, cross-sectional studies for prevalence, cohort studies of participants with a given disease for exacerbation and severity), the reality is more disparate. The classification the Panel adopted is not perfect, as a mixture of different study designs were found for some outcomes. For instance, case-control studies investigated sometimes incidence, and sometimes prevalence of a condition; cohort studies were used to assess both incidence and prevalence of a specific condition during follow-up, especially when repeated assessments were done; and cross-sectional designs were used to assess disease severity in asthma and COPD studies.
- As indicated in the 2010 HEI Traffic Review, the usual paradigm of distinguishing between risk factors for incidence and those for exacerbation is appealing biologically, but it is difficult to follow in practice. The main problem is being able to distinguish between (a) onset of new disease and (b) exacerbation of a condition that has been present but previously unrecognized or undiagnosed. First, the occurrence of symptoms, both for asthma and COPD, typically varies over time due to many risk factors, including environmental factors, and those risk factors often act as triggers. In cohort and in cross-sectional studies, therefore, it is not unambiguously clear whether one is characterizing the contribution of air pollution to the acute, intermittent nature of the disease (in other words, active asthma) or to the onset of the disease among persons who had not previously been ill. Second, while repeated measurements at different ages within birth cohorts may be the most appropriate study design for investigating the causes of asthma incidence during childhood, the definitions of asthma onset and active asthma, either as doctor diagnosis or as reporting of symptoms during the previous 12 months, may reflect the changing nature and recognition of the disease rather than the actual time of the first onset of the chronic disease. This issue results in the challenge in distinguishing the role of a given risk factor (such as TRAP) in the development of the disease from its role in exacerbating the disease.
- The described obstacles for fully capturing the time sequence of the pathophysiological processes characterizing these diseases and their manifestations (e.g., asthma and COPD) are associated with the challenge to precisely assess the exact times (or age) of onset, prevalence, and exacerbation, especially in children. Additionally, the term asthma onset can be misleading when it is used in studies of children younger than school age, as asthma is difficult to diagnose at this age. Most often asthma and asthma-like symptoms at a very young age are transient and do not result in asthma that persists into adulthood. These factors make it difficult to recognize the relevant time windows of exposure.
- In studies on children, the exposure window of most importance for the disease onset (e.g., asthma or ALRI), or for prevalence of asthma and wheeze, is not known. Different periods can be relevant, such as prenatal, early life or postnatal, but critical exposure windows remain difficult to investigate in epidemiological studies. Although there is potential for exposures at these different time points in the life course, there are not enough studies for us to confidently separate and compare associations across different exposure windows in the current HEI Traffic Review. Furthermore, such exposures are likely to be highly correlated between periods.
- Many of the studies the Panel has included provide, within the same study, results related to more than one outcome, and they report associations of the same outcome with multiple exposure metrics related to TRAP (e.g., EC, NO_2). As such, the assessments are not completely independent.
- One important outcome, lung function, was omitted from the review because the Panel decided to focus efforts on reviewing the evidence for a selected number of clinical outcomes. However, the results of lung function tests are clinically relevant and may provide important information for other clinical outcomes. This is a limitation that the Panel acknowledges.

administrative claims data to define the disease. Case definitions differ in the quantity and types of diagnoses and medications required to classify a child or an adult as having asthma. For example, an algorithm has been developed to identify children with asthma from health claims data in the province of Ontario in Canada (at least one hospitalization for asthma at any time during the child's life or two separate ambulatory or emergency room visits for asthma within a two-year time frame) showing 91.4% sensitivity and 82.9% specificity for correctly identifying asthma when compared with an expert consensus diagnosis of asthma (To et al. 2006). However, a validation study aimed to determine the prevalence of asthma in a population of children in Denmark, using three classification methods (self-report, population-based hospitalization data, and population-based prescription data) in a large prospective birth cohort, did find a substantial nonoverlap between cases identified by the three methods (Hansen et al. 2012), suggesting that the three methods may identify asthma cases with biologically distinct phenotypes. For example, the hospitalization registry may capture more severe phenotypes than do the prescription registry or maternal self-reporting. In summary, studies in this review using questionnaire data have moderate sensitivity in identifying asthma cases whereas the specificity was higher. The specificity is also high in cohort studies when stricter definitions (e.g., hospitalization) were employed, selecting more severe cases. Generally, in prevalence comparisons, the Youden index (the sensitivity plus the specificity minus 1.0) provides an appropriate measure of the validity of a particular question or technique; however, in a cohort study or a case-control study specificity is the most important validity measure (Pekkanen and Pearce 1999). Therefore, because specificity is more important than sensitivity in determining bias in epidemiological studies, it is likely that both type of studies (based on questionnaire and administrative data) in general are not prone to bias due to outcome misclassification.

9.2.1 ASTHMA

There are multiple ways to characterize the effects of an exposure on asthma, including: incidence rate of new onset asthma, prevalence of asthma at a specific point in time, prevalence of asthma across the life course, and exacerbation of symptoms of asthma among diseased patients. The most important outcome from an etiological point of view is the first diagnosis of the disease (incidence) during the life course (asthma onset). As indicated, this has been mainly evaluated with a follow-up of disease-free individuals (often a birth cohort) and using a positive response to a questionnaire about a medical diagnosis of the disease (physician diagnosis of asthma). Algorithms based on medication and health services for that condition have also been used when administrative health data were available. Although cohort studies, especially birth cohorts for children (follow-up of children since they were born), have been used for this specific outcome, in some cases, case-control studies have been employed based on incidence cases.

An additional measure, lifetime (or childhood) prevalence of asthma (asthma ever) (mainly based on questionnaire responses, but also potentially on medical records or drug prescriptions), indicates the proportion of people who have had a diagnosis of the disease during their lifetime. In this case, cross-sectional assessments have been used either in the form of prevalence studies or case-control studies based on prevalence; note that prevalence has been also assessed within cohort studies. Is it worth noting that asthma ever, a prevalence measure, is conceptually equivalent to a lifetime incidence measure except that the two approaches differ in the way the population is approached and the resultant potential risk of bias.

Finally, prevalence of active asthma in the last 12 months (prevalence of active asthma) refers to a prevalence measure based on questionnaires (based on either asthma diagnosis in the last 12 months or asthma symptoms in the last 12 months when an asthma diagnosis was given in the past); active asthma is also based on the use of medical services (emergency department visits and hospital admissions). Most cohort studies reporting prevalence of active asthma also reported incidence measures that are included in the asthma onset section. Studies reporting lifetime prevalence of asthma have often also reported prevalence of active asthma. It is worth noting that there is an overlap between the measures ever asthma and active asthma because active cases would also be classified as having ever had asthma. Some birth cohort studies have assessed ever and active asthma at various ages and have reported different occurrence measures, mostly prevalence of ever and active asthma at the age of the clinical visits (e.g., Mölter et al. 2015) but also incidence measures for the time intervals between the visits (e.g., Gehring et al. 2015). The effect estimates of the relationship between incidence or prevalence and TRAP reflect the association between the exposure and the outcomes across the entire follow-up period, using both the cross-sectional and the longitudinal analyses, and making full use of the repeated measurements.

The use of a medical diagnosis of asthma in epidemiological studies can overestimate or underestimate the occurrence of the disease in a population, depending on different factors, including physician practices and the availability of medical care (Kemp et al. 1996). Several studies have found the prevalence of physician-diagnosed asthma to be substantially lower than the prevalence of asthma symptoms in the community. For these reasons, questionnaires of self-reported symptoms (or parental report) have become the method of choice for large comparative prevalence studies (Asher et al. 1995; Burney et al. 1994), especially for wheezing (the dominant symptom of asthma). However, use of self-reported symptoms to identify asthma cases may cause the occurrence of asthma to be overestimated in populations of preschool aged

children, because asthmatic symptoms including wheezing, chest tightness, breathlessness, and coughing may be related to viral infections rather than to a true asthmatic condition (transient wheezing) and the children may be too young for a medical diagnosis of asthma (Martinez et al. 1995).

Asthma exacerbations are common in children and adults with asthma; the main goal of asthma management is the prevention of exacerbations and airflow limitation. Asthma exacerbations can range from mild to severe with the most severe forms generally requiring an emergency department visit, hospitalization, or both. Several studies have assessed the role of acute exposure to air pollutants on asthma exacerbations using a panel design, time-series, or case-crossover analyses (Orellano et al. 2017; Weinmayr et al. 2010), but few studies are available that report the effects of long-term exposures to air pollutants on asthma exacerbations. These studies include cohort studies of patients with asthma, which are usually based on emergency room visits and hospitalizations (children and adults), and cross-sectional studies assessing asthma-control questions, which are limited to asthma patients.

9.2.2 WHEEZE

The Panel distinguished between studies assessing prevalence of wheeze ever (any episode of wheeze occurring during the lifetime) and active wheeze (wheezing or other asthma-like symptoms in the last 12 months). Many studies using questionnaires have analyzed the prevalence of asthma and the prevalence of wheeze as separate outcomes, sometimes in the same study. As discussed for active asthma, some birth cohort studies have assessed current wheeze at various ages and have reported different occurrence measures, mostly prevalence of active and ever wheeze at the age of the clinical visits but also incidence measures for the time intervals between the visits. The Panel gave more weight to the epidemiological literature on asthma and gave less importance to the studies on wheeze as they were considered only ancillary to the main evaluation regarding the disease. For this reason, the evaluations related to wheeze, both in children and in adults are reported entirely in Appendix 9A (available on the HEI website).

9.2.3 ACUTE LOWER RESPIRATORY INFECTIONS

The types of ALRI considered in the literature include pneumonia, acute bronchitis with or without wheeze, and bronchiolitis. Some studies report results for these outcomes lumped together while others report results individually for one or more of these types of infections. The majority of published studies focus on young children, and the few studies on adults are based largely on pneumonia. In the summary assessment, the Panel combined results among the infection types, similar to a previous review on air pollution and ALRI (Mehta et al. 2013) as there are relatively few studies overall. Considering them together generally assumes that the mechanisms of action of TRAP on ALRI of different etiologies are similar in that the inhaled pollutants impact the capacity of the immune system to combat the infection. The nature of the reported outcome varies from parental questionnaires asking about doctor-diagnosed infections within set retrospective time windows, to administrative data such as hospital admissions records. In all cases, these are viewed as an indication of disease incidence given their acute nature and expected absence of the infection prior to diagnosis or between repeated infections in the same individual. Parental reports of acute lower respiratory diseases in children have shown high quality, both with sensitivity and specificity above 90% (Vissing et al. 2012). For adults, cohort studies identifying the incidence of community-acquired pneumonia are largely based on administrative datasets from hospitals relying on specific administrative billing codes. Hospital admission data in adults tend to have moderate sensitivity (55%) and high specificity (99%) (Aronsky et al. 2005). However, one additional problem with the use of Internal Classification of Diseases pneumonia codes in adults is that they do not distinguish between community-acquired and hospital-acquired disease. The fraction of hospital-acquired pneumonia may vary depending on several factors, including age, and it may reach one-third of the total hospitalizations for pneumonia (Giorgi Rossi et al. 2004). This complication tends to decrease the reliability of studies in adults based on hospital admissions only.

9.2.4 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The epidemiological definition of COPD has been extensively discussed (Bakke et al. 2011). Population studies on COPD have used a variety of operational diagnostic criteria, usually based on one or more of the following: lung function, respiratory symptoms, clinical examination, and administrative records. The GOLD initiative (Global Initiative for Chronic Obstructive Lung Disease global strategy for diagnosis, management, and prevention of COPD) has provided guidelines that are useful also for epidemiological studies, and it involves the use of a lung function test (Pauwels et al. 2001). For this reason, the Panel excluded investigations that used only questionnaire-based definitions (e.g., chronic symptoms, doctor-diagnosed COPD, etc.), similar to an earlier review on COPD (Schikowski et al. 2014). Furthermore, the Panel evaluated separately studies on the incidence of COPD, prevalence of COPD, and exacerbations of COPD. For the latter, the Panel has searched studies evaluating long-term exposures associated with emergency room visits or hospitalizations among participants with COPD.

The clinical definition of COPD is based on a lung function test conducted after bronchodilation with the fixed ratio of forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <0.7 (Pauwels et al. 2001). This recommendation (fixed ratio of FEV_1/FVC <0.7) has been challenged as it may cause overestimation of COPD in the older population (Fragoso and Gill 2010). One study in this review used only

the lung function test to identify COPD cases (Schikowski et al. 2014), whereas others have used a combination of physician diagnosis with a lung function test (Fisher et al. 2016b), or routine administrative databases such as records of general practitioners or hospital admissions records (Atkinson et al. 2015; Weichenthal et al. 2017), or simply hospital admissions (Andersen et al. 2011; Gan et al. 2013; Salimi et al. 2018). Physician-diagnosed COPD alone has been validated in relation to a spirometric gold standard with rather low sensitivity (11%) and high specificity (99%) (Torén et al. 2017). On the other hand, hospital admissions for COPD are an appealing source of information, but such patients represent only those with severe or poorly controlled COPD so that specificity is high but sensitivity very low. Therefore, studies with multiple independent sources are preferable (Atkinson et al. 2015; Weichenthal et al. 2017), such as hospital admissions records to identify participants with severe disease and primary care records incorporating participants with COPD who had not yet required admission to the hospital. However, the consistency in recording of a COPD diagnosis between the two sources was not complete in the Atkinson and colleagues (2015) study as 36% of incident hospital admissions for COPD were not confirmed by a corresponding general practitioner diagnosis, indicating that the problems of assessing COPD in epidemiological investigations remain. In conclusion, spirometric diagnosis of COPD is a sensitive instrument, but it may entail false-positive diagnoses in the elderly. On the other hand, physician diagnoses or hospital admissions have high specificity and a poor sensitivity, as they select participants with a more advanced stage of the disease.

9.2.5 SUMMARY

In summary, for respiratory outcomes, the Panel selected asthma and asthma-related symptoms (wheeze), COPD, and ALRI. Respiratory outcomes were separately assessed for children (<18 years) and adults (18+ years) (Chapter 5). For asthma, the Panel considered evidence of the impacts of TRAP on incidence of asthma, prevalence of asthma, and exacerbation of the disease among individuals with pre-existing asthma. Prevalence has been further divided into asthma ever and active asthma. The Panel also included studies of wheeze and distinguished between studies assessing prevalence of wheeze ever (any episode of wheeze occurring during the lifetime) and active wheeze (wheezing or other asthma-like symptoms in the last 12 months). The Panel included studies using both hospital-based and questionnaire definitions of ALRI. For children the Panel considered respiratory infections such as bronchiolitis, pneumonia, bronchitis, and croup while for adults, pneumonia was the main outcome studied. Finally, the Panel evaluated separately studies on incidence of COPD, prevalence of COPD, and exacerbations of COPD. For the latter, the Panel searched studies evaluating long-term exposures associated with emergency department visits or hospitalizations among participants with COPD.

The Panel did not consider additional respiratory outcomes, including rhinitis, or studies based only on the results of lung function or allergy tests. Although the Panel has made this list of important clinical outcomes, there remain uncertainties among the various methods for ascertaining the outcome and studying associations with TRAP, which are further discussed in Sidebar 9.1. These uncertainties have been considered in the overall confidence assessments.

9.3 RESPIRATORY OUTCOMES IN CHILDREN

9.3.1 ASTHMA ONSET

9.3.1.1 Study Selection and Description

The Panel identified and reviewed 25 studies that reported associations between TRAP or indirect traffic measures (i.e., distance and density) and asthma onset in children; four of these studies only reported associations with indirect traffic measures. Asthma onset refers to asthma incidence that is usually assessed through questionnaires (self-reported or with interviews) or with algorithms with administrative health data (e.g., two health services for asthma within one or two years; first hospital admission or prescription drug for asthma; one health service and one prescription drug). Most studies used questionnaires or information from administrative health data, and two studies assessed asthma onset through clinical examinations (Brunst et al. 2015; Carlsten et al. 2011).

Tables 9.2 and 9.3 summarize the identified studies and their main results. Most studies were conducted in European (N = 9) and North American countries (N = 13). The majority of the studies were published after 2008 (the end of the search date for the review of the 2010 HEI Traffic Review).

Most studies that the Panel included were birth cohorts. Exceptions were the CHS (Jerrett et al. 2008; McConnell et al. 2010; Weaver et al. 2018), a Korean cohort (Lee et al. 2018b) and a Japanese cohort (Shima et al. 2003), as well as a French (Zmirou et al. 2004) and a Japanese (Hasunuma et al. 2016) case-control study. Carlsten and colleagues (2011) was the only study on high-risk infants, which was defined as having at least one first-degree relative with asthma or two first-degree relatives with other IgE-mediated allergic disease according to parental report.

Studies differed substantially in sample size, ranging from a few hundred to several hundred thousand participants in cohorts based on administrative health data. Follow-up periods differed across studies and extended up to teenage years for some cohorts (Gehring et al. 2015). Age at asthma onset also differed between studies and when a study assessed onset at a different age (e.g., Sbihi et al. 2016), the Panel selected estimates of association for the latest age of asthma onset assessment.

Table 9.2. Key Study Characteristics of Articles Included in the Systematic Review for Asthma Onset in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Brunst 2015	CCAAPS	Cohort	Cincinnati, Ohio, United States	2001–2010	589	1–7	LUR	EC	About 0.4	Annual average at birth	OR	1.15 (0.88–1.51)	>0.39 vs. <0.39 µg/m^3
										Average first year		1.09 (0.82–1.46)	>0.39 vs. <0.39 µg/m^3
										Cumulative average		1.20 (0.89–1.63)	>0.39 vs. <0.39 µg/m^3
Carlsten 2011	Vancouver High Risk Asthma Infants	Cohort	Vancouver, British Columbia, Canada	1995–2002	184	7	LUR	NO_2	32.6	Annual average at birth	OR	**1.5 (0.9–2.5)**	7.2 µg/m^3
								NO	35.7			1.2 (0.9–1.7)	12.7 µg/m^3
								BC	1.6			**1.1 (0.7–1.9)**	1.2 µg/m^3
								$PM_{2.5}$ mass	5.6			**3.1 (1.3–7.4)**	4.1 µg/m^3
Clark 2010	BC 99/00 Birth Cohort	Case-control	Multiple cities, Canada	1999–2003	16,806	3–5	LUR	NO_2	31.68–31.73	Entire pregnancy	RR	1.02 (0.97–1.07)	10 µg/m^3
										Average first year		1.13 (1.04–1.23)	
						3–5	LUR	NO	30.38–31.03	Entire pregnancy		1.05 (1.02–1.09)	10 µg/m^3
										Average first year		1.03 (1.00–1.07)	
					19,488	3–5	Surface monitoring	CO	612.2–618.8	Entire pregnancy		1.07 (1.04–1.10)	100 µg/m^3
										Average first year		1.10 (1.06–1.13)	
					19,524	3–5	LUR	BC	1.34–1.37	Entire pregnancy		1.08 (1.02–1.15)	1 1×10^{-5}/m

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Table 9.2 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Asthma Onset in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Measure	Effect Estimate (95% CI)[c]	Increment
										Average first year		1.14 (1.01–1.29)	
						3–5	LUR	$PM_{2.5}$ mass	4.67–4.78	Entire pregnancy		1.02 (1.00–1.03)	1 μg/m^3
										Average first year		1.01 (0.99–1.03)	
Clough-erty 2007	EBNHC	Cohort	Boston, Massachu-setts, United States	1987–2004	413	4–10	LUR	NO_2	27.5	Annual average for the year of diagnosis	OR	**1.63 (1.14–2.33)**[d] (high violence)	4.3 ppb
												0.99 (0.73–1.34)[d] (low violence)	
Gehring 2010	PIAMA	Cohort	The Netherlands	1996–2006	3,184	1–8	LUR	NO_2	25.4	Annual average at birth	OR	**1.17 (0.96–1.42)**	10.4 μg/m^3
								$PM_{2.5\ abs}$	1.72			**1.17 (0.95–1.42)**	0.57 1×10^{-5}/m
								$PM_{2.5}$ mass	16.9			**1.26 (0.97–1.63)**	3.2 μg/m^3
Gehring 2015	ESCAPE	Cohort	Multiple cit-ies, multiple countries	1994–2013	14,085	1–16	LUR	NO_2	14.1–23.8	Annual average at birth[e]	OR	**1.13 (1.02–1.25)**	10 μg/m^3
										Annual average current year		1.03 (0.88–1.19)	

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Table 9.2 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Asthma Onset in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Measure	Effect Estimate (95% CI)[c]	Increment
								$PM_{2.5\ abs}$	0.7–1.7	Annual average at birth[e]		**1.29 (1.00–1.66)**	1 1×10^{-5}/m
										Annual average current year		1.05 (0.72–1.52)	
								PM_{10} mass	15.7–25.5	Annual average at birth[e]		1.08 (0.77–1.51)	10 µg/m^3
										Annual average current year		0.91 (0.75–1.11)	
								PM_{coarse} mass	6.8–8.5	Annual average at birth[e]		1.15 (0.83–1.59)	5 µg/m^3
										Annual average current year		1.06 (0.75–1.51)	
								$PM_{2.5}$ mass	7.8–17.4	Annual average at birth[e]		**1.25 (0.94–1.66)**	5 µg/m^3
										Annual average current year		1.13 (0.85–1.49)	
Gruzieva 2013	BAMSE	Cohort	Stockholm County, Sweden	1994–2008	3,633	1–12	Dispersion/ CTM	NO_x	7.8–21.4	Average first year	OR	**1.21 (0.79–1.84)**	46.8 µg/m^3
										Cumu-lative average		0.83 (0.51–1.34)	

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Table 9.2 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Asthma Onset in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Measure	Effect Estimate (95% CI)[c]	Increment
								PM_{10} mass	3.5–4.6	Average first year		1.34 (0.80–2.23)	7.2 μg/m^3
										Cumulative average		0.93 (0.63–1.39)	
Hasunuma 2016	SORA	Nested case-control	Multiple cities, Japan	2006–2010	416	1–3	Personal exposure	NO_x	37.7	Cumulative average	OR	0.97 (0.95–1.00)	1 ppb
								EC	2.85			0.93 (0.85–1.01)	0.1 μg/m^3
Jerrett 2008	CHS	Cohort	California, United States	1993–2004	217	10–18	Surface monitoring	NO_2	9.6–51.3	Annual average	HR	**1.29 (1.07–1.56)**	6.2 ppb
Krämer 2009	GINI, LISA: Wesel	Cohort	Multiple cities, Germany	1995–2005	2,059	6	LUR	NO_2	24.0	Annual average at birth	RR	**1.17 (0.86–1.58)**	9 μg/m^3
								$PM_{2.5\ abs}$	1.6			**1.16 (0.87–1.54)**	0.5 1×10^{-5}/m
Lavigne 2018	BORN Ontario	Cohort	Ontario, Canada	2006–2012	761,172	0–6	LUR	NO_2	13.2	Entire pregnancy	HR	**1.09 (1.07–1.12)**	8.6 ppb
										Average first year		1.08 (1.06–1.09)	8.9 ppb
										Cumulative average		1.00 (0.98–1.02)	8.6 ppb
Lavigne 2019	BORN Toronto	Cohort	Toronto, Canada	2006–2015	160,641	0–6	LUR	NO_2	25	Entire pregnancy	HR	**1.02 (0.98–1.06)**	9.7 ppb
										Cumulative average		1.01 (0.97–1.05)	8.7 ppb

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Table 9.2 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Asthma Onset in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Measure	Effect Estimate (95% CI)[c]	Increment
								PNC > 10 nm	28,910	Entire pregnancy		1.03 (0.99–1.07)	10,820 particles/ cm^3
										Cumulative average		1.03 (1.00–1.06)	10,551 particles/ cm^3
Lee 2018a	ACCESS	Cohort	Boston, Massachusetts, United States	2002–2015	736	0–6	LUR	$PM_{2.5}$ mass	11.2	Entire pregnancy	OR	**1.17 (1.04–1.30)**	1.7 µg/m^3
Lindgren 2013	Scania Birth Cohort 05/11	Cohort	Scania including Malmö, Sweden	2005–2011	6,005	0–6	Dispersion/ CTM	NO_x	22	Annual average at birth	HR	0.7 (0.5–0.9)	>25 vs. <15 µg/m^3
												0.8 (0.7–0.9)	15–25 vs. <15 µg/m^3
										Cumulative average		0.7 (0.5–1.0)	>25 vs. <15 µg/m^3
												0.7 (0.6–0.9)	15–25 vs. <15 µg/m^3
McConnell 2010	CHS	Cohort	California, United States	2002–2006	2,497	5–7	Dispersion/ CTM	NO_x	7.3	Annual average recent year	HR	**1.51 (1.25–1.81)**	8 ppb
Mölter 2014	MAAS	Cohort	Manchester, United Kingdom	1995–2008	373	3–11	Personal exposure	NO_2	20.3–31.9	Cumulative average	OR	1.06 (0.90–1.23)	1 µg/m^3
								PM_{10} mass	15.1–20			1.17 (0.88–1.56)	1 µg/m^3
Oftedal 2009	Oslo Birth Cohort	Cohort	Oslo, Norway	1992–2002	2,329	9–10	Dispersion/ CTM	NO_2	39.3	Average first year	RR	**0.82 (0.67–1.02)**	27.3 µg/m^3
										Cumulative average		0.82 (0.67–1.02)	19.6 µg/m^3

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Table 9.2 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Asthma Onset in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Pennington 2018	KAPPA	Cohort	Atlanta, Georgia, United States	2000–2013	19,951	2–6	Dispersion/ CTM	NO_x	59.4	Entire pregnancy	Mean difference	**0.00 (–0.01–0.02)**	40 ppb
										Average first year		0.01 (–0.00–0.02)	
								CO	0.62	Entire pregnancy		0.01 (–0.01–0.02)	0.4 ppm
										Average first year		0.01 (–0.00–0.02)	
								traffic $PM_{2.5}$	1.49	Entire pregnancy		0.01 (–0.00–0.02)	1 µg/m^3
										Average first year		0.01 (–0.00–0.03)	
Ranzi 2014	GASPII	Cohort	Rome, Italy	2003–2011	672	0–7	LUR	NO_2	37.88	Annual average at birth	OR	**1.07 (0.76–1.51)**	10 µg/m^3
										Cumulative average		1.09 (0.78–1.52)	
Sbihi 2016	BC 99/02 Birth Cohort	Case-control	Vancouver, British Columbia, Canada	1999–2012	41,569	0–5	LUR	NO_2	33.6	Entire pregnancy	OR	0.99 (0.96–1.02)	9.5 µg/m^3
					10,288	6–10						**0.95 (0.90–1.01)**	
					41,569	0–5	LUR	NO	31.3			1.00 (0.97–1.03)	14.4 µg/m^3
					10,288	6–10						1.00 (0.94–1.06)	

Continues next page

Table 9.2 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Asthma Onset in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Measure	Effect Estimate (95% CI)[c]	Increment
					41,569	0–5	Surface monitoring	CO	628.7			1.05 (1.01–1.10)	163.9 μg/m^3
					10,288	6–10						0.90 (0.83–0.98)	
					41,569	0–5	LUR	BC	1.6			1.01 (0.99–1.04)	1.13 1×10^{-5}/m
					10,288	6–10						**0.99 (0.95–1.05)**	
					41,569	0–5	LUR	$PM_{2.5}$ mass	4.09			0.99 (0.97–1.01)	1.45 μg/m^3
					10,288	6–10						**1.01 (0.97–1.06)**	
Tétreault 2016	Quebec Birth Cohort	Cohort	Montreal, Quebec, Canada	1996–2011	319,356	0–13	LUR	NO_2	15.51	Annual average at birth	HR	**1.04 (1.02–1.05)**	5.45 ppb
										Cumulative average		1.04 (1.03–1.06)	

BC = black carbon; HR = hazard ratio; OR = odds ratio; PNC = particle number concentration; RR = relative risk.

[a] All studies included male and female participants.

[b] Units are in the increment column.

[c] **Bold** indicates the effect estimate was included in the meta-analysis.

[d] Estimates were combined by a fixed effect meta-analysis before entering the random-effects model.

[e] Not extrapolated.

There were traditional cohorts based on individual information and cohorts based exclusively on administrative health data. Traditional cohorts were usually designed to investigate the development of asthma and allergies and their relation to various risk factors that were not limited to outdoor air pollution or TRAP. They had extensive information on individual risk factors such as parental smoking and indoor air quality but involved only a few thousand participants. Traditional cohorts included a number of European cohorts such as: the Oslo birth cohort (Oftedal et al. 2009), the Dutch PIAMA (Gehring et al. 2010), BAMSE (Gruzieva et al. 2013), GINIplus (Krämer et al. 2009), LISAplus (Krämer et al. 2009), and GASPII (Ranzi et al. 2014). Some of these European cohorts were also pooled as part of the ESCAPE project, thus increasing the sample size substantially (Gehring et al. 2015). A few North American traditional cohorts were included such as: CHS (Jerrett et al. 2008; McConnell et al. 2010), ACCESS (Lee et al. 2018a), EBNHC (Clougherty et al. 2007), and a cohort of high-risk infants (i.e., with first degree relatives with asthma or IgE-mediated allergies) from Vancouver (Canada) (Carlsten et al. 2011). The Korean CHEER (Lee et al. 2018a) and the Japanese cohort (Shima et al. 2003) were also traditional cohorts.

Administrative cohorts typically had data on area-level SES, but individual information was limited. Almost all administrative cohorts (Clark et al. 2010; Lavigne et al. 2018, 2019; Pennington et al. 2018; Sbihi et al. 2016; Tétreault et al. 2016) were from North America, and more specifically from Canada where there is universal health care coverage, except the American study by Pennington and colleagues (2018) (which was based on the Kaiser Permanent Georgia Health Maintenance Organization data) and the Swedish study by Lindgren and colleagues (2013).

Pollutant exposure assessment was usually based on LUR or dispersion models. Most studies reported estimates of exposure during pregnancy, at birth, or for the first year of life, and the Panel gave preference to such exposures in selecting the estimates based on the assumption that early exposure would be more likely to affect respiratory development, although several studies only reported associations with postnatal exposure (e.g., Clougherty et al. 2007; Jerrett et al. 2008). Mean air pollution levels were mostly moderate (e.g., $PM_{2.5}$ <20 µg/m^3) but differed widely across studies. Thus, the identified studies differed substantially in size, exposure, and population studied.

9.3.1.2 Primary Meta-analysis

Figure 9.1 shows the combined effect estimates for all pollutants for asthma onset in children based on meta-analyses, with preference given to the earliest exposures in the case of multiple effect estimates reported. As described in Chapter 5 the Panel decided to be inclusive. Thus, some studies (e.g., Gehring et al. 2010; Krämer et al. 2009) were included in the meta-analyses, even though the same cohorts were also analyzed in the ESCAPE multicohort analysis (Gehring et al. 2015),

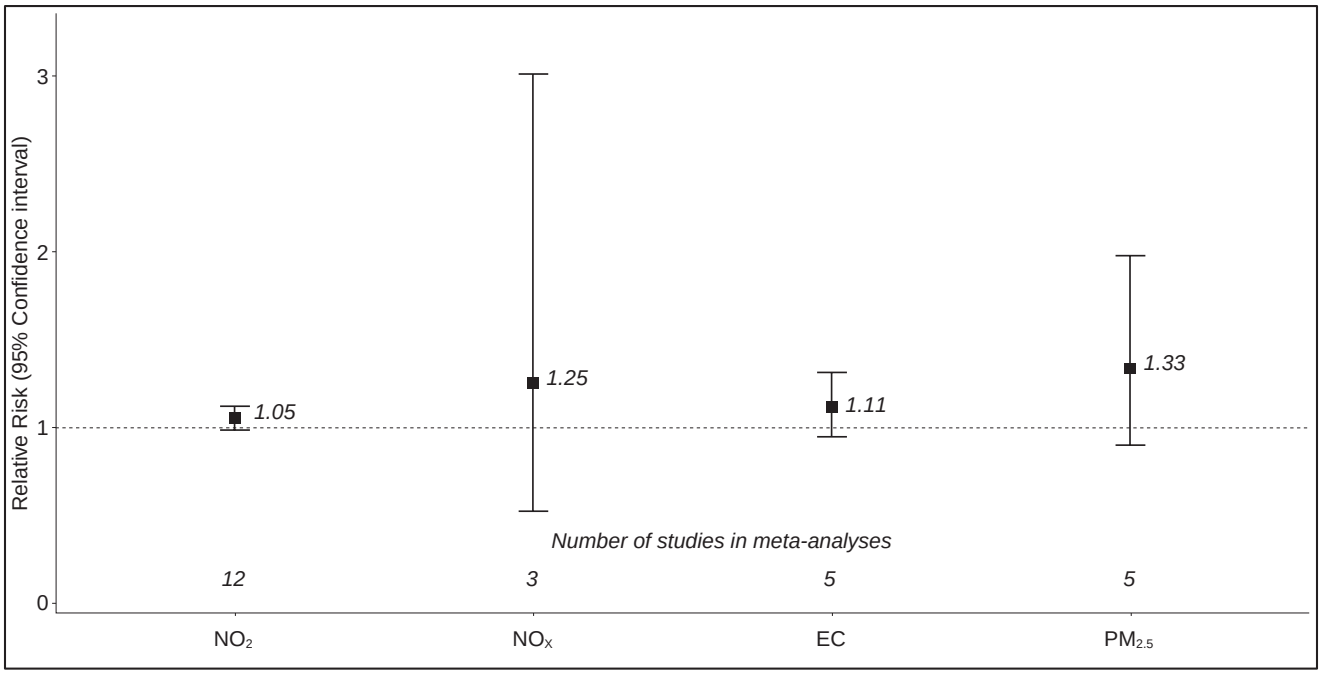

Figure 9.1. Meta-analysis of associations between traffic-related air pollutants and asthma onset in children. The following increments were used: 10 µg/m^3 for NO_2, 20 µg/m^3 for NO_x, 1 µg/m^3 for EC, and 5 µg/m^3 for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

because different exposure-assessment methods were used. In addition, both Lavigne and colleagues (2018) and Lavigne and colleagues (2019) were included because the overlap in populations was marginal and different exposure-assessment methods were used. Estimates were excluded from meta-analyses when pollutant levels were log transformed or categorized (Brunst et al. 2015; Lindgren et al. 2013) or when indoor pollutant levels or exposures related to time–activity patterns were modeled (Hasunuma et al. 2016; Mölter et al. 2014). Less informative studies for the same population were also excluded, for example Clark and colleagues (2010) was a much smaller study than the extended analyses in Sbihi and colleagues (2016). Therefore, the latter study entered the meta-analysis.

NO_2 (N = 12 studies), EC (N = 5, including different metrics that were combined as described in Chapter 5), and $PM_{2.5}$ (N = 5) were the most frequently studied pollutants in meta-analyses. Of those studies identified for potential inclusion in meta-analysis, only three entered the meta-analysis for NO_x.

Only two studies reported associations with nitric oxide (NO), CO, and PM_{10}; and there was only one study for pollutants such as PM_{coarse}, UFPs, and $PM_{2.5}$ specifically modeled from traffic sources. Therefore no meta-analysis was conducted for those pollutants. Moreover, studies reporting epidemiological results for associations of asthma onset in children with other traffic-related pollutants (e.g., polycyclic aromatic hydrocarbons (PAH) and benzene) were not identified in the search. Note that many studies reported estimates with multiple exposure metrics related to TRAP (e.g., both EC and NO_2).

The meta-analytic summary estimates documented positive associations between all pollutants with enough studies for meta-analysis (i.e., NO_2, NO_x, EC, and $PM_{2.5}$) and asthma onset in children, but all meta-analytic confidence intervals included unity. The summary estimate for NO_2 based on 12 studies had the narrowest confidence interval with a lower bound at 0.99 (Figure 9.1).

Forest plots with individual studies for the pollutants most widely studied (NO_2, EC, and $PM_{2.5}$) (Figure 9.2) show that effect estimates derived from studies based on administrative health data were typically lower and confidence intervals narrower (Lavigne et al. 2018, 2019; Pennington et al. 2018; Sbihi et al. 2016; Tétreault et al. 2016) than those of smaller traditional cohorts with detailed individual-level risk factor information.

Most associations between NO_2 and asthma onset in individual studies were positive, but confidence intervals often included unity and a few estimates were also negative (e.g., Oftedal et al. 2009; Sbihi et al. 2016). Therefore, the NO_2 meta-analysis of 12 studies showed a moderate degree of heterogeneity (I^2 = 73%) with RRs ranging from 0.93 to 1.76 per 10-μg/m^3. The meta-analytic summary estimate for the association of asthma onset in children with NO_2 was 1.05 (95% CI: 0.99–1.12) per 10-μg/m^3 NO_2. The summary estimate was not heavily influenced by any one study, as indicated by the weights in the forest plot. Results for the few studies on NO (a precursor of NO_2; Carlsten et al. 2011; Sbihi et al. 2016) and NO_x (NO_2+NO; Gruzieva et al. 2013; McConnell et al. 2010; Pennington et al. 2018) were either null or positive.

The three meta-analyzed estimates of associations with NO_x were highly heterogeneous, with RRs ranging from 1.00–1.94 (Appendix Figure 9B-1), and one categorical analysis reported negative associations with NO_x (Lindgren et al. 2013).

Five studies provided estimates for meta-analysis for EC and $PM_{2.5}$ (Figure 9.2). The individual studies reported positive associations, except for Sbihi and colleagues (2016) for EC, but most of the confidence intervals included unity. Brunst and colleagues (2015), which was not meta-analyzed, also reported positive EC associations. The heterogeneity of the associations with EC was low (I^2 = 47%), while it was moderate for $PM_{2.5}$ (I^2 = 67%). The summary estimate was 1.11 (95% CI: 0.94–1.31) per 1-μg/m^3 increase in EC, and 1.33 (95% CI: 0.90–1.98) per 5-μg/m^3 increase in $PM_{2.5}$. The null results from Sbihi and colleagues (2016) had a large influence on the EC meta-analysis with a 45% weight.

Regarding the studies and pollutants not meta-analyzed, Lavigne and colleagues (2019) provides additional information for the overall confidence assessment. Lavigne and colleagues (2019) is a large study of 160,641 singleton live births in the City of Toronto, Canada, with a follow-up at the age of 6 years and control of some individual (maternal smoking and maternal asthma) and area-based confounding factors. The researchers reported an association between childhood exposure to UFPs and asthma onset (1.03; 95% CI: 1.00–1.06, per 10,551-particles/cm^3); the association was particularly strong for exposure during the second trimester of pregnancy (1.09; 95% CI: 1.06–1.12, per 10,770-particles/cm^3). The remaining studies provided only limited information for the overall confidence assessment. The estimate of Sbihi and colleagues (2016) and of Pennington and colleagues (2018) for prenatal exposure to CO were somewhat contradictory; Pennington and colleagues (2018) reported a slightly positive borderline association) while Sbihi and colleagues (2016) reported a positive and negative association, depending on age group. However, estimates of association between prenatal or first year exposure to PM_{10} (Gehring et al. 2015; Gruzieva et al. 2013), PM_{coarse} (Gehring et al. 2015), and $PM_{2.5}$ from traffic (Pennington et al. 2018) and asthma onset were all positive although their confidence intervals were large (mainly for PM_{10} and PM_{coarse}) and all included unity.

9.3.1.3 Additional Meta-analyses

Figure 9.3 shows that most studies for NO_2 were rated as high traffic specificity. Only two studies were rated as moderate traffic specificity (Jerrett et al. 2008; Lavigne et al. 2018). The summary estimates with and without the moderate traffic specificity studies were similar. The estimates were slightly

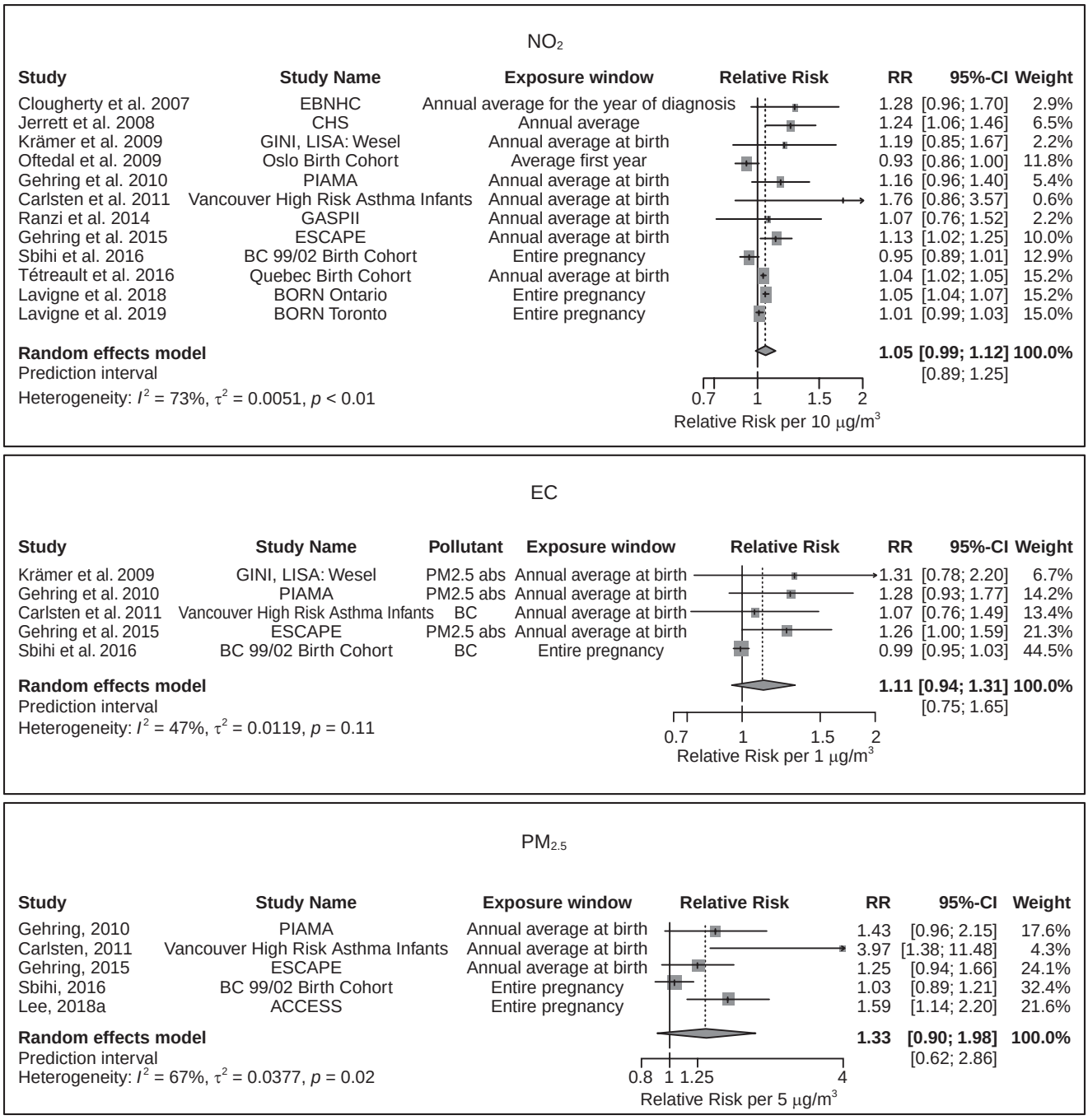

Figure 9.2. Association between NO_2, EC, and $PM_{2.5}$ and asthma onset in children: meta-analysis.

less heterogeneous without the moderate traffic specificity estimates (I^2 = 69% compared with 73% overall). All EC estimates were rated high traffic specificity and all $PM_{2.5}$ were rated moderate, thus stratified analyses for these pollutants were not possible.

Appendix Figure 9B-2 illustrates that NO_2 summary estimates for Europe and North America were positive, but the confidence intervals included unity. The heterogeneity of estimates of association with NO_2 was virtually similar when restricted to studies from Europe (I^2 = 67% in European studies compared with 73% overall). Administrative cohorts were only based in North America, and associations were lower than the estimates from the European studies, which were all traditional cohorts with smaller sample sizes and

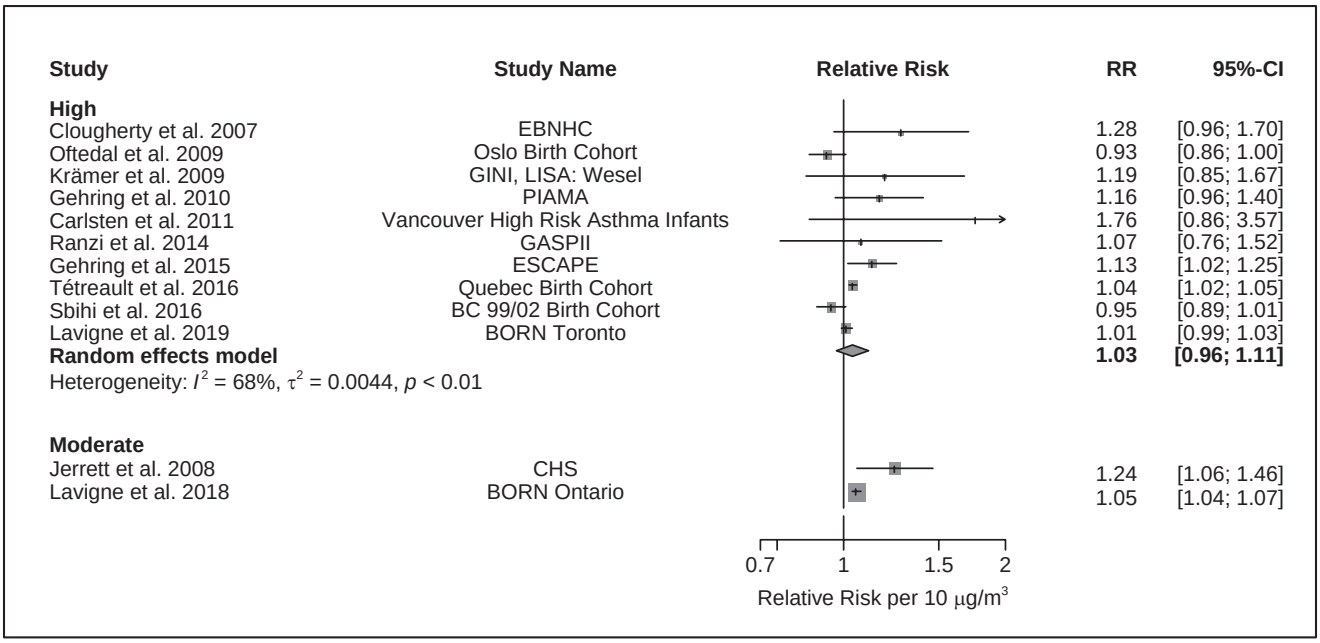

Figure 9.3. Association between NO_2 and asthma onset in children: meta-analysis by traffic specificity.

more extensive adjustments for individual-level potential confounding factors. The EC summary estimate of the three European studies was larger (1.27; 95% CI: 1.22–1.33) and did not include unity, compared with the main analyses that included two estimates from North America (Additional Materials; available on the HEI website). In, addition, heterogeneity was reduced to 0% when restricted to European studies. The three estimates of association with $PM_{2.5}$ from North America and the two from Europe varied substantially (Additional Materials). Some studies reported NO_2 effect estimates adjusted for general $PM_{2.5}$ exposure (Lavigne et al. 2018, 2019; McConnell et al. 2010). In the two-pollutant models, NO_2 effect estimates were generally attenuated, but the increased RR remained statistically significant in two studies (Lavigne et al. 2018; McConnell et al. 2010).

To advance the Panel's understanding of the exposure time window most likely related to asthma onset, an additional meta-analysis was also performed giving priority to postnatal NO_2 exposure instead of to the earliest exposures during pregnancy, at birth, or in the first year of life. In this sensitivity analysis the effect estimate included in the meta-analysis changed for five of the 12 studies. As shown in Figure 9.4, the summary estimate that prioritized postnatal exposures was slightly lower but very similar to the summary estimate giving priority to early life exposures.

9.3.1.4 Associations with Indirect Traffic Measures

Studies on indirect traffic measures (i.e., distance and traffic density measures) are an additional source of information to assess the evidence of associations between TRAP broadly and asthma onset in children. The indirect traffic measures were too heterogeneous in definitions to allow meta-analysis.

The nine studies investigating distance to roadways provided mixed information for the overall confidence assessment, as positive, negative, and null associations were reported (Table 9.3). Confidence intervals were also very large and often included unity. Only two studies reported estimates of association with traffic density measures, and they were in opposite directions (Lindgren et al. 2013; Zmirou et al. 2004). Most of the indirect traffic measure studies also reported on traffic-related air pollutants.

9.3.1.5 Narrative Assessment

The evidence base included mostly cohort studies from Europe and North America (23 out of a total of 25 studies, mostly birth cohorts); 19 were traditional cohorts with detailed individual information (sample size ranging from 184 to 14,085 children for the ESCAPE pooled cohorts), while six were large cohorts based on administrative data (including up to 761,172 children) with limited information on lifestyle factors. Traditional cohorts usually assessed asthma onset with questionnaires. Most studies used air pollutants estimated with LUR and dispersion models.

The evidence base provides moderate evidence of an association between TRAP and asthma onset in children. The summary estimates for the association between TRAP and asthma onset in children were positive, both in administrative cohorts and in traditional cohorts with extensive confounding adjustment. However, estimates from administrative

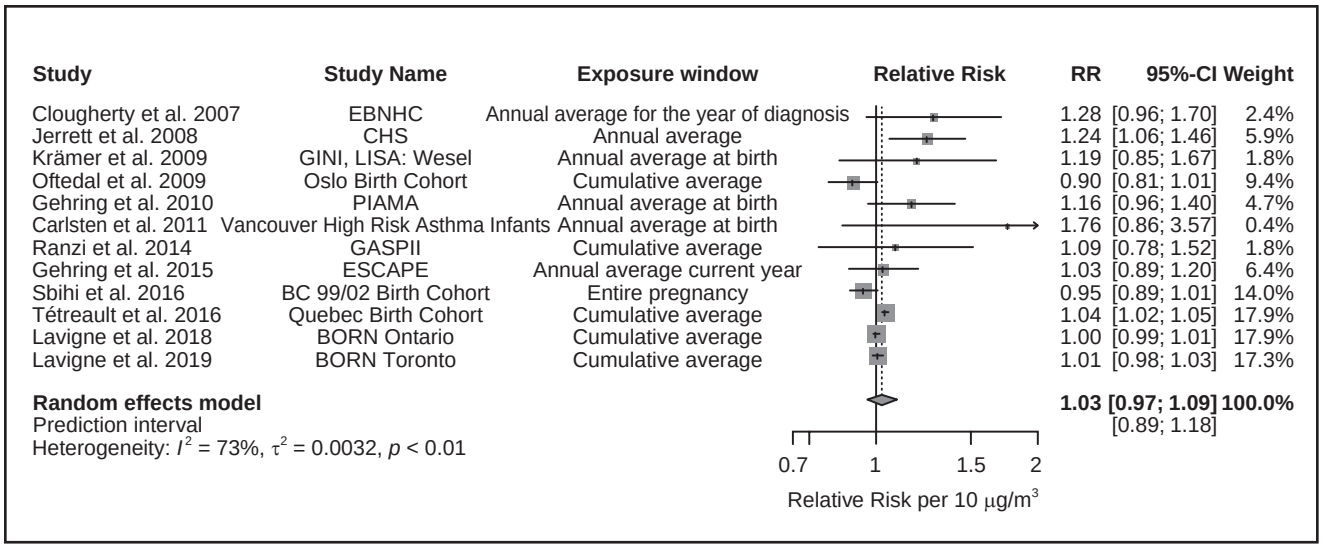

Figure 9.4. Association between NO_2 and asthma onset in children: meta-analysis giving priority to postnatal exposures.

cohorts were lower and more precise. Confidence intervals of NO_2 estimates marginally overlapped the null, and imprecise summary estimates for the other pollutants were found. All summary estimates were heterogeneous. Factors like type of cohort (traditional or administrative) and age at which asthma onset was assessed, which differed widely between studies, might have contributed to this heterogeneity. Nonetheless, the consistent associations in substantially different populations lent further support to the confidence in the presence of the observed associations with asthma onset in children. Moreover, the fact that the majority of studies with pollutants not meta-analyzed (e.g., PM_{10}, PM_{coarse}, UFPs, and $PM_{2.5}$ from traffic emissions) also reported positive associations, provided additional support. The presence of a positive association was further supported by positive monotonic exposure–response relationships from two Canadian administrative cohorts (Lavigne et al. 2018; Tétreault et al. 2016). Furthermore, all the assessed studies were carefully screened for traffic specificity, increasing the likelihood that the associations found pertain to traffic emissions. On the other hand, indirect traffic measures provided limited evidence of an association.

The Panel's assessment of the level of confidence in the presence of an association was moderate, effect estimates for most traffic-related air pollutants were highly heterogeneous, and all confidence intervals of the summary estimates included unity, which suggests that some uncertainties remain regarding the association between TRAP and asthma onset in children.

9.3.1.6 Risk of Bias Assessment

Table 9.4 shows an overview of the results of the risk of bias assessment for studies on asthma onset that were meta-analyzed; Appendix Table 9B-1 presents the assessment for each individual study. Risk of bias assessment is about a potential risk of bias; it is not a determination of actual bias and it does not inform on the magnitude or direction of the bias. The large majority of the estimates of association were rated moderate risk of bias for at least one domain. Blinding of outcome measurements and missing data were the domains most often reported for moderate risk of bias. For all pollutants except EC, one or two estimates of association were rated as having a high risk of bias due to confounding or to missing data. Risk of bias due to confounding was usually due to lack of adjustment for important potential confounders. Most of the administrative cohort studies were rated as moderate risk of bias (for indirect adjustment for parental smoking) or high risk of bias (for missing parental smoking).

Most studies used a cohort design with limited loss to follow-up. The only study with potential concern related to selection bias was also the only study that reported a negative association for NO_2 (Oftedal et al. 2009). Additionally, studies were extensively evaluated for their exposure assessment to only include studies indicative of traffic; therefore, all studies were rated low risk of bias for exposure methods. Several studies were rated moderate risk of bias for change in exposure status. This assessment was applied when a study had a long follow-up period and exposure was assessed for a limited part of the follow-up period, such as the ESCAPE study (Gehring et al. 2015).

9.3.1.7 Confidence Assessment of the Body of Evidence

Table 9.5 provides the Panel's confidence assessment. The table includes the pollutants that had three or more studies, for which a meta-analysis was conducted. The table does not include the pollutants with fewer studies and the indirect traffic measures, for which a meta-analysis was not possible.

Table 9.3. Key Study Characteristics of Articles Included in the Systematic Review for Asthma Onset in Children—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Age	Sex	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
Clark 2010	BC 99/00 Birth Cohort	Case-control	Multiple cities, Canada	1999–2003	20,892	3–5	Both	Distance	RR	0.97 (0.82–1.15)	<50 m to major road or <150 m to highway vs. higher
Hasunuma 2016	SORA	Nested case-control	Multiple cities, Japan	2006–2010	415	1–3	Both	Distance	OR	1.30 (0.42–3.99)	<50 vs. >100 m
										1.63 (0.57–4.69)	50–100 vs. >100 m
Krämer 2009	GINI, LISA: Wesel	Cohort	Multiple cities, Germany	1995–2005	2,059	6	Both	Distance	RR	0.86 (0.66–1.14)	<50 vs. >50 m
Lee 2018b	CHEER	Cohort	Multiple cities, South Korea	2005–2008	825	6–16	Both	Distance	RR	1.88 (0.67–5.29)	<75 m vs. >75 m and no bronchiolitis
										3.62 (1.07–12.26)	<75 m and bronchiolitis vs. <75 m and no bronchiolitis
										1.93 (1.01–3.39)	bronchiolitis only vs. >75 m and no bronchiolitis
Lindgren 2013	Scania Birth Cohort 05/11	Cohort	Scania including Malmö, Sweden	2005–2011	6,007	0–6	Both	Density	HR	0.7 (0.6–0.9)	<8,640 vs. >8,640 vehicles/day
Oftedal 2009	Oslo Birth Cohort	Cohort	Oslo, Norway	1992–2002	2,329	9–10	Both	Distance	RR	0.99 (0.90–1.08)	540.6 m
Ranzi 2014	GASPII	Cohort	Rome, Italy	2003–2011	672	0–7	Both	Distance	OR	0.69 (0.40–1.20)	<86.1 vs. >86.1 m
Sbihi 2016	BC 99/02 Birth Cohort	Case-control	Vancouver, British Columbia, Canada	1999–2012	41,569	0–5	Both	Distance	OR	1.00 (0.94–1.08)	<50 m to major road or <150 m to highway vs. higher
					10,288	6–10				1.06 (0.92–1.21)	

Continues next page

Table 9.3 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Asthma Onset in Children—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Age	Sex	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
Shima 2003	Chiba Cohort	Cohort	Chiba Prefecture, Japan	1992–1995	1,858	6–13	Female	Distance	OR	4.03 (0.90–17.96)	<50 m vs. rural areas
							Male			3.77 (1.00–14.16)	
							Female			1.74 (0.63–4.81)	>50 m vs. rural areas
							Male			1.99 (0.79–4.99)	
Weaver 2018	CHS	Cohort	California, United States	1993–2014	5,337	5–20	Both	Distance	OR	1.10 (0.61–1.99)[a] (Hispanic whites)	<500 vs. >500 m to freeway
										0.82 (0.42–1.61)[a] (non-Hispanic whites)	
										2.20 (1.14–4.25)[a] (Hispanic whites)	<75 vs. >75 m to nonfreeway major road
										0.81 (0.33–1.99)[a] (non-Hispanic whites)	
Zmirou 2004	VESTA	Case-control	Multiple cities, France	1998–2000	390	2–14	Both	Density	OR	2.28 (1.14–4.56)	>30 vs. <11.2 vehicles/day/m
										1.48 (0.73–3.02)	11.2–28.8 vs. <11.2 vehicles/day/m

HR = hazard ratio; OR = odds ratio; RR = relative risk.

[a] Cube root transformed.

Table 9.4. Summary of Risk of Bias Rating for Studies on Asthma Onset in Children

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low-risk	Moderate-risk	High-risk	Low-risk	Moderate-risk	High-risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	10	2	4	17	2	6
	Validity of measuring of confounding factors	13	3	0	22	3	0
	Control in analysis	14	2	0	23	2	0
	Overall	7	5	4	14	5	6
2. Selection bias	Selection of participants into the study	15	1	0	24	1	0
3. Exposure assessment	Methods used for exposure assessment	16	0	0	25	0	0
	Exposure measurement methods comparable across the range of exposure	16	0	0	25	0	0
	Change in exposure status	13	3	0	20	5	0
	Overall	13	3	0	20	5	0
4. Outcome measurements	Blinding of outcome measurements	6	10	0	10	15	0
	Validity of outcome measurements	12	4	0	21	4	0
	Outcome measurements	12	4	0	21	4	0
	Overall	4	12	0	8	17	0
5. Missing data	Missing data on outcome measures	8	6	2	12	11	2
	Missing data on exposures	12	2	2	20	3	2
	Overall	7	6	3	11	11	3
6. Selective reporting	Authors reported a priori primary and secondary study aims	16	0	0	25	0	0

All studies on traffic pollutants used cohort or case-control study designs, thus the initial rating was moderate. Here, the Panel first discusses four factors that may reduce confidence (downgrades). For the downgrade factor indirectness, all studies addressed the research question directly, and therefore no downgrade was applied. Next, factors that may increase confidence (upgrades) are discussed. The Panel decided a priori not to consider the upgrading factor large magnitude of the effect.

Downgrading Factor Risk of Bias The number of risk of bias ratings for each exposure–outcome pair that was meta-analyzed for asthma onset in children is presented in Table 9.4. Very few exposure–outcome pair estimates (5 of 25 across different pollutants) were rated at high risk of bias, thus a formal comparison between the low and moderate versus the high risk of bias subgroups was not possible for most risk of bias domains.

Nonetheless, subgroup analyses with respect to risk of bias (Appendix Figure 9B-3) showed that excluding the one estimate of association with NO_2 rated at high risk of bias due to confounding (Sbihi et al. 2016) reduced the heterogeneity (as this estimate was in the negative direction). The meta-analytic estimate excluding Sbihi and colleagues (2016) was similar to the estimate considering all studies (RR: 1.07 per 10-μg/m^3; 95% CI: 1.00–1.14). Estimates rated at low, moderate, and high risk of bias due to missing data were similar (Additional Materials). Excluding the one NO_2 estimate from Lavigne and colleagues (2018) that was rated at high risk of bias due to missing data had no influence on the meta-analytic estimate.

For EC, the magnitude and precision of the meta-analytic estimate increased (from RR: 1.11; 95% CI: 0.94–1.31 to RR: 1.22; 95% CI: 1.07–1.40) when the single estimate rated at high risk of bias for confounding was excluded (Sbihi et al. 2016).

Estimates of association with $PM_{2.5}$ were all positive but of varying magnitude; the summary estimate did not change substantially, and its confidence interval remained large

Table 9.5. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Asthma Onset in Children[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ (N = 12)	0	0	0	0	+	0	0	++++ (High)
	Rationale	Cohort design initially rated as moderate.	One study at high RoB and exclusion did not alter substantially the summary estimate.	Moderate heterogeneity (I^2 = 73%). Plausible reasons to explain inconsistency.	Sample size met and estimate consistent with an association.	No evidence found.	Clear evidence of plausible shape of ERF (Lavigne 2018; Tetreault 2016).	Confounding in both directions possible.	Variability too large to assess consistency.	
NO_X	Cohort	+++ (N = 3)	–	–	–	0	0	0	0	+ (Very low)
	Rationale	Cohort design initially rated as moderate.	2 of 3 studies high RoB.	High heterogeneity (I^2 = 90%) due to magnitude and direction.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	
EC	Cohort	+++ (N = 5)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	One study at high RoB but exclusion increased the summary estimate.	Low heterogeneity (I^2 = 47%). Plausible reasons to explain inconsistency.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	
$PM_{2.5}$	Cohort	+++ (N = 5)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	Few studies at high RoB and exclusion did not alter substantially the summary estimate.	Moderate heterogeneity (I^2 = 67%). Plausible reasons to explain inconsistency.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

when exposure–outcome pairs rated as high risk of bias for confounding or missing data were excluded.

Thus, the stratified analysis by risk of bias does not suggest a need to downgrade the confidence in the body of evidence for NO_2, EC, and $PM_{2.5}$, rather it indicates more robust findings. This judgment is supported by the finding of limited changes in meta-analytic estimates when excluding the studies rated at high risk of bias.

For NO_x there were just three studies carrying equal weights, making the judgment difficult. As two out of three were rated at high risk of bias for confounding or missing data, a downgrade was considered appropriate.

Downgrading Factor Unexplained Inconsistency The Panel observed a moderate degree of heterogeneity of effect estimates across studies for NO_2 (Figure 9.2). The I^2 was 73%. Effect estimates in individual studies ranged from 0.93 to 1.76 per 10-μg/m^3 NO_2. The confidence interval of most estimates of association included unity, and while 10 of the 12 estimates were positive (N = 10), estimates from Oftedal and colleagues (2009) and Sbihi and colleagues (2016) were negative. The RR reported by Carlsten and colleagues (2011) was relatively high compared with the other studies, but this may be explained by the fact that this study was the only one with high-risk infants, which may be a population particularly sensitive to TRAP. Nonetheless, several RRs were not included in the confidence interval of other studies. Bias may partly explain the heterogeneity as it was reduced with the exclusion of the high risk of bias estimates due to confounding (Sbihi et al. 2016); Oftedal and colleagues (2009) (the other negative estimate) is also the only study rated as high risk of bias due to selection. The heterogeneity was also lower in the subgroup of European versus North American studies; this may be related to the fact that North American studies included both traditional and administrative cohorts and the European studies included only traditional cohorts. Although estimates were not entirely consistent in direction nor magnitude, no downgrade was applied because most of them were positive (i.e., in the same direction), and there were plausible explanations for the variability, including identified biases and different populations.

The few estimates for NO_x that were meta-analyzed were heterogeneous (I^2 = 90%) and not consistent in direction (one null and two positive estimates of very different magnitude). Thus, a downgrade was warranted. Although $PM_{2.5}$ estimates were all positive, they were heterogeneous (I^2 = 67%). Effect estimates in individual studies ranged from 1.03–3.97 per 5-μg/m^3 $PM_{2.5}$, with the largest estimate from the high-risk infant study (Carlsten et al. 2011); the increased vulnerability to air pollutants of high-risk infants is one good reason to explain for the variability. The I^2 decreased but remained moderate to high when excluding the high risk of bias estimates. Because risk of bias is one plausible reason to explain some inconsistency, a downgrade was not applied.

Regarding estimates from studies on EC, the Panel observed a low degree of heterogeneity. The I^2 was 47%. Effect estimates in individual studies ranged from 0.99–1.31 per 1-μg/m^3 EC. All but one of the five estimates of association were positive, but most confidence intervals (except the estimate from the administrative cohort by Sbihi et al. 2016) were large and all included unity. The estimate of association in a counterintuitive negative direction by Sbihi and colleagues (2016) was rated high risk of bias due to confounding. Because potential confounding appeared to be a plausible reason to account for this variability, no downgrade was applied.

Other Factors That Reduce Confidence Regarding imprecision, for all pollutants included in the meta-analysis, the sample size was larger than the specified needed minimum sample size in the protocol, mainly due to the inclusion of the administrative cohorts. NO_2 was consistent with an association (borderline significant) (RR: 1.05 per-10 μg/m^3; 95% CI: 0.99–1.12). The confidence intervals for NO_x, $PM_{2.5}$, and EC were wide and clearly included unity. The evidence for $PM_{2.5}$, NO_x, and EC was therefore downgraded.

The Panel did not downgrade for publication bias. For NO_2, there were more than 10 studies, so funnel plots and Egger tests were produced (Additional Materials). The funnel plot and the Egger test did not suggest asymmetry (P value was 0.613). Due to the small number of studies, it was not possible to assess publication bias for studies on associations with the other pollutants meta-analyzed; as there was no evidence of bias for NO_2, the Panel chose to not downgrade the evidence for all pollutants.

Factors That Increase Confidence For NO_2, Tétreault and colleagues (2016) and Lavigne and colleagues (2018), which had considerable weights in the meta-analysis, provided evidence of a plausible monotonic exposure–response function, so an upgrade was applied. No upgrade was applied for the other pollutants meta-analyzed because of lack of evidence. In the current body of evidence, the Panel found no clear indication that residual confounding or other factors are likely to lead to underestimation of the associations. An upgrade was thus not considered appropriate. Finally, the Panel did not upgrade for consistency across geographic regions, populations or study period. For NO_2 and $PM_{2.5}$, the Panel found associations in the two identified geographical areas (Europe, North America), although the estimates were highly variable, and the confidence intervals wide. Because of the variability of the estimates, the Panel did not upgrade the evidence for NO_2 and $PM_{2.5}$. The EC summary estimate from the three European studies was larger and did not include unity, compared with the main analyses of all studies, but studies were too few to meaningfully assess this difference, thus no upgrade was applied. For NO_x, consistency was not assessed due to the small number of studies. Also note that most studies were published after 2008, so the Panel could not assess consistency across time periods.

Evaluation of Confidence for Combined Measures of TRAP The Panel had four confidence assessments in the quality of the body of evidence for asthma onset in children. One assessment was high (NO_2), two low ($PM_{2.5}$, EC) and one was very low (NO_x) (Table 9.5). The Panel's overall confidence assessment for TRAP is high because the highest rating is high. The very low or low confidence assessments are for pollutants with substantially fewer than 10 studies. The meta-analytic summary estimates of those pollutants were also positive but much less certain, so they provide some additional support for the overall confidence assessment. In conclusion, based on the modified OHAT assessment, the overall confidence in the quality of the body of evidence of TRAP exposure with asthma onset in children is high.

9.3.1.8 Overall Confidence Assessment

Based on the narrative assessment (moderate) and the modified OHAT assessment (high), the overall confidence in the evidence for an association between TRAP exposure and asthma onset in children is moderate to high.

9.3.2 PREVALENCE OF ASTHMA EVER

9.3.2.1 Study Selection and Description

Forty-five studies reported associations between TRAP or indirect traffic measures and having ever been diagnosed with asthma (i.e., prevalence of asthma ever) in children. Of these studies, 14 only reported associations with indirect traffic measures. Tables 9.6 and 9.7 present key details of all the identified studies, including effect estimates. Most of the studies were conducted in European (N = 21) and Asian countries (N = 14). 16 were published in 2008 or earlier.

Ever been diagnosed with asthma refers to a prevalence measure usually self-reported through questionnaires; the ISAAC and the ATS questionnaires were most often used. However, information on the prevalence of asthma ever was also obtained from medical records (Puklová et al. 2019) and from records on two dispensed medications for asthma during a four-year follow-up period (Oudin et al. 2017). In this review, records of a single dispensed mediation were used for wheeze outcomes.

Most studies performed cross-sectional analyses of associations between TRAP exposures and having ever been diagnosed with asthma at assessment, except Dell and colleagues (2014) which was a case-control study. About a quarter of the cross-sectional analyses were from cohort studies, mostly birth cohorts. For example, some birth cohorts assessed the occurrence of a specific respiratory condition at specific ages during the course of the follow-up and the results were properly analyzed as prevalence (at a specific age) rather than incidence. In this case, the design of the study was a cohort, although the specific analysis was cross-sectional.

Studies differed in sample size, ranging from a few hundred to several hundred thousand participants. Oudin and colleagues (2017) was the largest study (N = 745,171 children) and was based on dispensed medication. The largest questionnaire survey involved 57,682 children in Japan (Hasunuma et al. 2016); other very large Asian surveys were also conducted (Hwang et al. 2005; Liu et al. 2014). The study by Pujades-Rodríguez and colleagues (2009a) also surveyed more than 50,000 children with three waves in the Health Survey for England.

Most of the studies that assessed the asthma ever outcome with questionnaires had extensive information on individual risk factors such as parental smoking, indoor air quality, and family history of respiratory disease or allergies. These studies were often designed to investigate asthma and allergies; their relationship to various risk factors was not limited to TRAP.

Age at outcome assessment was usually during elementary school years, although some assessed the prevalence of asthma in very young children or in older adolescents. For instance, Morgenstern and colleagues (2007) and Miyake and colleagues (2010) assessed the prevalence of asthma ever during the first two years of life, and Dong and colleagues (2008) included children from one to 6 years of age. Kuo and colleagues (2002) studied only adolescents while others included both children and adolescents (Hwang et al. 2005; Jung et al. 2015; Lee et al. 2018b; Oudin et al. 2017; Pujades-Rodríguez et al. 2009a; Puklová et al. 2019; Rosenlund et al. 2009; Sahsuvaroglu et al. 2009; Skrzypek et al. 2013). Pujades-Rodríguez and colleagues (2009a) included even very young children, from age 2 up to 16 years of age. Oudin and colleagues (2017) and Puklová and colleagues (2019) included children and adolescents up to 17–18 years of age.

Exposure assessment was usually based on LUR or dispersion models, although most studies from Asian countries used surface monitoring. Studies reported various exposure windows, including annual recent exposure, cumulative exposure, and exposure during pregnancy. Mean air pollutant levels such as NO_2 varied widely, but were highest for older studies (e.g., Krämer et al. 2000) and in Asian countries (e.g., Liu et al. 2016). Thus, the identified studies differed substantially in size, exposure assessment, and population studied.

9.3.2.2 Primary Meta-analysis

Figure 9.5 shows the meta-analytic summary effect estimates for all pollutants for the prevalence of asthma ever in children. The number of studies included in Figure 9.5 is less than the total number of selected studies (Tables 9.6 and 9.7) because the Panel only considered the most informative estimate (i.e., longer follow-up) per study population (e.g., the Panel selected Deng et al. 2016 over Deng et al. 2015; Morgenstern et al. 2008 over Morgenstern et al. 2007; Mölter et al. 2015 and Morgenstern et al. 2008 over Fuertes et al. 2013).

Table 9.6. Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Asthma Ever in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
Abidin 2014	ISAAC Malaysia	Cross sectional	Kuala Lumpur, Malaysia	2009	1,892	Surface monitoring	NO_2	15.8–43.9	Annual average current year	**1.50 (0.87–2.57)**	10 µg/m^3
Dell 2014	T-CHEQ	Case-control	Toronto, Canada	2006	1,441	LUR	NO_2	18.3–28.3	Average first year	**1.10 (0.91–1.33)**	5.7 ppb
									Annual average current year	1.17 (0.96–1.43)	5.3 ppb
									Cumulative average	0.96 (0.80–1.15)	3.3 ppb
Deng 2015	CCHH Changsha	Cross sectional	Changsha, China	2011–2012	2,490	Surface monitoring	NO_2	46	Average first year	1.91 (1.21–3.02)	15 µg/m^3
Deng 2016	CCHH Changsha	Cross sectional	Changsha, China	2011–2012	2,598	Surface monitoring	NO_2	46	Entire pregnancy	**1.75 (1.23–2.48)**	16 µg/m^3
									Cumulative average	1.56 (1.14–2.14)	12 µg/m^3
Fuertes 2013	GINI, LISA	Cohort	Multiple cities, Germany	1995–2009	4,585	LUR	NO_2	22.4	Annual average at birth	0.89 (0.73–1.08)	6.1 µg/m^3
							$PM_{2.5\ abs}$	1.5		0.82 (0.55–1.21)	0.5 1×10^{-5}/m
							$PM_{2.5}$ mass	13.3		0.97 (0.59–1.58)	4 µg/m^3
Gauderman 2005	CHS	Cohort	Multiple cities, United States	1993–2000	208	Dispersion/ CTM	NO_2 (freeways)	About 40	Annual average recent year	2.22 (1.36–3.63)[d]	0.64 ppb
							NO_2 (non-freeways)			1.00 (0.75–1.33)[d]	0.49 ppb
							NO_2 (all roads)			1.40 (0.86–2.27)[d]	1.27 ppb

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Table 9.6 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Asthma Ever in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
Hasunuma 2016	SORA	Cross sectional	Multiple cities, Japan	2006–2010	57,682	Personal exposure	NO_x	37.7	Cumulative average	1.00 (0.99–1.01)	1 ppb
							EC	2.85		1.01 (0.98–1.03)	0.1 μg/m^3
Hirsch 1999	ISAAC Dresden	Cross sectional	Dresden, Germany	1995–1996	4,477	Surface monitoring	NO_2	33.8	Annual mean	**1.16 (0.94–1.42)**	10 μg/m^3
							CO	0.69		**1.07 (0.94–1.21)**	0.2 mg/m^3
							Benzene	4.0		1.11 (0.97–1.25)	1 μg/m^3
Hwang 2005	ISAAC Taiwan	Cross sectional	Taiwan	2001	32,672	Surface monitoring	NO_x	27.64	Annual average previous year	**1.00 (0.95–1.06)**	10 ppb
							CO	664		**1.04 (1.02–1.07)**	100 ppb
Janssen 2003	ISAAC Southwestern Netherlands	Cross sectional	Multiple cities, the Netherlands	1997–1998	2,053	Surface monitoring	NO_2	34.8	Annual average current year	**1.39 (0.75–2.56)**	17.6 μg/m^3
							BS	10.3		**1.36 (0.62–2.98)**	9.3 μg/m^3
Knibbs 2018	ACHAPS	Cross sectional	Multiple cities, Australia	2007–2008	2,603	LUR	NO_2	8.8	Previous year annual average	**1.29 (1.06–1.56)**	4.03 ppb
Krämer 2000	Düsseldorf School Survey	Cross sectional	Düsseldorf, Germany	1996	317	Surface monitoring	NO_2	44.4–61.7	Annual average current year	**0.90 (0.52–1.57)**	10 μg/m^3
Kuo 2002	ISAAC Taiwan	Cross sectional	Multiple cities, Taiwan	1996	12,926	Surface monitoring	NO_2	15.5–28.1	Annual average current year	1.69 (1.16–2.48)	≥23 vs. <23 ppb
Liu 2013	SNEC Kindergarten	Cross sectional	Liaoning Province, China	2009	6,730	Surface monitoring	NO_2	36.7	Three-year average at baseline	**1.16 (0.98–1.38)**	10 μg/m^3

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Table 9.6 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Asthma Ever in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
Liu 2014	SNEC	Cross sectional	Liaoning Province, China	2009	23,326	Surface monitoring	NO_2	36.7	Three-year average at baseline	**1.25 (1.16–1.36)**	10 μg/m^3
Liu 2016	CCHH Shanghai	Cross sectional	Shanghai, China	2011–2012	3,259	Surface monitoring	NO_2	55.4	Entire pregnancy	**1.17 (0.83–1.67)**	20 μg/m^3
									Average first year	1.55 (1.26–1.92)	
									Cumulative average	1.38 (1.02–1.85)	
McConnell 2006	CHS	Cross sectional	California, United States	2003	4,762	Dispersion/ CTM	NO_x	25.9	Early life exposure	**1.09 (0.94–1.28)**	28.7 ppb
Mölter 2015	ESCAPE	Cohort	Multiple cities, multiple countries	1994–2010	10,377	LUR	NO_2	11.9–23.7	Cumulative average	1.17 (0.84–1.62) (age 4–5)	10 μg/m^3
										1.10 (0.81–1.49) (age 8–10)	
							NO_x	21.1–39.6		1.10 (0.86–1.40) (age 4–5)	20 μg/m^3
										1.07 (0.86–1.33) (age 8–10)	
							$PM_{2.5\ abs}$	0.6–1.65		1.33 (0.80–2.21) (age 4–5)	1 1×10^{-5}/m
										1.25 (0.84–1.86) (age 8–10)	
							PM_{10} mass	15.3–25.5		0.96 (0.65–1.40) (age 4–5)	10 μg/m^3

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Table 9.6 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Asthma Ever in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
										0.88 (0.63–1.24) (age 8–10)	
							PM_{coarse} mass	6.3–8.5		0.79 (0.66–1.43) (age 4–5)	5 μg/m^3
										1.10 (0.72–1.69) (age 8–10)	
							$PM_{2.5}$ mass	7.4–17.4		1.34 (0.89–2.02) (age 4–5)	5 μg/m^3
										1.23 (0.78–1.95) (age 8–10)	
Morgen-stern 2007	GINI, LISA: Munich	Cohort	Multiple cities, Germany	1995–2001	2,861	LUR	NO_2	35.3	Annual average at birth	1.30 (1.03–1.66) (age 1)	5.7 μg/m^3
										0.82 (0.33–2.03) (age 2)	
							$PM_{2.5\ abs}$	1.7		1.14 (0.88–1.48) (age 1)	0.22 1×10^{-5}/m
										0.85 (0.31–2.34) (age 2)	
							$PM_{2.5}$ mass	12.8		1.04 (0.90–1.29) (age 1)	1.04 μg/m^3
										1.05 (0.92–1.20) (age 2)	

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Table 9.6 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Asthma Ever in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
Morgenstern 2008	GINI, LISA: Munich	Cohort	Multiple cities, Germany	1995–2005	2,436	LUR	NO_2	34.6	Annual average at current address	**1.04 (0.67–1.39)**	6.4 μg/m³
							$PM_{2.5\ abs}$	1.7		**1.56 (1.03–2.57)**	0.2 1×10⁻⁵/m
							$PM_{2.5}$ mass	11.1		**1.12 (0.94–1.29)**	1 μg/m³
Nicolai 2003	ISAAC Munich	Cross sectional	Munich, Germany	1995–1996	about 3,000	LUR	NO_2	About 45	Annual average current year	1.28 (0.82–2.01)	>57.44 vs. <57.44 μg/m³
							EC	About 9		1.42 (0.92–2.20)	>10.73 vs. <10.73 μg/m³
							Benzene	About 5		1.27 (0.82–1.98)	>7.27 vs. <7.27 μg/m³
Oudin 2017	SIMSAM Medication	Cohort	Multiple cities, Sweden	2007–2010	745,171	LUR	NO_2	10.3	Baseline year average	**1.06 (1.02–1.11)**	10 μg/m³
Pedersen 2013	EDEN	Cohort	Nancy and Poitiers, France	2003–2007	879	Dispersion/ CTM	NO_2	18.8	Entire pregnancy	**0.78 (0.52–1.15)**	10 μg/m³
							PM_{10} mass	20.3		**0.38 (0.10–1.38)**	
Pénard-Morand 2010	French Six Cities	Cross sectional	Multiple cities, France	1999–2000	4,907	Dispersion/ CTM	NO_2	30.5–56.6	Annual average current year	**1.09 (0.85–1.39)**	18.5 μg/m³
							NO_x	51.6–108.6		**1.08 (0.96–1.38)**	52.1 μg/m³
							CO	381.4–637.5		**1.21 (1.03–1.54)**	199 μg/m³
							Benzene	1.5–3.3		1.25 (1.08–1.43)	1.1 μg/m³
							PM_{10} mass	19.7–33.3		**1.28 (1.06–1.51)**	10.5 μg/m³

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Table 9.6 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Asthma Ever in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
Puklová 2019	Czech Respiratory Cohort	Cross sectional	Moravian-Silesian Region, Czech Republic	2014	7,239	LUR	NO_2	18.8	Five-year average at baseline	**0.86 (0.67–1.10)**	11.2 µg/m^3
							PM_{10} mass	38.6		**0.85 (0.68–1.07)**	10.8 µg/m^3
Ranzi 2014	GASPII	Cohort	Rome, Italy	2003–2011	672	LUR	NO_2	37.88	Annual average at birth	**1.03 (0.71–1.50)**	10 µg/m^3
									Cumulative average	1.01 (0.69–1.47)	10 µg/m^3
Rosenlund 2009	ISAAC Rome	Cross sectional	Rome, Italy	2000–2001	1,760	LUR	NO_2	45	Exposure in 2000–2001 (recent year)	**0.8 (0.6–1.1)**	14.16 µg/m^3
Sahsuvaroglu 2009	ISAAC Hamilton	Cross sectional	Hamilton, Ontario, Canada	1994–1995	729[e]	LUR	NO_2	14.84	Cumulative average	**1.15 (1.00–1.33)**	1 ppb
Svendsen 2012	El Paso Children's Health	Cross sectional	El Paso and Texas, United States	2001	4,231	LUR	NO_2	20–27	Average recent	**0.78 (0.52–1.16)**[f] (Valley schools)	10 ppb
										1.31 (0.87–1.97)[f] (Upland schools)	
Wood 2015	ISAAC East London	Cross sectional	London, United Kingdom	2008–2011	995	Dispersion/CTM	NO_2	43.5	Annual average current year	**0.97 (0.93–1.02)**	1 µg/m^3
							NO_x	75.7		**0.99 (0.97–1.01)**	1 µg/m^3

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Table 9.6 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Asthma Ever in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
							PM_{10} mass	23.4		**0.93 (0.79–1.09)**	1 μg/m^3
							$PM_{2.5}$ mass	13.7		**0.86 (0.59–1.24)**	1 μg/m^3
Zhang 2002	Chinese 4-City School Survey	Cross sectional	Multiple cities, China	1993–1996	7,392	Surface monitoring	NO_x	90	At baseline	**0.95 (0.63–1.43)**	64 μg/m^3

BS = black smoke.

[a] Unless otherwise indicated, the study included male and female participants.

[b] Units are in the increment column.

[c] The effect estimate in all studies was odds ratio. **Bold** indicates the effect estimate was included in the meta-analysis.

[d] Natural log.

[e] Only females.

[f] Estimates were combined by a fixed effect meta-analysis before entering the random-effects model.

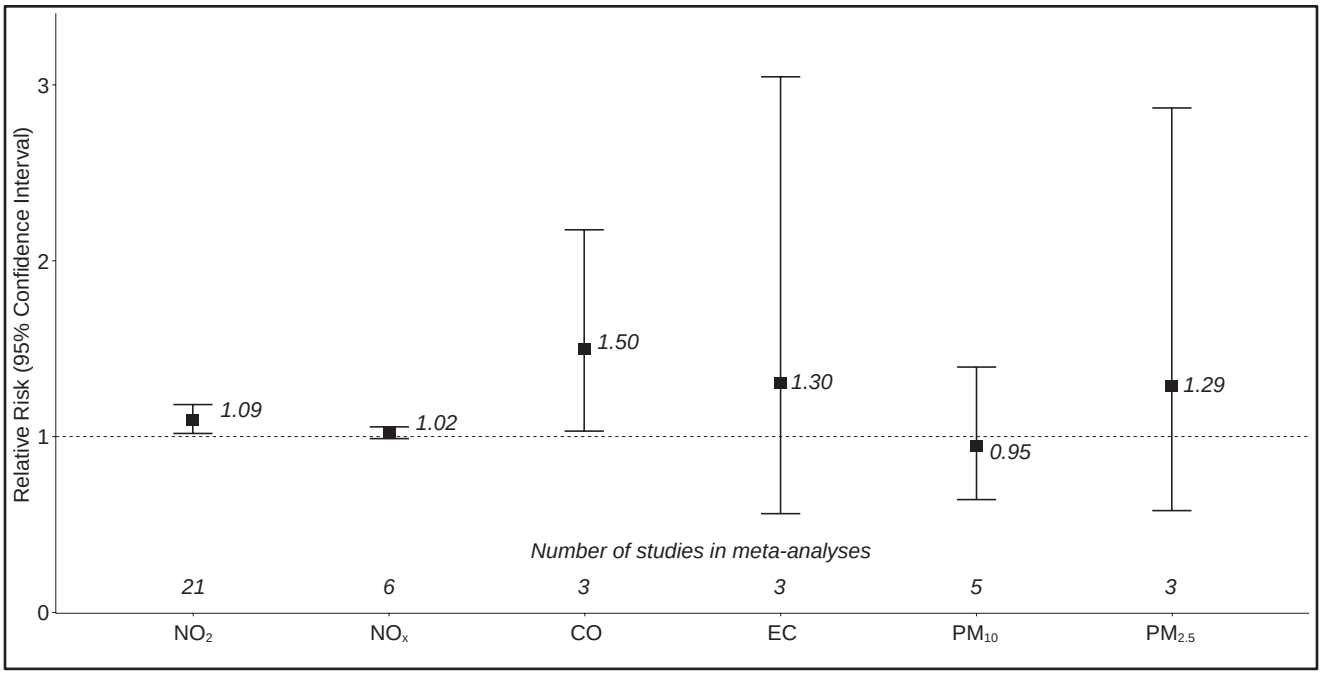


Figure 9.5. Meta-analysis of associations between traffic-related air pollutants and prevalence of asthma ever in children. The following increments were used: 10 μg/m³ for NO_2, 20 μg/m³ for NO_x, 1 mg/m³ for CO, 1 μg/m³ for EC, 10 μg/m³ for PM_{10}, and 5 μg/m³ for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

The Panel also excluded studies from the meta-analyses that had log-transformed or categorized pollutant levels (Gauderman et al. 2005; Kuo et al. 2002; Nicolai et al. 2003). Furthermore, the Panel excluded the study by Hasunuma and colleagues (2016) because the methodology differed from the other studies; personal exposure was modeled considering time–activity patterns (see Chapter 5).

NO_2 and NO_x were the most studied pollutants with 21 and 6 estimates of association meta-analyzed, respectively. There were also only three studies that reported estimates of association for CO, EC, and $PM_{2.5}$, and five for PM_{10} that were meta-analyzed. Additionally, one study reported an estimate of association between PM_{coarse} and the prevalence of asthma ever (Mölter et al. 2015), three studies reported associations with benzene, but one of those studies used categorized exposures (Hirsch et al. 1999; Nicolai et al. 2003; Pénard-Morand et al. 2010), and no studies reported associations with other pollutants such as NO, UFPs, or PAH.

All meta-analytic summary estimates for TRAP and asthma ever in children were above unity except for PM_{10} (0.95). Additionally, 95% confidence intervals clearly included unity except for NO_2 and CO (Figure 9.5). The NO_x summary estimate (1.02) was borderline significant. The summary estimates were, respectively for EC, $PM_{2.5}$, and PM_{10}: 1.30 per 1-μg/m³ (95% CI: 0.56–3.04), 1.29 per 5-μg/m³ (0.58–2.87), and 0.95 per 10-μg/m³ (0.64–1.40).

Figure 9.6 shows the forest plots with individual studies for NO_2 and NO_x. 16 of the NO_2 estimates that were meta-analyzed were positive, but confidence intervals often included unity and a few estimates were also negative (Krämer et al. 2000; Pedersen et al. 2013; Puklová et al. 2019; Rosenlund et al. 2009; Wood et al. 2015). These associations with NO_2 were moderately heterogeneous with RRs ranging from 0.74 to 2.12 per 10-μg/m³ NO_2; the I^2 for the summary estimate was 55%. The NO_2 summary estimate was 1.09 (95% CI: 1.01–1.18) per 10-μg/m³. There were two large studies, contributing 10% and 12% (Liu et al. 2014; Oudin et al. 2017). The six NO_x studies that were meta-analyzed reported either a slightly positive (four studies) or negative association (two studies), and all had confidence intervals that included unity (RR ranging from 0.82 to 1.07 per 20-μg/m³ NO_x); the summary NO_x estimate was 1.02 per 20-μg/m³ NO_x (0.99–1.05) (Figure 9.6).

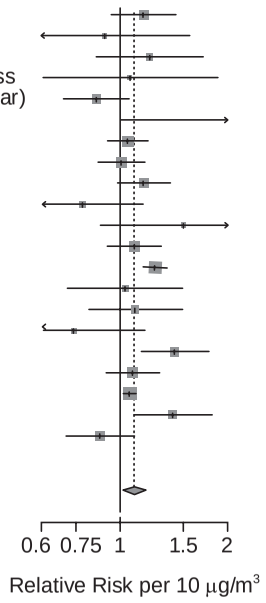
The three studies investigating the association between CO and prevalence of asthma ever in children were positive but also differed (ranging from 1.40 to 2.61) and their confidence intervals were large (Hirsch et al. 1999; Hwang et al. 2005; Pénard-Morand et al. 2010). The summary estimate for CO was positive and did not include unity (RR: 1.50 per 1-mg/m³ CO; 95% CI: 1.03–2.17) (Appendix Figure 9B-4).

For particulate pollutants, the three studies entering the EC meta-analysis reported positive associations, but were highly variable, with the RRs ranging 1.22 to 7.55 per 1-μg/m³ EC

NO_2

Study	Study Name	Study Design	Exposure window	RR	95%-CI	Weight
Hirsch et al. 1999	ISAAC Dresden	Cross sectional	Annual mean	1.16	[0.94; 1.43]	5.6%
Krämer et al. 2000	Düsseldorf School Survey	Cross sectional	Annual average current year	0.90	[0.52; 1.56]	1.3%
Janssen et al. 2003	ISAAC Southwestern Netherlands	Cross sectional	Annual average current year	1.21	[0.85; 1.71]	2.8%
Morgenstern et al. 2008	GINI, LISA: Munich	Cohort	Annual average at current address	1.06	[0.60; 1.88]	1.2%
Rosenlund et al. 2009	ISAAC Rome	Cross sectional	Exposure in 2000-2001 (recent year)	0.85	[0.69; 1.06]	5.3%
Sahsuvaroglu et al. 2009	ISAAC Hamilton	Cross sectional	Cumulative average	2.12	[1.00; 4.48]	0.7%
Pénard-Morand et al. 2010	French Six Cities	Cross sectional	Annual average current year	1.05	[0.92; 1.20]	8.2%
Svendsen et al. 2012	El Paso Children's Health	Cross sectional	Average recent	1.00	[0.86; 1.17]	7.4%
Liu et al. 2013	SNEC Kindergarten	Cross sectional	Three year average at baseline	1.16	[0.98; 1.38]	6.7%
Pedersen et al. 2013	EDEN	Cohort	Entire pregnancy	0.78	[0.52; 1.16]	2.2%
Abidin et al. 2014	ISAAC Malaysia	Cross sectional	Annual average current year	1.50	[0.87; 2.58]	1.3%
Dell et al. 2014	T-CHEQ	Case-control	Average first year	1.09	[0.92; 1.30]	6.5%
Liu et al. 2014	SNEC	Cross sectional	Three year average at baseline	1.25	[1.15; 1.35]	10.4%
Ranzi et al. 2014	GASPII	Cohort	Annual average at birth	1.03	[0.71; 1.49]	2.5%
Mölter et al. 2015	ESCAPE	Cohort	Cumulative average	1.10	[0.81; 1.49]	3.4%
Wood et al. 2015	ISAAC East London	Cross sectional	Annual average current year	0.74	[0.46; 1.17]	1.7%
Deng et al. 2016	CCHH Changsha	Cross sectional	Entire pregnancy	1.42	[1.14; 1.77]	5.2%
Liu et al. 2016	CCHH Shanghai	Cross sectional	Entire pregnancy	1.08	[0.91; 1.29]	6.6%
Oudin et al. 2017	SIMSAM Medication	Cohort	Baseline year average	1.06	[1.02; 1.11]	11.7%
Knibbs et al. 2018	ACHAPS	Cross sectional	Previous year annual average	1.40	[1.08; 1.81]	4.3%
Puklová et al. 2019	Czech Respiratory Cohort	Cross sectional	Five year average at baseline	0.87	[0.70; 1.09]	5.1%
Random effects model				**1.09**	**[1.01; 1.18]**	**100.0%**
Prediction interval					[0.88; 1.35]	

Heterogeneity: $I^2 = 55\%$, $\tau^2 = 0.0091$, $p < 0.11$



NO_X

Study	Study Name	Exposure window	RR	95%-CI	Weight
Zhang et al. 2002	Chinese 4-City School Survey	At baseline	0.98	[0.87; 1.12]	8.5%
Hwang et al. 2005	ISAAC Taiwan	Annual average previous year	1.01	[0.94; 1.08]	30.2%
McConnell et al. 2006	CHS	Early life exposure	1.04	[0.97; 1.11]	29.0%
Pénard-Morand et al. 2010	French Six Cities	Annual average current year	1.03	[0.96; 1.10]	28.6%
Mölter et al. 2015	ESCAPE	Cumulative average	1.07	[0.86; 1.33]	2.9%
Wood et al. 2015	ISAAC East London	Annual average current year	0.82	[0.55; 1.23]	0.9%
Random effects model			**1.02**	**[0.99; 1.05]**	**100.0%**
Prediction interval				[0.99; 1.06]	

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.83$

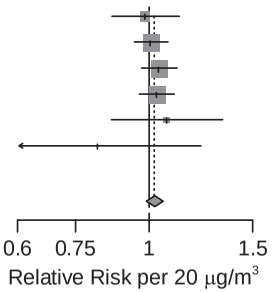


Figure 9.6. Association between NO_2 and NO_x and prevalence of asthma ever in children: meta-analysis.

(Appendix Figure 9B-5). For $PM_{2.5}$ and PM_{10} both positive and negative associations were reported (Appendix Figure 9B-6 and Figure 9B-7). Except for a single positive and significant association for PM_{10} from Pénard-Morand and colleagues (2010), confidence intervals for EC, $PM_{2.5}$, and PM_{10} were very large and included unity, resulting in imprecise summary estimates for the particulate pollutants. Small studies such as Wood and colleagues (2015) were not informative, while others such as the one from the ESCAPE project (Mölter et al. 2015) were influential as evidenced by their weights in the meta-analyses (e.g., Mölter had an 80% weight in EC meta-analysis). The only estimates of association with PM_{coarse} were from the ESCAPE project (Mölter et al. 2015), and the estimates differed on the age at asthma assessment (negative at 4–5 years of age or positive at 8–10 years of age), although their confidence intervals included unity.

The benzene estimates were not meta-analyzed but were all positive and the confidence intervals of two out of three included unity (Hirsch et al. 1999; Nicolai et al. 2003; Pénard-Morand et al. 2010).

9.3.2.3 Additional Meta-analyses

Figure 9.7 shows that excluding studies from the meta-analysis that were of moderate traffic specificity, reduced the heterogeneity of estimates of association between NO_2 and the prevalence of asthma ever in children (I^2 was reduced from 55% to 39%), but both negative and positive estimates were

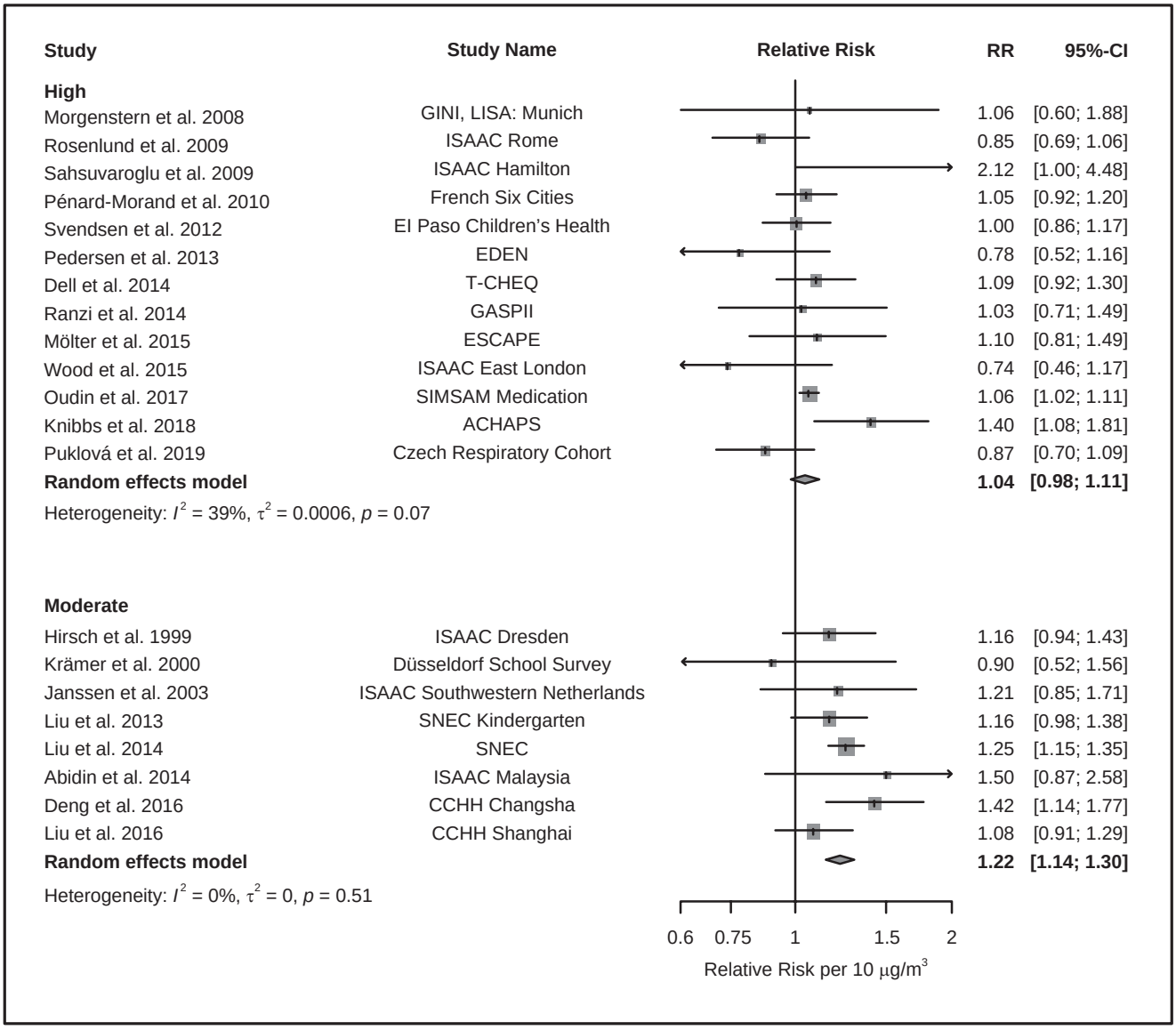


Figure 9.7. Association between NO_2 and prevalence of asthma ever in children: meta-analysis by traffic specificity.

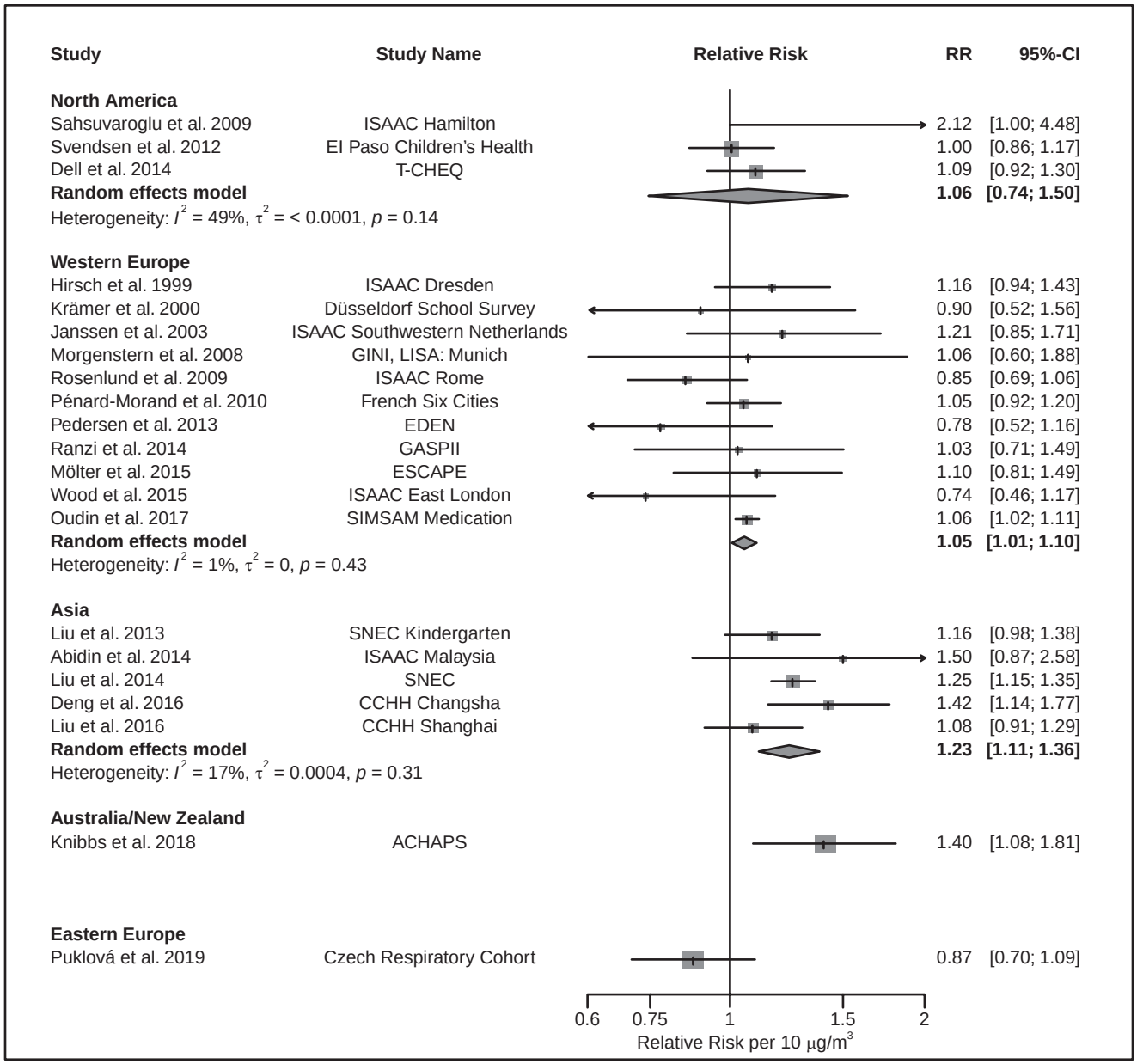


Figure 9.8. Association between NO_2 and prevalence of asthma ever in children: meta-analysis by region.

found in the subset of high traffic specificity studies. The summary estimate including only high traffic specificity studies decreased to 1.04 per 10-μg/m^3 NO_2; 95% CI: 0.98–1.11), thus slightly reducing the confidence of the association with NO_2. The six NO_x studies that were meta-analyzed had only two studies with moderate traffic specificity, and stratification of these few studies by traffic specificity was not informative (Appendix Figure 9B-8). Two out of the three EC estimates were of high traffic specificity, while estimates of association with $PM_{2.5}$ and PM_{10} were all of moderate traffic specificity. Two of the three CO estimates were of moderate traffic specificity, except for Pénard-Morand and colleagues (2010), which was classified as high traffic specificity.

Figure 9.8 illustrates that three out of five regions had positive summary estimates (two with confidence intervals that did not include unity) for associations between NO_2 and prevalence of asthma ever in children. The heterogeneity of meta-analyzed estimates of association between NO_2 and asthma ever in children was lowest for Asian studies (I^2 = 17%). Estimates from Asian studies were all positive and the summary estimate larger than for all studies combined

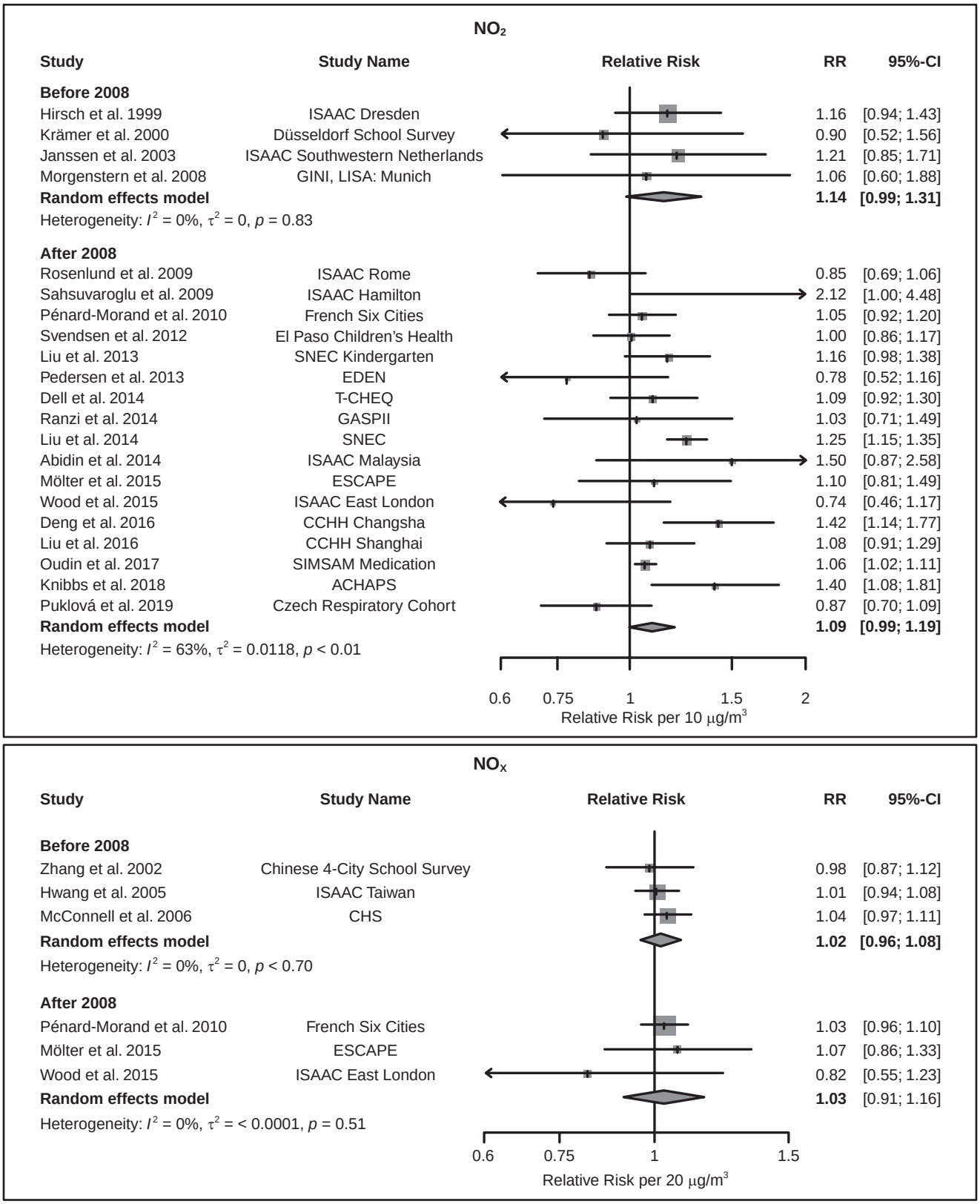


Figure 9.9. Association between NO_2 and NO_x and prevalence of asthma ever in children: meta-analysis by year of publication.

(RR 1.23; 95% CI: 1.11–1.36 per 10-μg/m^3); it is worth noting that all estimates meta-analyzed from Asia were based on NO_2 surface monitoring. The six estimates of association with NO_x were from countries around the globe; they were so few that no clear trend with stratification by region could be discerned (see Additional Materials). All studies with associations for $PM_{2.5}$, PM_{10}, EC, and CO were from Europe except for one investigating CO in Taiwan (Hwang et al. 2005).

Although most studies in the meta-analyses were published after 2008 as shown in Figure 9.9, excluding the studies published in 2008 or earlier did not reduce the heterogeneity, and the NO_2 or NO_x summary estimates were similar for the two periods.

The internal validity of cohort studies is usually better than cross-sectional studies; the outcome assessment is likely more accurate because with cohort studies one can assess the age of disease onset. Stratification by design was conducted for estimates of association with NO_2. The summary estimate for cohort studies of associations with NO_2 (1.06; 95% CI: 1.01–1.11 per 10-μg/m^3) was smaller than for cross-sectional studies (1.11; 1.00–1.24 per 10-μg/m^3), although the confidence intervals overlapped. The I^2 for cross-sectional studies (62%) was slightly larger than for all studies combined (55%) (Figure 9.10).

In two-pollutant models of associations of asthma ever with TRAP, effect estimates were unchanged or slightly increased when effect estimates for NO_2 (Sahsuvaroglu et al.

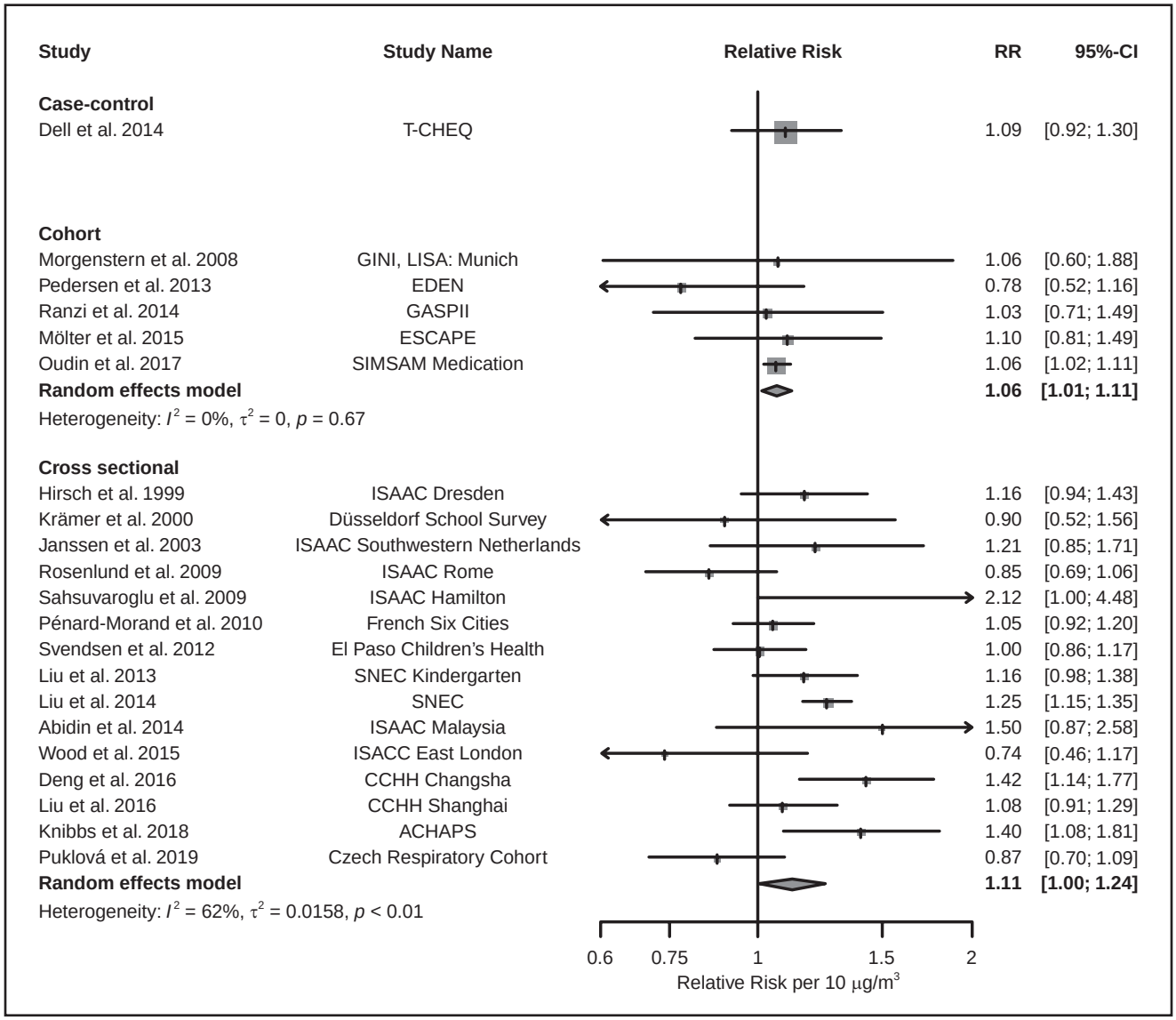


Figure 9.10. Association between NO_2 and prevalence of asthma ever in children: meta-analysis by study design.

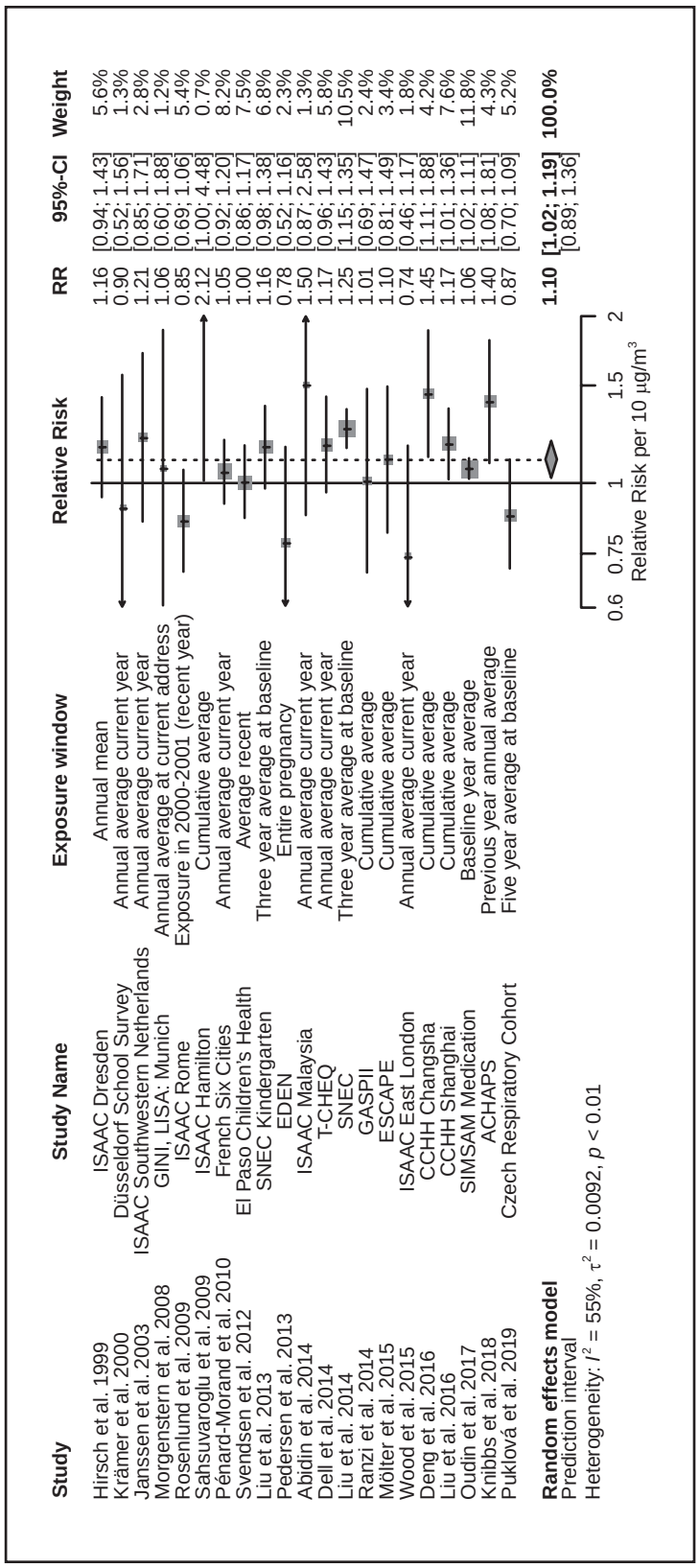


Figure 9.11. Association between NO_2 and prevalence of asthma ever in children: meta-analysis giving priority to postnatal exposures.

2009) and for CO and NO_2 (Hwang et al. 2005) were adjusted for general $PM_{2.5}$ or O_3.

The summary estimate obtained prioritizing either prenatal (Figure 9.6) or postnatal NO_2 exposures (Figure 9.11) were very similar and provided no indication that either prenatal or postnatal NO_2 exposure presents a higher risk of asthma ever in children. The heterogeneity was also similar.

9.3.2.4 Associations with Indirect Traffic Measures

Studies on indirect traffic measures were too heterogeneous in their definitions to allow meta-analysis; as an additional source of information they provided limited evidence of associations between TRAP broadly and the prevalence of asthma ever in children. Estimates of association with distance and density measures from 23 studies (of which 9 also provided estimates of association with some traffic pollutants) were highly variable with large confidence intervals (Table 9.7).

9.3.2.5 Narrative Assessment

The evidence for associations of TRAP with prevalence of asthma ever in children included studies mostly from Europe and Asia and some from North America. The majority of studies were cross-sectional using questionnaires to assess children with asthma diagnoses (cross-sectional assessments from 10 cohort studies were included but only four were meta-analyzed) and included extensive information on individual risk factors for adjustments of potential confounding variables. Populations assessed by questionnaire ranged from a few hundred to more than 50,000. A few studies based on dispensed medication and medical records included several hundred thousand participants. Age at assessment was variable but often included children from elementary schools. NO_2 was usually assessed, and it was often modeled with dispersion or LUR models; however Asian studies usually used monitoring stations to estimate NO_2 exposure. Studies on associations with other pollutants were mostly from European countries.

The evidence base provides moderate confidence in the presence of an association between TRAP and asthma ever in children. All meta-analytic summary estimates for TRAP and asthma ever in children were above unity except for PM_{10} (0.95). The benzene estimates (not meta-analyzed) were also positive. The meta-analytic estimates of EC, PM_{10}, and $PM_{2.5}$ were imprecise. Most estimates of association from the individual meta-analyzed studies had large confidence intervals and included unity. Except for EC which had only positive estimates, positive and negative estimates were pooled in meta-analyses. Additionally, associations with indirect traffic measures were highly variable. Surprisingly, no study tested the assumption of a monotonic exposure–response relationship. There was some potential information bias in the associations of most studies considered because the outcome of asthma ever was usually self-reported through questionnaires, which can be influenced by knowledge of exposure.

In summary, plausibility of an association between TRAP and prevalence of asthma ever in children is supported by: (1) a sizable number of well-designed large cross-sectional studies and some cohort studies in a variety of locations, and (2) positive meta-analytic summary estimates in substantially different populations. However, due to the cross-sectional nature of most studies assessed, the potential bias in outcome reporting and the heterogeneity of the estimates (with both positive and negative effect estimates), uncertainties remain regarding the association between TRAP and the prevalence of asthma ever in children. Thus, the Panel considered the confidence in the presence of an association between TRAP and the prevalence of asthma ever in children as moderate.

9.3.2.6 Risk of Bias Assessment

Table 9.8 shows an overview of the results of the risk of bias assessment for exposure–outcome pairs of studies on asthma ever that were meta-analyzed; Appendix Table 9B-2 presents the assessment for each individual study. The large majority of the estimates of association were rated moderate risk of bias for outcome measurement. This is because in most studies, the outcome was self-reported through questionnaires and outcome reporting can be influenced (i.e., over-reported) by exposure knowledge when self-reported, especially for those living in proximity to major roads and aware of potential health risks of this exposure. Estimates from one study (Wood et al. 2015) were rated at high risk of bias for blinding of outcome because the study specifically pertained to assessing the reduction of the impacts of TRAP due to the implementation of the London Low Emission Zone. Estimates from Wood and colleagues (2015) were also rated at high risk of selection bias because the study was on a very specific and highly exposed population; however, as this was a small population the study was not influential in the meta-analyses. A few studies did not control for important potential confounders, such as tobacco smoke and SES, and were also rated at high risk of bias for confounding. Finally, as studies were extensively evaluated for their exposure assessment at the inclusion stage to include only studies indicative of TRAP, no study was rated at a high risk of bias for exposure methods. However, some studies with a long follow-up (such as the ESCAPE study) were rated moderate risk of bias for change in exposure status.

9.3.2.7 Confidence Assessment of the Body of Evidence

Table 9.9 provides the Panel's confidence assessment for associations with pollutants that were meta-analyzed; thus, the table includes the pollutants that had three or more studies. Here, the Panel first discusses four factors that may reduce confidence (downgrades). Next, factors that may increase confidence (upgrades) are discussed. The Panel decided a priori not to consider the upgrading factor large magnitude of the effect.

Table 9.7. Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Asthma Ever in Children—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Traffic Measure	Effect Estimate (95% CI)[b]	Increment
Andersson 2011	OLIN	Cross sectional	Lulea, Sweden	2006	1,357	Density	1.5 (0.8–2.9)	>500 vs. <500 heavy vehicles/day
							1.4 (0.8–2.5)	>8,000 vs. <8,000 vehicles/day
Cakmak 2012	Windsor Children's Health 05	Cross sectional	Windsor, Ontario, Canada	2005	1,570	Density	1.00 (0.89–1.19)[c]	33,787.5 vehicles/day
Dell 2014	T-CHEQ	Case-control	Toronto, Canada	2006	1,454	Distance	1.28 (0.33–4.96)	<100 vs. >100 m
Dong 2008	Liaoning Survey 2007	Cross sectional	Shenyang and Anshan and Dalian, China	2007	3,945	Distance	1.17 (0.83–1.63)	<20 vs. >100 m
							0.84 (0.63–1.11)	20–100 vs. >100 m
Gauderman 2005	CHS	Cohort	Multiple cities, United States	1993–2000	208	Density	1.45 (0.73–2.91)[c]	2,720 vehicles/day/m_2
						Distance	1.89 (1.19–3.02)[c]	1.2 km
Gordian 2006	Anchorage Respiratory	Cross sectional	Anchorage, Alaska, United States	2003	671	Density	2.83 (1.23–6.51)	>8,000 vs. <4,000 vehicle-km/day
							1.40 (0.77–2.55)	4,000 to 8,000 vs. <4,000 vehicle-km/day
Hansell 2014	CAPS	Cross sectional	Sydney, Australia	2005–2009	398	Density	1.04 (0.87–1.23)[c,d]	per 100 m local road or 33.3 m of motorway
Janssen 2003	ISAAC South-western Netherlands	Cross sectional	Multiple cities, the Netherlands	1997–1998	2,053	Distance	1.04 (0.74–1.45)	100 vs. 400 m
Jung 2015	CHEER	Cross sectional	Multiple cities, South Korea	2005–2006	4,203	Distance	1.11 (0.84–1.46)	<75 vs. >225 m
							1.23 (0.98–1.56)	75–150 vs. >225 m
							1.13 (0.81–1.59)	150–225 vs. >225 m
Lee 2018b	CHEER	Cohort	Multiple cities, South Korea	2005–2008	2,627	Distance	1.79 (1.05–3.06)	<75 vs. >700 m
							1.36 (0.83–2.24)	75–700 vs. >700 m

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Table 9.7 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Asthma Ever in Children—Indirect Traffic measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Traffic Measure	Effect Estimate (95% CI)[b]	Increment
Lewis 2005	ISAAC Eastern UK	Cross sectional	England	2003	11,546	Distance	0.85 (0.6–1.05)	<30 vs. >150 m
							1.05 (0.90–1.25)	30–89 vs. >150 m
							1.03 (0.87–1.23)	90–149 vs. >150 m
McConnell 2006	CHS	Cross sectional	California, United States	2003	4,762	Distance	1.29 (1.01–1.66)	<75 vs. >300 m
							1.06 (0.82–1.36)	75–150 vs. >300 m
							0.92 (0.73–1.15)	150–300 vs. >300 m
Miyake 2010	OMCHS	Cohort	Osaka, Japan	2001–2005	756	Distance	4.01 (1.44–11.24)	<50 vs. >200 m
							1.39 (0.36–4.54)	50–100 vs. >200 m
							2.38 (0.91–6.28)	100–200 vs. >200 m
Morgenstern 2007	GINI, LISA: Munich	Cohort	Multiple cities, Germany	1995–2001	2,861	Distance	1.12 (0.88–1.44) (age 1)	<50 vs. >50 m
							1.23 (1.00–1.51) (age 2)	<50 vs. >50 m
Morgenstern 2008	GINI, LISA: Munich	Cohort	Multiple cities, Germany	1995–2005	2,436	Distance	1.66 (1.01–2.59)	<50 vs. >50 m
Nicolai 2003	ISAAC Munich	Cross sectional	Munich, Germany	1995–1996	about 3,000	Density	1.19 (0.76–1.87)	>30,000 vehicles/day vs. none
							0.93 (0.58–1.51)	15,001–30,000 vehicles/day vs. none
							0.90 (0.54–1.49)	2,600–15,000 vehicles/day vs. none
Pujades-Rodríguez 2009a	Health Survey England	Cross sectional	England	1995–2001	50,994	Distance	0.94 (0.78–1.13) (age 2–6)	<150 vs. >150 m
							0.92 (0.80–1.05) (age 7–15)	
							1.01 (0.95–1.07) (age 16+)	
Ranzi 2014	GASPII	Cohort	Rome, Italy	2003–2011	672	Distance	0.61 (0.33–1.13)	<86.1 vs. >86.1 m

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Table 9.7 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Asthma Ever in Children—Indirect Traffic measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Traffic Measure	Effect Estimate (95% CI)[b]	Increment
Rosenlund 2009	ISAAC Rome	Cross sectional	Rome, Italy	2000–2001	1,760	Distance	0.7 (0.40–1.1)	<100 vs. >100 m
Skrzypek 2013	ISAAC Bytom	Cross sectional	Bytom, Poland	2003–2004	5,733	Density	1.60 (1.07–2.39)	>90th vs. <90th percentile
						Distance	1.47 (0.95–2.27)	<100 vs. >100 m
van Vliet 1997	South Holland Respiratory Survey	Cross sectional	Multiple cities, the Netherlands	1995	878	Density	0.30 (0.09–0.97)	High vs. low car volume
							0.54 (0.18–1.60)	High vs. low truck volume
						Distance	1.68 (0.68–4.14)	<100 vs. >100–1,000 m
Weaver 2018	CHS	Cohort	California, United States	1993–2014	5,337	Distance	0.87 (0.55–1.36)[c] (Hispanic whites)	<500 vs. >500 m to freeway
							1.05 (0.70–1.59)[c] (non-Hispanic whites)	
							2.10 (1.30–3.39)[c] (Hispanic whites)	<75 vs. >75 m to major nonfreeway road
							0.91 (0.51–1.65)[c] (non-Hispanic whites)	
Wjst 1993	Munich Asthma and Allergy	Cross sectional	Munich, Germany	1989–1990	4,678	Density	1.06 (0.97–1.16)	25,000 vehicles/day

[a] All studies included male and female participants.

[b] Unless otherwise indicated, the effect estimate was odds ratio.

[c] Log transformed or another transformation.

[d] Relative risk.

All studies that provided estimates of association between traffic pollutants and asthma ever in children that were included in meta-analyses performed cross-sectional analysis, except the study by Dell and colleagues (2014), which was a case-control study. The initial rating for all pollutants was nonetheless set at low because the majority of studies were cross-sectional.

Factors That Decrease Confidence The Panel did not downgrade associations for risk of bias. The overview of the risk of bias ratings for each exposure–outcome pair that was meta-analyzed is presented in Table 9.8 for asthma ever in children. Very few estimates from several studies were rated at high risk of bias. Therefore, a formal comparison between the low and moderate versus the high risk of bias subgroups was usually not possible. Nonetheless, subgroup analyses with respect to risk of bias for NO_2 (Appendix Figure 9B-9) showed that excluding the few estimates of association rated at high risk of bias due to confounding, as well as specifically not adjusting for tobacco smoke, had minimal influence on the summary estimate, although heterogeneity was reduced. Excluding studies that did not assess the outcome with questionnaires also reduced heterogeneity but had minimal influence on the summary estimate.

There were only five estimates of association of asthma ever in children with PM_{10} and they were very imprecise; thus, excluding the study at high risk of bias was not informative. For NO_x, excluding the only high risk of bias study for selection bias (Wood et al. 2015)—which was also at high risk of bias for

Table 9.8. Summary of Risk of Bias Rating for Studies on Prevalence of Asthma Ever in Children

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low-risk	Moderate-risk	High-risk	Low-risk	Moderate-risk	High-risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	20	1	3	36	1	4
	Validity of measuring of confounding factors	23	1	0	40	1	0
	Control in analysis	22	2	0	39	2	0
	Overall	17	4	3	33	4	4
2. Selection bias	Selection of participants into the study	16	6	2	27	9	5
3. Exposure assessment	Methods used for exposure assessment	24	0	0	41	0	0
	Exposure measurement methods comparable across the range of exposure	24	0	0	41	0	0
	Change in exposure status	21	3	0	33	8	0
	Overall	21	3	0	33	8	0
4. Outcome measurements	Blinding of outcome measurements	2	21	1	3	34	4
	Validity of outcome measurements	24	0	0	41	0	0
	Outcome measurements	24	0	0	41	0	0
	Overall	2	21	1	3	34	4
5. Missing data	Missing data on outcome measures	23	1	0	40	1	0
	Missing data on exposures	23	1	0	39	2	0
	Overall	22	2	0	38	3	0
6. Selective reporting	Authors reported a priori primary and secondary study aims	23	1	0	40	1	0

outcome measurement—had minimal influence on the summary estimate (Appendix Figure 9B-10). Additionally, none of the EC and CO estimates of association were rated at high risk of bias. Although the one estimate from Wood and colleagues (2015) investigating the Low Emission Zone for $PM_{2.5}$ was rated at high risk of bias for several domains, the small number of studies did not permit stratification of the meta-analyses.

Thus, the subgroup analysis with respect to risk of bias assessment does not suggest a need to downgrade the confidence in the evidence for the pollutants included in the meta-analyses. This judgment is supported by the small number of estimates from a few studies that were rated high risk of bias and the limited changes in meta-analytic estimates when including or excluding the studies rated at high risk of bias.

The Panel did not downgrade associations for unexplained inconsistency. The effect estimates for NO_2 ($N = 21$) and NO_x ($N = 6$)—the pollutants for which effect estimates were reported more frequently—had moderate and low heterogeneity (I^2 was 55% and 0%, respectively) and the majority of these estimates were positive. Nonetheless, confidence intervals of most estimates included unity (Figure 9.6). The I^2 for NO_x estimates was 0%, so stratification did not add insight. Stratifications of NO_2 estimates showed that several factors reduced the heterogeneity of NO_2 estimates, although the exclusion of studies had minimal influence on the NO_2 summary estimate. The heterogeneity of NO_2 estimates was reduced when considering only high traffic specificity studies and when excluding studies at high risk of bias for confounding. NO_2 estimates of association from Asian countries (all based on surface monitoring) were also higher in magnitude than those from other countries, contributing to the heterogeneity. As the majority of the estimates of association between NO_2 and asthma ever in children were positive, and considering that there were several plausible reasons to explain inconsistencies, the Panel did not downgrade the evidence for NO_2. The Panel also did not downgrade the evidence for any of the other pollutants because heterogeneity was low or moderate.

Table 9.9. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and the Prevalence of Asthma Ever in Children[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cross-sectional	++ (N = 21)	0	0	0	0	0	0	+	+++ (Moderate)
	Rationale	Cross-sectional analyses initially rated as low.	Few studies at high RoB and exclusion did not alter substantially the summary estimate.	Moderate heterogeneity (I^2 = 55%). Plausible reasons to explain inconsistency.	Sample size met, and confidence interval does not include unity.	No evidence found.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Consistent effect across different geographic regions.	
NO_X	Cross-sectional	++ (N = 6)	0	0	0	0	0	0	0	++ (Low)
	Rationale	Cross-sectional analyses initially rated as low.	1 of 6 studies at high RoB and exclusion did not alter substantially the summary estimate.	Low heterogeneity (I^2 = 0%). No heterogeneity to be explained.	Sample size met and estimate consistent with an association.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	
CO	Cross-sectional	++ (N = 3)	0	0	0	0	0	0	0	++ (Low)
	Rationale	Cross-sectional analyses initially rated as low.	No study at high RoB.	Low heterogeneity (I^2 = 0%). No heterogeneity to be explained.	Sample size not met, but confidence interval does not include unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	

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Table 9.9 (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and the Prevalence of Asthma Ever in Children

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
EC	Cross-sectional	++ (N = 3)	0	0	–	0	0	0	0	+ (Very low)
	Rationale	Cross-sectional analyses initially rated as low.	No study at high RoB.	Low heterogeneity (I^2 = 30%).	Sample size not met, confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	
PM_{10}	Cross-sectional	++ (N = 5)	0	0	–	0	0	0	0	+ (Very low)
	Rationale	Cross-sectional analyses initially rated as low.	1 of 5 studies at high RoB; exclusion not informative and not sensitive to exclusion.	Moderate heterogeneity (I^2 = 68%).	Sample size not met, confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	
$PM_{2.5}$	Cross-sectional	++ (N = 3)	0	0	–	0	0	0	0	+ (Very low)
	Rationale	Cross-sectional analyses initially rated as low.	1 of 3 studies at high RoB.	Low heterogeneity (I^2 = 0%). No heterogeneity to be explained.	Sample size not met, confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

Regarding imprecision, the Panel downgraded evidence for EC, PM_{10}, and $PM_{2.5}$ because the sample size requirement was not met for those pollutants and confidence intervals clearly included unity. The Panel did not downgrade the other pollutants for various reasons. The summary estimate for NO_2 was based on large studies and had a narrow confidence interval that did not include unity. The NO_x summary estimate was consistent with an association (borderline). Although the sample size requirements were not met for CO, the confidence interval did not include unity, and so no downgrade was applied, per protocol.

About publication bias, there were more than 10 studies, so funnel plots and Egger tests were produced for NO_2. The funnel plot and the Egger test did not suggest asymmetry (Appendix Figure 9B-11). Because of the small number of studies, it was not possible to assess publication bias for studies on associations with the other pollutants. As there was no evidence of bias for NO_2, the Panel chose to not downgrade the confidence for all pollutants.

Factors That Increase Confidence No study provided evidence of a plausible monotonic exposure–response function, so an upgrade was not applied. Also, the Panel found no clear indication that residual confounding or other factors are likely to lead to an underestimation of the associations. Regarding consistency across geographic regions, populations or study period, most studies were published after 2008, but NO_2 and NO_x estimates were consistent across time periods. For NO_2, the Panel found positive associations in all identified geographical areas that had more than one study (Europe, Asia, North America), although the estimates were larger in Asian countries and the confidence interval for the North America summary estimate, which was only based on three studies, included unity. The Panel upgraded the evidence for consistency for NO_2. For all other pollutants, there were too few estimates of association to assess consistency across populations.

Evaluation of Confidence for Combined Measures of TRAP The Panel did not conduct separate evaluations for the prevalence of asthma ever from cohort and cross-sectional studies because most assessments were cross-sectional, and stratification by design did not influence meta-analytic estimates of associations. Furthermore, similar conclusions regarding the confidence in the body of evidence were reached when this outcome was assessed separately for the two epidemiological study designs.

The Panel had six assessments of the level of confidence in the quality of the body of evidence for asthma ever. The Panel's overall confidence assessment in the body of evidence for associations of asthma ever with TRAP was moderate because the highest rating was moderate. NO_2 had moderate confidence and also had by far the largest number of studies. The Panel had low (NO_x, CO) and very low (EC, PM_{10}, and $PM_{2.5}$) confidence assessments for pollutants with substantially fewer than 10 studies. The meta-analytic summary estimates of these pollutants (except PM_{10}) were also positive but less certain. These other pollutants thus provide some additional support. In conclusion, based on the modified OHAT assessment, the Panel's confidence in the body of evidence of the association between TRAP exposure and asthma ever in children is moderate.

9.3.2.8 Overall Confidence Assessment

The Panel found a moderate level of confidence in the evidence for an association of exposure to TRAP with asthma ever in children based on the narrative assessment (moderate) and the same rating was given in the modified OHAT assessment (moderate).

9.3.3 PREVALENCE OF ACTIVE ASTHMA

9.3.3.1 Study Selection and Description

Thirty-four studies reported associations between TRAP or indirect traffic measures and the prevalence of active asthma in children. The prevalence of active asthma refers to a prevalence measure (usually self-reported through questionnaires) of either asthma diagnosis in the last 12 months or asthma symptoms in the last 12 months when an asthma diagnosis was given in the past. Active asthma is also based on the use of medical services (emergency department visits and hospital admissions if not first occurrence ever).

Tables 9.10 and 9.11 show details of all the identified studies including effect estimates. Of the 35 studies on active asthma in children, 15 reported associations only with indirect traffic measures. Most of the studies were performed in 2008 or earlier. Studies were from countries around the world. Studies usually assessed a few hundred to several thousand participants; however, some Asian studies assessed more than 20,000 (Liu et al. 2014) and up to 155,000 children (Wang et al. 1999). The European ESCAPE study also used information from four cohorts leading to a study population of 14,000 children (Gehring et al. 2015).

Most studies were cross-sectional studies by design. In addition, several cross-sectional analyses were embedded within cohort studies. Most of these cohort studies also analyzed asthma onset (see Section 9.3.1). The case-control studies were all based on administrative health data and only reported indirect traffic measures, except for Dell and colleagues (2014), which reported on NO_2. Similar to the asthma ever studies, the ISAAC and the ATS questionnaires were most often used and most studies had extensive information on individual risk factors, such as parental smoking and family history of respiratory disease or allergy. Approximately a quarter of the studies that assessed active asthma also assessed asthma ever (Dell et al. 2014; Hansell et al. 2014; Jung et al. 2015; Knibbs et al. 2018; Liu et al. 2013, 2014; McConnell et al. 2006; Nicolai et al. 2003; Puklová et al. 2019; van Vliet et al. 1997; Wjst et al. 1993).

Table 9.10. Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Active Asthma in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
Brauer 2002	PIAMA	Cohort	The Netherlands	1996–1999	2,029	LUR	NO_2	25.6	Annual average	1.48 (1.00–2.19)	10.3 µg/m^3
							$PM_{2.5\ abs}$	1.72		1.29 (0.88–1.96)	0.54 1×10^{-5}/m
							$PM_{2.5}$ mass	16.9		1.35 (0.77–2.37)	3.2 µg/m^3
Cakmak 2016	Windsor Children's Health 05	Cross sectional	Windsor, Ontario, Canada	2005	1,570	LUR	NO_2	11.6	Annual average current year	**1.02 (0.89–1.18)** (income > $80,000)[g]	2.27 ppb
										0.99 (0.71–1.34) (income $35,000–80,000)[g]	
										1.16 (0.79–1.69) (income < $35,000)[g]	
Clifford 2018	Brisbane Respiratory	Cross sectional	Brisbane Metropolitan Area, Australia	2010–2012	474	Personal exposure	PNC > 5 nm	15,000	Annual average current year	0.96 (0.84–1.11)	1,000 particles/cm^3
Dell 2014	T-CHEQ	Case-control	Toronto, Canada	2006	1,441	LUR	NO_2	18.3–28.3	Average first year	**1.11 (0.90–1.37)**	5.7 ppb
									Annual average current year	1.14 (0.91–1.42)	5.3 ppb
									Cumulative average	0.98 (0.81–1.20)	3.3 ppb
Gehring 2010	PIAMA	Cohort	The Netherlands	1996–2006	3,184	LUR	NO_2	25.4	Annual average at birth	**1.22 (0.94–1.57)**	10.4 µg/m^3
							$PM_{2.5\ abs}$	1.72	Annual average at birth	**1.25 (0.97–1.61)**	0.57 1×10^{-5}/m
							$PM_{2.5}$ mass	16.9	Annual average at birth	1.36 (0.99–1.88)	3.2 µg/m^3

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Table 9.10 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Active Asthma in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
Gehring 2015	ESCAPE	Cohort	Multiple cities, multiple countries	1994–2013	14,085	LUR	NO_2	14.1–23.8	Annual average at birth[d]	**1.06 (0.88–1.26)**	10 μg/m^3
									Annual average current year	1.04 (0.93–1.16)	
							$PM_{2.5\ abs}$	0.7–1.7	Annual average at birth[d]	**1.24 (0.97–1.60)**	1 1×10^{-5}/m
									Annual average current year	1.14 (0.91–1.43)	
							PM_{10} mass	15.7–25.5	Annual average at birth[d]	**1.10 (0.74–1.63)**	10 μg/m^3
									Annual average current year	1.03 (0.80–1.34)	
							PM_{coarse} mass	6.8–8.5	Annual average at birth[d]	1.06 (0.80–1.39)	5 μg/m^3
									Annual average current year	1.00 (0.88–1.15)	
							$PM_{2.5}$ mass	7.8–17.4	Annual average at birth[d]	1.34 (1.00–1.79)	5 μg/m^3
									Annual average current year	1.18 (0.91–1.53)	
Gruzieva 2013	BAMSE	Cohort	Stockholm County, Sweden	1994–2008	3,633	Dispersion/ CTM	NO_x	7.8–21.4	Average first year	**1.18 (0.75–1.84)**	46.8 μg/m^3
									Cumulative average	0.72 (0.45–1.14)	
							PM_{10} mass	3.5–4.6	Average first year	**1.26 (0.73–2.16)**	7.2 μg/m^3
									Cumulative average	0.89 (0.63–1.25)	

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Table 9.10 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Active Asthma in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
Kim 2004	East Bay Childrens Health	Cross sectional	San Francisco, California, United States	2001	705	Surface monitoring	NO_2	23	Annual average current year	1.02 (0.97–1.07)[e]	3.6 ppb
							NO	25		1.05 (0.98–1.12)[e]	11.6 ppb
							NO_x	49		1.04 (0.97–1.11)[e]	14.9 ppb
							BC	0.8		1.02 (0.96–1.09)[e]	0.15 µg/m^3
Knibbs 2018	ACHAPS	Cross sectional	Multiple cities, Australia	2007–2008	2,593	LUR	NO_2	8.8	Previous year annual average	**1.54 (1.26–1.87)**	4.03 ppb
Krämer 2009	GINI, LISA: Wesel	Cohort	Multi-ple cities, Germany	1995–2005	1,745	LUR	NO_2	24.0	Cumulative average	**0.95 (0.59–1.52)**[f]	9 µg/m^3
							$PM_{2.5\ abs}$	1.6		**1.03 (0.67–1.59)**[f]	0.5 1×10^{-5}/m
Liu 2013	SNEC Kin-dergarten	Cross sectional	Liaoning Province, China	2009	6,730	Surface monitoring	NO_2	36.7	Three-year average at baseline	**1.21 (0.93–1.57)**	10 µg/m^3
Liu 2014	SNEC	Cross sectional	Liaoning Province, China	2009	23,326	Surface monitoring	NO_2	36.7	Three-year average at baseline	**1.22 (1.06–1.40)**	10 µg/m^3
McConnell 2006	CHS	Cross sectional	California, United States	2003	4,762	Dispersion/ CTM	NO_x	25.9	Early life exposure	**1.10 (0.94–1.30)**	28.7 ppb
Mölter 2014	MAAS	Cohort	Manchester, United Kingdom	1995–2008	373	Personal exposure	NO_2	20.3–31.9	Cumulative average	0.99 (0.84–1.2)	1 µg/m^3
							PM_{10} mass	15.1–20		0.80 (0.60–1.18)	1 µg/m^3

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Table 9.10 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Active Asthma in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
Nicolai 2003	ISAAC Munich	Cross sectional	Munich, Germany	1995–1996	about 3,000	LUR	NO_2	About 45	Annual average current year	1.66 (0.94–2.90)	>57.44 vs. <57.44 µg/m^3
							EC	About 9		1.76 (1.02–3.04)	>10.73 vs. <10.73 µg/m^3
							Benzene	About 5		2.04 (1.23–3.41)	>7.27 vs. <7.27 µg/m^3
Pan 2010	Liaoning Survey 2002	Cross sectional	Liaoning Province, China	2002	11,860	Surface monitoring	NO_2	53	Four-year average at baseline	**1.39 (1.11–1.74)**	30 µg/m^3
Puklová 2019	Czech Respiratory Cohort	Cross sectional	Moravian-Silesian Region, Czech Republic	2014	7,239	LUR	NO_2	18.8	Five-year average at baseline	**0.92 (0.70–1.21)**	11.2 µg/m^3
							PM_{10} mass	38.6		**0.76 (0.58–0.98)**	10.8 µg/m^3
Svendsen 2012	El Paso Children's Health	Cross sectional	El Paso and Texas, United States	2001	4,231	LUR	NO_2	20–27	Average recent	**1.34 (0.89–2.01)** (Upland schools)[g]	10 ppb
										0.83 (0.57–1.20) (Valley schools)[g]	
Wang 1999	ISAAC Taiwan	Cross sectional	Multiple cities, Taiwan	1995–1996	155,283	Surface monitoring	NO_2	0.028	Annual average current year	1.08 (1.04–1.13)	>0.028 vs. <0.028 ppm
							CO	0.80		1.15 (1.10–1.20)	>0.80 vs. <0.80 ppm
Zhou 2013	French Six Cities	Cross sectional	Multiple cities, France	1999–2000	4,209	Dispersion/ CTM	NO_2	44.19	Annual average current year	**1.00 (0.80–1.24)**	16.41 µg/m^3
							NO_x	78.82		**1.03 (0.86–1.25)**	50.66 µg/m^3

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Table 9.10 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Active Asthma in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
							CO	558.94		0.98 (0.84–1.15)	200.57 µg/m^3
							PM_{10} mass	26.68		**1.02 (0.84–1.24)**	10 µg/m^3
							Benzene	2.41		0.97 (0.81–1.15)	1.19 µg/m^3

BC = black carbon; OR = odds ratio; PNC = particle number concentration; RR = relative risk.

[a] All studies included male and female participants.

[b] Units are in the increment column.

[c] Unless otherwise indicated, the effect estimate was odds ratio. **Bold** indicates the effect estimate was included in the meta-analysis.

[d] Not extrapolated.

[e] Log transformed.

[f] Relative risk.

[g] Estimates were combined by a fixed effect meta-analysis before entering the random-effects model.

Age at assessment of active asthma by questionnaire was usually during elementary school years, although some assessed the prevalence of active asthma only in preschool children (Brauer et al. 2002) or included infants and preschool children with children of older ages (e.g., Dong et al. 2008; Gehring et al. 2010; Kim et al. 2004; Liu et al. 2013; Mölter et al. 2014; Pan et al. 2010; Patel et al. 2011; Yi et al. 2017). Studies that used administrative health data typically included children and adolescents up to 18 years of age (except Livingstone et al. 1996 who excluded children younger than two years and Wilkinson et al. 1999 who included children aged 5–14).

Average air pollutant levels such as NO_2 varied widely, ranging from 8.8 µg/m³ in cities of Australia (Knibbs et al. 2018) to 53 µg/m³ in the Liaoning Province of China (Pan et al. 2010). Pollutant exposure assessment was more often based on LUR, but dispersion or CTM models and surface monitoring were also used; a few studies estimated exposures related to time–activity patterns (Clifford et al. 2018; Mölter et al. 2014). Although active asthma refers to symptoms occurring in the past year, studies reported various exposure windows, including annual recent exposure, cumulative exposure, and exposure during pregnancy. Thus, the identified studies differed substantially in size, exposure assessment, and population studied.

9.3.3.2 Primary Meta-analysis

Figure 9.12 shows the summary estimates for all pollutants for the prevalence of active asthma in children based on meta-analyses. For distance and traffic density metrics and pollutants with fewer than three estimates of association, no meta-analysis was conducted. The number of studies included in meta-analysis is less than the total number of selected studies (Tables 9.10 and 9.11) because the Panel considered only the most informative estimate per study population (e.g., the Panel selected Gehring et al. 2010 over Brauer et al. 2002 because of the longer study period and larger sample size in Gehring). Note that in the specific case of the PIAMA study, the estimates were either from a sensitivity analysis of participants living in the western and middle parts of the Netherlands (Brauer et al. 2002), or from a sensitivity analysis corrected for region (Gehring et al. 2010), because of our exposure framework requirements. The Panel also excluded studies from the meta-analyses that had log transformed or categorized pollutant levels (Kim et al. 2004; Nicolai et al. 2003; Wang et al. 1999). The studies by Mölter and colleagues (2014) and Clifford and colleagues (2018) were also not included in meta-analyses because these studies assessed personal exposure considering time–activity patterns; the exposures were therefore not comparable with the ambient exposures assessed in other studies.

NO_2 was the most studied pollutant with 12 estimates of association meta-analyzed. Three estimates of association were available for meta-analyses of EC and NO_x, and four for PM_{10}. Meta-analytic summary estimates for NO_2, NO_x, and EC and active asthma in children were positive while there was no

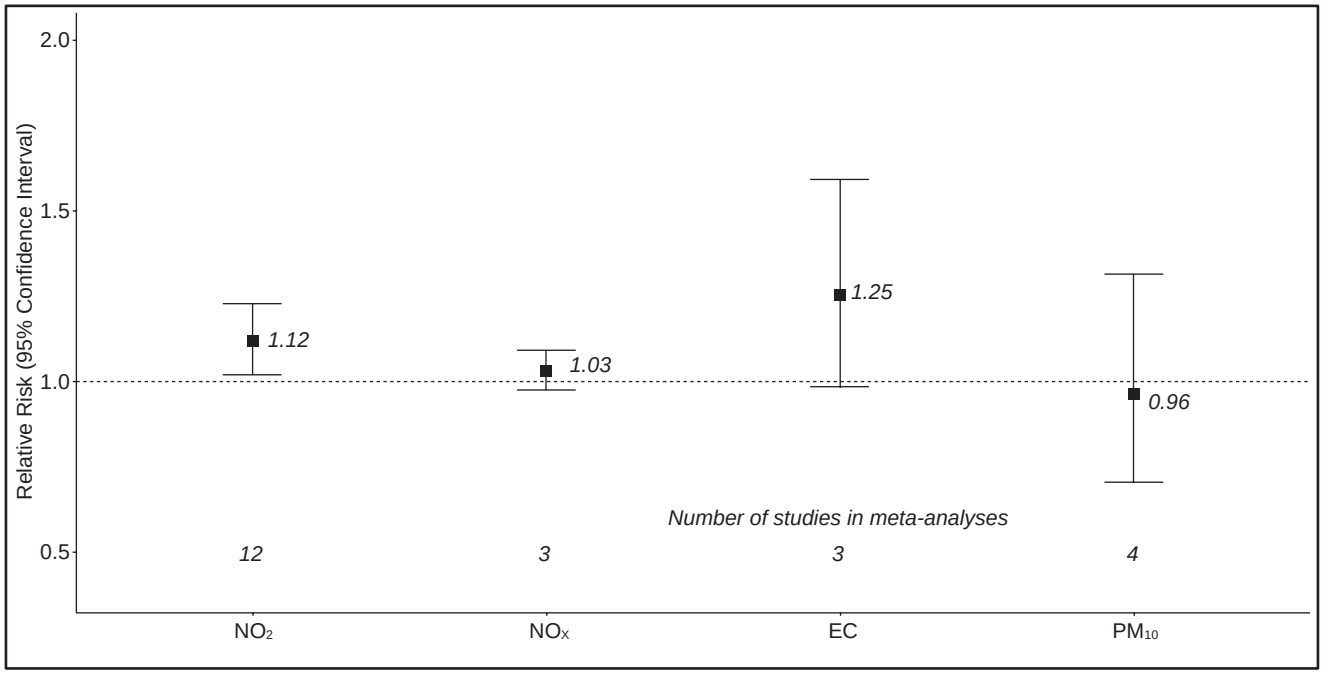

Figure 9.12. Meta-analysis of associations between traffic-related air pollutants and prevalence of active asthma in children. The following increments were used: 10 µg/m³ for NO_2, 20 µg/m³ for NO_x, 1 µg/m³ for EC and 10 µg/m³ for PM_{10}. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

association with PM_{10}. Additionally, confidence intervals for all meta-analytic summaries were wide, and estimates included unity except for the relationship with NO_2 (Figure 9.12).

Figure 9.13 shows the forest plots with individual studies for NO_2. The majority of estimates of association between NO_2 and active asthma in children that were meta-analyzed were positive, but confidence intervals often included unity and a few estimates were also inverse or null (e.g., Krämer et al. 2009; Puklová et al. 2019; Zhou et al. 2013). The I^2 showed low heterogeneity (49%). The summary estimate for the association of active asthma in children with NO_2 was 1.12 (95% CI: 1.02–1.23) per 10-μg/m^3; it was not heavily influenced by an individual study, as indicated by the weights in the forest plot.

The three meta-analyzed studies on NO_x (Appendix Figure 9B-12) and EC (Appendix Figure 9B-13) were all positive, but the confidence intervals were wide and included unity for all of the studies. Note that the study from Nicolai and colleagues (2003), which analyzed EC in categories, also reported a positive association with EC. The NO_x summary estimate for active asthma in children was 1.03 per 20-μg/m^3 (95% CI: 0.97–1.09). The EC summary estimate was larger, although less precise (1.25 per 1-μg/m^3; 95% CI: 0.98–1.59) and driven by Gehring and colleagues (2015) with a 71% weight. The I^2 for both NO_x and EC was null.

The PM_{10} estimates were either positive with confidence intervals including unity, or negative (Appendix Figure 9B-14). The confidence intervals of the studies largely overlapped and the resulting I^2 was 36%. The PM_{10} summary estimate for active asthma in children was 0.96 per 10-μg/m^3 and was imprecise (95% CI: 0.70–1.31). In addition, a few studies reported results on other pollutants, where there were too few studies available for meta-analysis. Gehring and colleagues (2015) reported no association with PM_{coarse} (Table 9.10). Gehring and colleagues (2010 and 2015) also reported positive but imprecise associations with $PM_{2.5}$. A positive or null association was reported for the two studies investigating CO (Wang et al. 1999; Zhou et al. 2013) and the two studies investigating benzene (Nicolai et al. 2003; Zhou et al. 2013). A small Australian study documented a negative relationship between UFP exposure and active asthma (Clifford et al. 2018).

9.3.3.3 Additional Meta-analyses

Figure 9.14 shows that excluding studies with moderate traffic specificity slightly increased heterogeneity (I^2 increased from 49% to 56%) and reduced the precision of the meta-analytic estimate. The meta-analytic summary estimate without the moderate traffic specificity studies (1.10 per 10-μg/m^3; 95% CI: 0.96–1.26), was nonetheless very similar to the estimate that included all studies (1.12 per 10-μg/m^3; 1.02–1.23).

Figure 9.15 illustrates that the estimates of association for NO_2 were positive in all regions except for one study in Eastern Europe (Puklová et al. 2019). This study differs from all the others meta-analyzed in that it used medical records and not a questionnaire to assess the outcome. Nonetheless, estimates from Asian countries and Australia were higher than those from European and American countries; those from Asian countries were based on surface monitoring.

All NO_2 estimates meta-analyzed were from studies published after 2008; therefore, it was not possible to assess consistency between periods. The internal validity of cohort studies is usually better than cross-sectional studies; the outcome assessment is likely more accurate because with cohort studies one can assess the age of disease onset. Stratification by design was possible for estimates of association with NO_2. The summary estimate for cohort studies of NO_2 (1.10

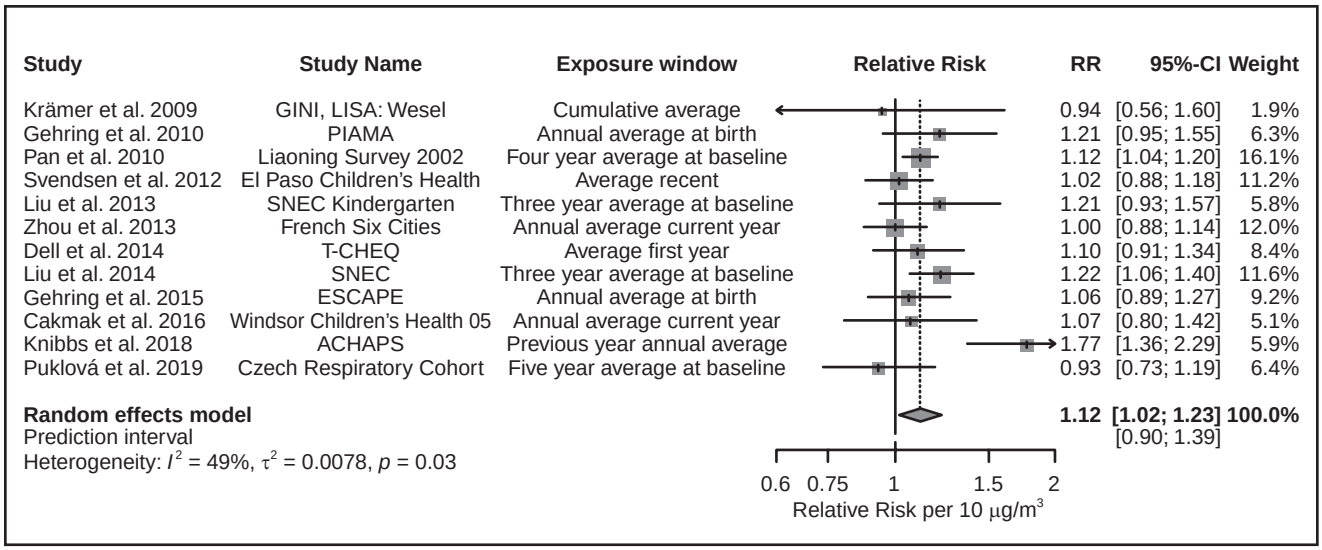

Figure 9.13. Association between NO_2 and prevalence of active asthma in children: meta-analysis.

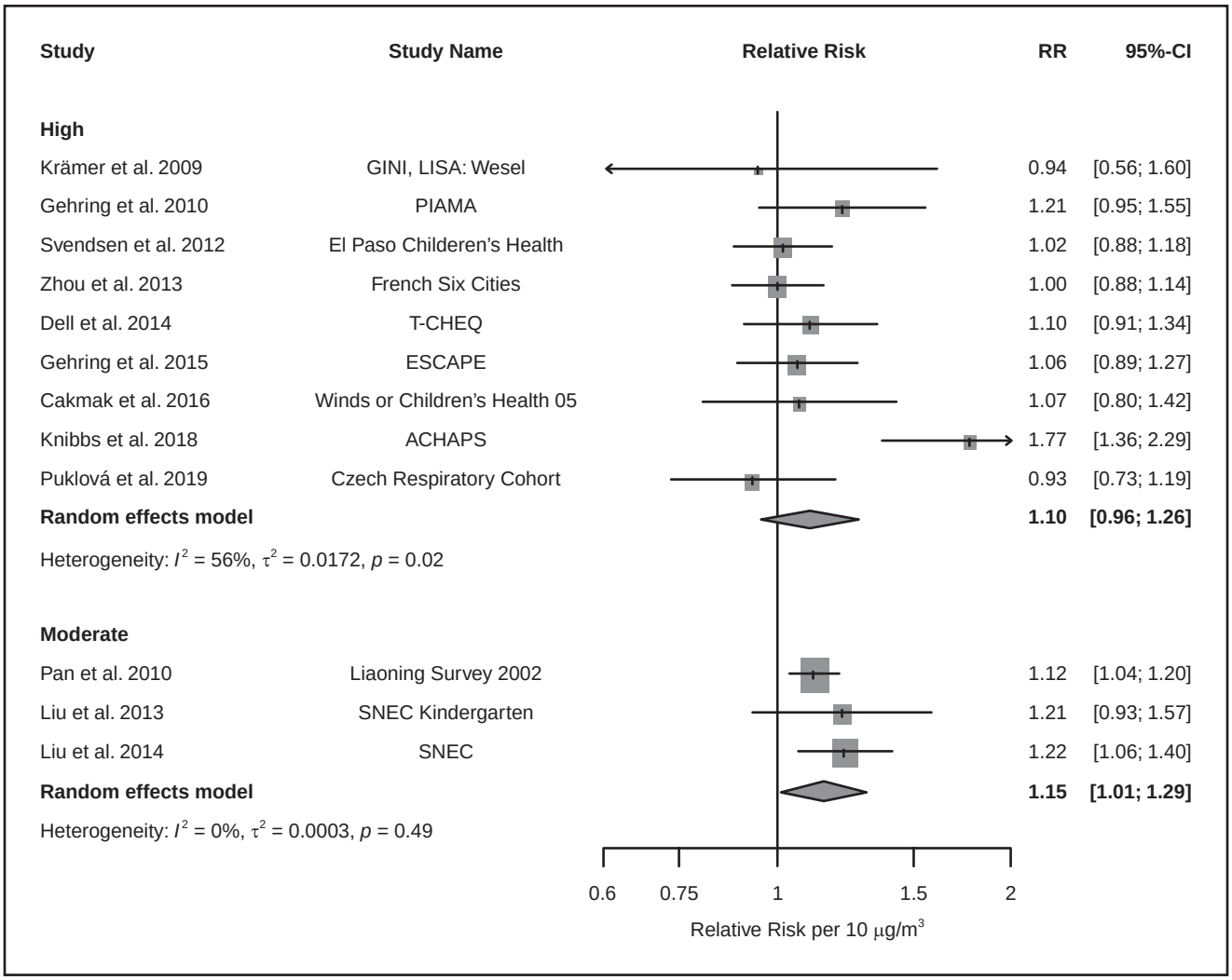

Figure 9.14. Association between NO_2 and prevalence of active asthma in children: meta-analysis by traffic specificity.

per 10-μg/m^3; 95% CI: 0.88–1.37) was similar to the one for cross-sectional studies (1.13 per 10-μg/m^3; 0.97–1.32). The I^2 for cross-sectional studies was greater than for cohort studies (Figure 9.16); it was also higher than for all studies combined.

Only Pan and colleagues (2010) adjusted the NO_2 effect estimate for general $PM_{2.5}$ exposure, and the NO_2 estimate was attenuated by the adjustment. However, the Panel recommends caution in interpreting the results, as an over-adjustment could be possible.

Finally, the meta-analytic estimate obtained prioritizing either prenatal (Figure 9.13) or postnatal NO_2 exposures (Figure 9.17), as well as the heterogeneity of the NO_2 estimates, were very similar and provided no indication that one exposure window presents more risk of active asthma in children then the other, although it is likely that exposures are highly correlated over time.

9.3.3.4 Associations with Indirect Traffic Measures

Studies on indirect traffic measures were too heterogeneous in their definitions to allow meta-analysis; as an additional source of information, they provided very limited evidence of associations between TRAP exposure and the prevalence of active asthma in children. The direction of the estimates of association with distance and density measures from 19 studies (of which four also provided estimates of association with some traffic pollutants) were inconsistent and some had large confidence intervals (Table 9.11).

9.3.3.5 Narrative Assessment

In summary, the evidence for associations of prevalence of active asthma in children with TRAP included studies from Europe, Asia, and North America. The majority of studies were cross-sectional and used questionnaires to

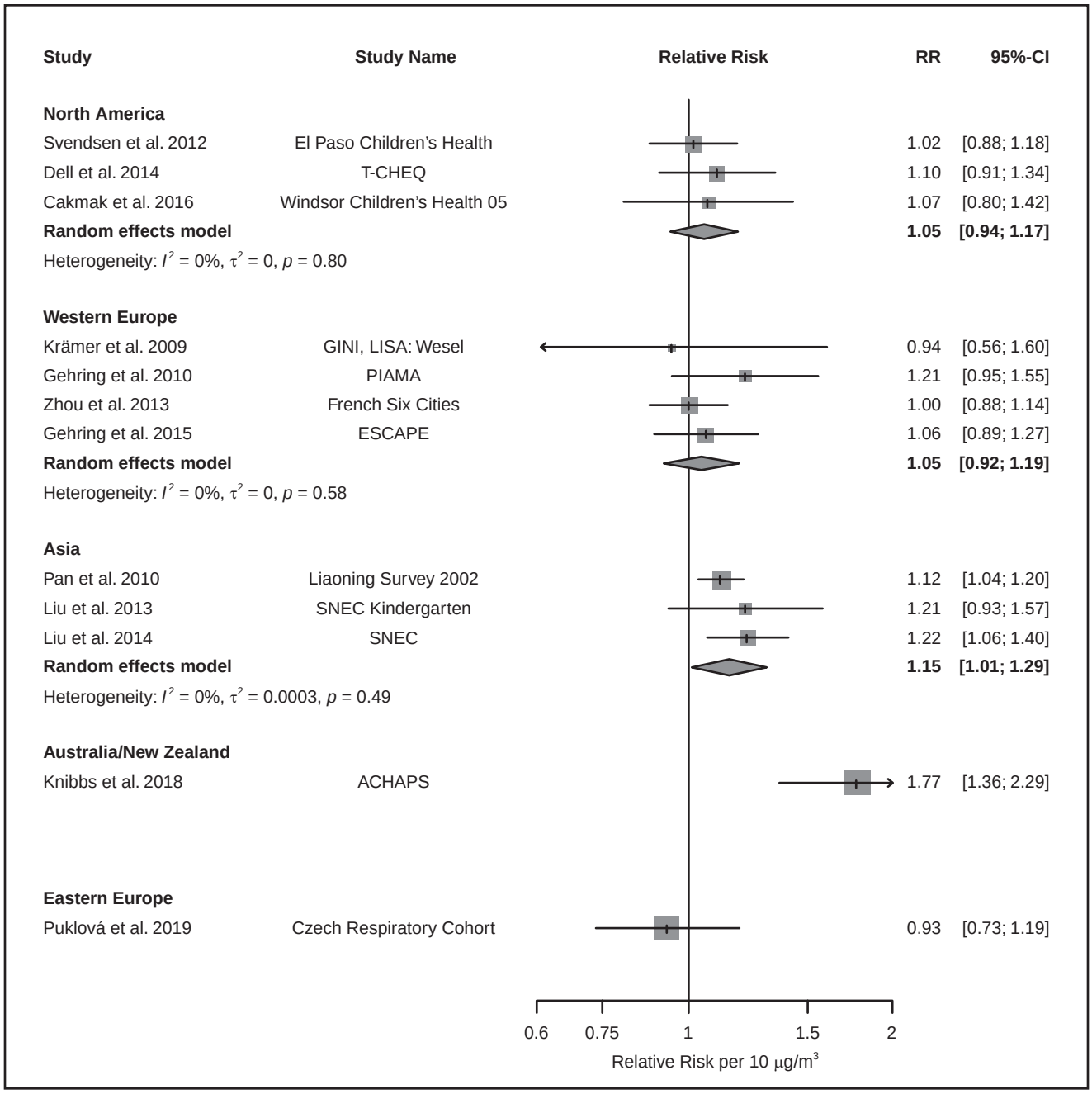

Figure 9.15. Association between NO_2 and prevalence of active asthma in children: meta-analysis by region.

assess children with active asthma; case-control studies used administrative health data and assessed associations with indirect traffic measures. Populations studied usually ranged from a few hundred to several thousand participants, although a very large survey from Taiwan included 155,000 children (Wang et al. 1999); the ESCAPE project (Gehring et al. 2015) also included 14,000 children. Age at assessment was variable but often included children from elementary schools. The majority of studies were cross-sectional and used questionnaires to assess children with active asthma; case-control studies used administrative health data and assessed associations with indirect traffic measures. Studies included extensive information on individual risk factors for adjustments of potential confounding variables. Associations with NO_2 were most often reported, and NO_2 estimates were often modeled with dispersion or LUR models,

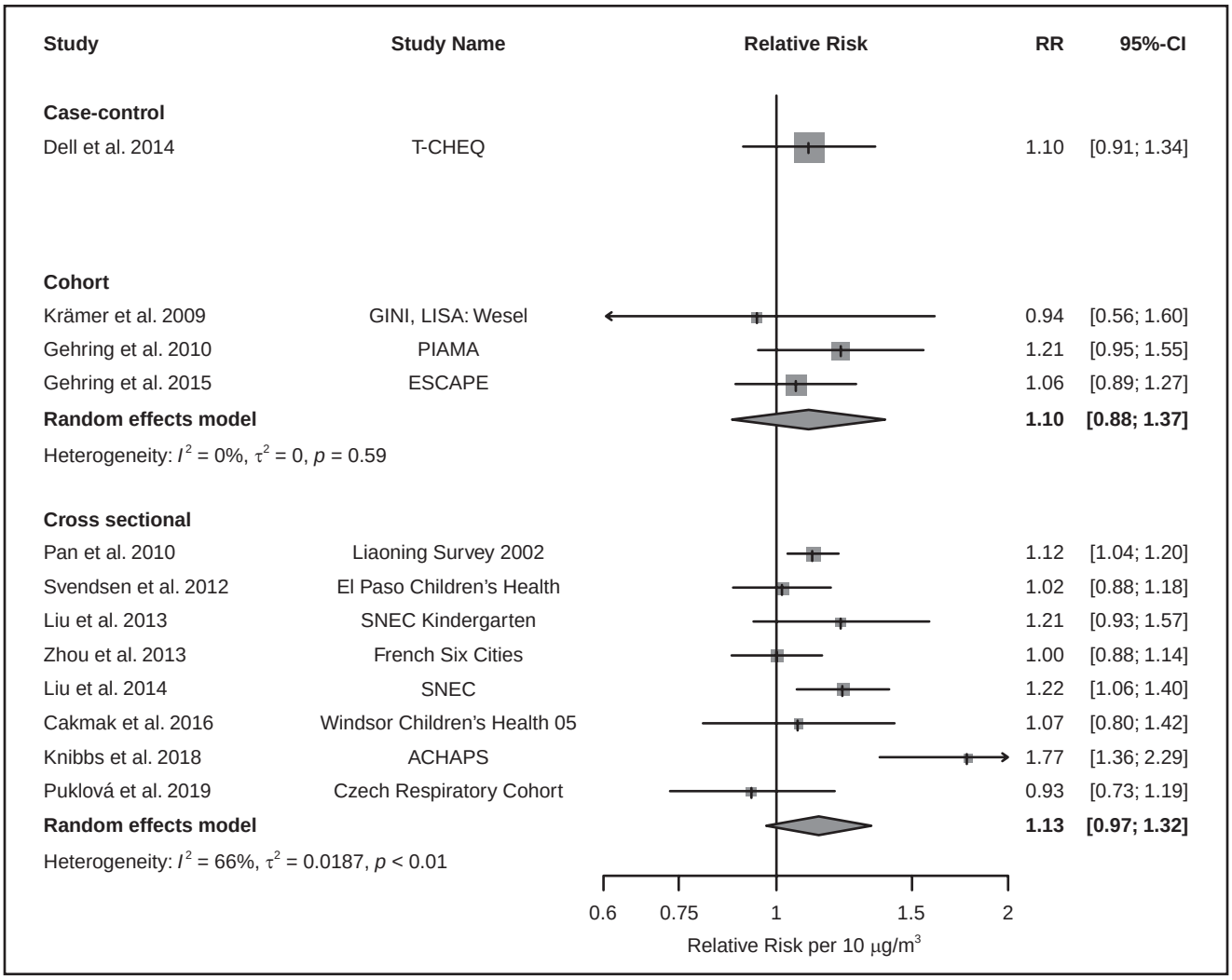

Figure 9.16. Association between NO_2 and prevalence of active asthma in children: meta-analysis by study design.

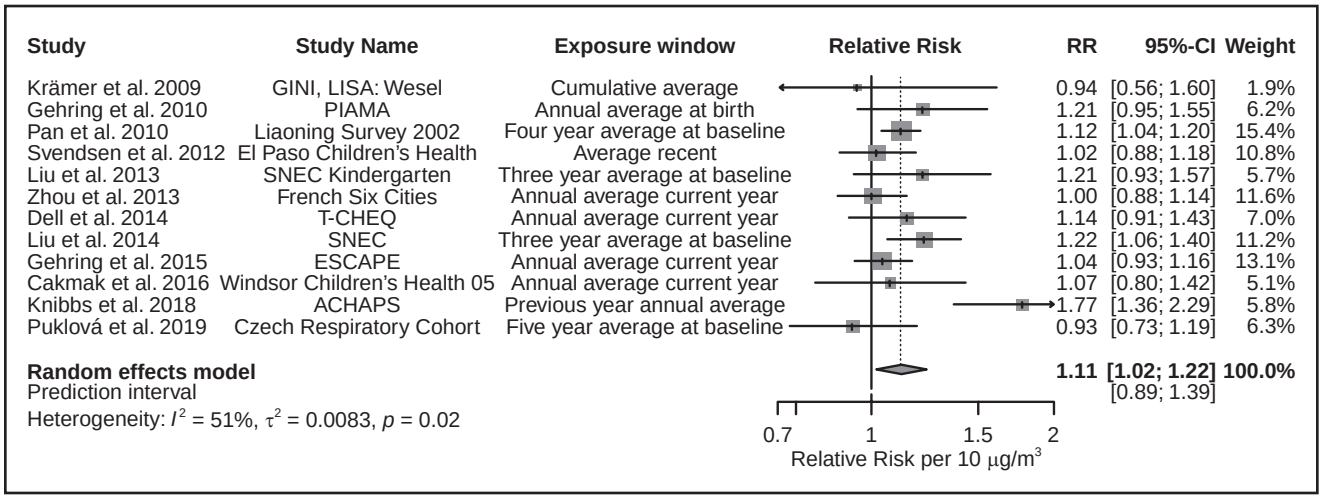

Figure 9.17. Association between NO_2 and prevalence of active asthma in children: meta-analysis giving priority to postnatal exposures.

Table 9.11. Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Active Asthma in Children—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
Dell 2014	T-CHEQ	Case-control	Toronto, Canada	2006	1,454	Distance	OR	1.91 (0.46, 7.94)	<100 vs. >100 m
Dong 2008	Liaoning Survey 2007	Cross sectional	Shenyang and Anshan and Dalian, China	2007	3,945	Distance	OR	1.25 (0.79, 1.98)	<20 vs. >100 m
								0.89 (0.56, 1.44)	20–100 vs. >100 m
English 1999	San Diego Children's Asthma	Case-control	San Diego County, California, United States	1993	6,232	Density	OR	1.05 (0.88, 1.26)	>50,100 vs. <9,100 vehicles/day
								1.00 (0.83, 1.19)	25,001–50,100 vs. <9,100 cars/day
								0.76 (0.63, 0.91)	16,701–25,000 vs. <9,100 cars/day
								0.83 (0.69, 1.00)	9,101–16,700 vs. <9,100 cars/day
Hansell 2014	CAPS	Cross sectional	Sydney, Australia	2005–2009	398	Density	RR	1.13 (0.87, 1.46)[b]	per 100 m local road or 33.3 m of motorway
Jung 2015	CHEER	Cross sectional	Multiple cities, South Korea	2005–2006	4,203	Distance	OR	1.08 (0.69, 1.68)	<75 vs. >225 m
								1.00 (0.68, 1.49)	75–150 vs. >225 m
								1.12 (0.64, 1.96)	150–225 vs. >225 m
Kim 2008	EBCRHS	Cross sectional	California, United States	2001	724	Density	OR	2.37 (1.05, 5.36)	9,414–74,041 vehicles-km/day vs. none
								1.40 (0.60, 3.30)	4,403–9,413 vehicles-km/day vs. none
								1.96 (0.85, 4.52)	1,920–4,402 vehicles-km/day vs. none
								1.23 (0.53, 2.83)	<1,919 vehicles-km/day vs. none

Continues next page

Table 9.11 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Active Asthma in Children—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
						Distance		3.80 (1.20, 11.71)	<75 vs. >300 m
								1.87 (0.71, 4.90)	75–150 vs. >300 m
								1.25 (0.50, 3.11)	150–300 vs. >300 m
Krämer 2009	GINI, LISA: Wesel	Cohort	Multiple cities, Germany	1995–2005	1,745	Distance	RR	0.82 (0.51, 1.32)	<50 vs. >50 m
Li 2011	Detroit Medicaid Children's Asthma	Case-control	Detroit, Michigan, United States	2004–2006	14,646	Distance	OR	0.98 (0.93, 1.03)	1,000 m
Lin 2002	Erie County Children's Asthma	Case-control	Erie County, New York, United States	1990–1993	878	Density	OR	1.93 (1.13, 3.29)	>4,043 vs. no vehicle-miles/day
								1.06 (0.64, 1.76)	2,367–4,042 vs. no vehicle-miles/day
								1.31 (0.79, 2.16)	<2,366 vs. no vehicle-miles/day
						Distance		1.24 (0.87, 1.77)	<200 vs. >600 m
								0.88 (0.61, 1.28)	201–400 vs. >600 m
								0.73 (0.50, 1.09)	401–600 vs. >600 m
Livingstone 1996	Tower Hamlets GP	Case-control	London, United Kingdom	1994	1,574	Distance	OR	0.96 (0.78, 1.22)	<150 vs. >150 m
McConnell 2006	CHS	Cross sectional	California, United States	2003	4,762	Distance	OR	1.50 (1.16, 1.95)	<75 vs. >300 m
								1.33 (1.02, 1.72)	75–150 vs. >300 m
								1.04 (0.82, 1.33)	150–300 vs. >300 m
Nicolai 2003	ISAAC Munich	Cross sectional	Munich, Germany	1995–1996	about 3,000	Density	OR	1.79 (1.05, 3.05)	>30,000 vehicles/day vs. none
								1.18 (0.64, 2.17)	15,001–30,000 vehicles/day vs. none
								0.61 (0.26, 1.40)	2,600–15,000 vehicles/day vs. none
Patel 2011	CCCEH	Cohort	New York City, New York, United States	1998–2010	593	Distance	OR	1.31 (0.88, 1.96)	–0.96 km

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Table 9.11 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Active Asthma in Children—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
Pereira 2009	Perth Asthma ED Visits	Case-control	Perth, Australia	2002–2006	1,809	Density	OR	0.73 (0.62, 0.85)	1,000 vehicle-km/peak morning hour
						Distance		1.20 (0.96, 1.49)	–1 km
van Vliet 1997	South Holland Respiratory Survey	Cross sectional	Multiple cities, the Netherlands	1995	878	Density	OR	0.38 (0.13, 1.12)	High vs. low car volume
								1.78 (0.66, 4.77)	High vs. low truck volume
						Distance		0.87 (0.32, 2.37)	<100 vs. 100–1,000 m
Wilkinson 1999	London Children's Asthma	Case-control	London, United Kingdom	1992–1994	7,083	Density	OR	0.88 (0.74, 1.06)	>50 vs. <1.5 vehicle-km/hour
								0.80 (0.68, 0.95)	15–50 vs. <1.5 vehicle-km/hour
								1.03 (0.87, 1.22)	1.5–15 vs. <1.5 vehicle-km/hour
Wjst 1993	Munich Asthma and Allergy	Cross sectional	Munich, Germany	1989–1990	4,678	Density	OR	1.04 (0.89, 1.21)	25,000 vehicles/day
Yang 2002	Kaohsiung Respiratory Survey	Cross sectional	Kaohsiung, Taiwan	1999–2000	6,190	Distance	OR	0.94 (0.78, 1.13)	150 vs. 1,500 m
Yi 2017	Seoul Atopy Friendly School	Cross sectional	Seoul, South Korea	2010	14,765	Distance	OR	0.93 (0.78, 1.11)	<150 vs. >500 m
								1.11 (0.93, 1.32)	150–300 vs. >500 m
								1.00 (0.83, 1.20)	300–500 vs. >500 m

OR = odds ratio; RR = relative risk.

[a] All studies included male and female participants.

[b] Log-transformed.

although Asian studies used surface monitoring to assess exposure to NO_2.

The evidence base, including meta-analyses, provided moderate evidence of an association between TRAP and active asthma in children. The summary estimates for associations between NO_2, NO_x, and EC and active asthma in children were positive, while there was no association with PM_{10}. Confidence intervals for the summary estimates were wide and included unity except for NO_2. Contradictory or imprecise estimates were reported for pollutants not meta-analyzed such as CO, $PM_{2.5}$ mass, benzene, and PM_{coarse} and for indirect traffic measures. No study provided evidence of a plausible monotonic exposure–response function, see the *Confidence Assessment of the Body of Evidence* section that follows.

As with studies on asthma ever, there was a potential bias of the estimates in most studies on active asthma because the outcome was usually self-reported through questionnaires. Associations may be biased because self-reporting can be influenced by knowledge of exposure.

Overall, the positive meta-analytic summary estimates between most traffic pollutants and the prevalence of active asthma in children in different populations provide confidence in the presence of an association. However, uncertainties remain due to the cross-sectional nature of most studies assessed, the potential bias in outcome reporting, and the heterogeneity of the estimates (with both positive and negative effect estimates). Therefore, the presence of an association between TRAP and active asthma in children was judged as moderate by the Panel.

9.3.3.6 Risk of Bias Assessment

Table 9.12 shows an overview of the results of the risk of bias assessment for exposure–outcome pairs of studies on active asthma that were meta-analyzed; Appendix Table 9B-3 presents the assessment for each individual study. Risk of bias assessment does not indicate that there is bias, nor does it inform on its potential direction; it only determines if there is potential risk of bias. As for the outcome asthma ever, the

Table 9.12. Summary of Risk of Bias Rating for Studies on Prevalence of Active Asthma in Children

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	9	1	4	15	1	6
	Validity of measuring of confounding factors	14	0	0	22	0	0
	Control in analysis	11	3	0	19	3	0
	Overall	7	3	4	13	3	6
2. Selection bias	Selection of participants into the study	10	4	0	16	6	0
3. Exposure assessment	Methods used for exposure assessment	14	0	0	22	0	0
	Exposure measurement methods comparable across the range of exposure	14	0	0	22	0	0
	Change in exposure status	13	1	0	18	4	0
	Overall	13	1	0	18	4	0
4. Outcome measurements	Blinding of outcome measurements	1	13	0	2	20	0
	Validity of outcome measurements	13	1	0	21	1	0
	Outcome measurements	13	1	0	21	1	0
	Overall	1	13	0	2	20	0
5. Missing data	Missing data on outcome measures	11	3	0	16	6	0
	Missing data on exposures	13	1	0	20	2	0
	Overall	11	3	0	16	6	0
6. Selective reporting	Authors reported a priori primary and secondary study aims	14	0	0	22	0	0

large majority of the estimates of association for active asthma were rated moderate risk of bias for outcome measurement. This is because in most studies, the outcome active asthma was self-reported through questionnaires. It was rated at moderate risk of bias because outcome reporting can be influenced (i.e., over-reported) by exposure knowledge when self-reported, especially for those living in proximity to major roads and aware of potential health risks of this exposure. Four studies were rated at high risk of bias for confounding due to incomplete adjustment. As studies were extensively evaluated for their exposure assessment to include only TRAP studies, no study was rated at high risk of bias for exposure methods. However, some studies with long follow-up (such as the ESCAPE study) were rated moderate risk of bias for change in exposure assessment. A few estimates were also rated at moderate risk of bias due to potential selection bias.

9.3.3.7 Confidence Assessment of the Body of Evidence

Table 9.13 provides the Panel's confidence assessment for associations with pollutants that were meta-analyzed; thus, the table includes the pollutants that had three or more studies. Here, the Panel first discusses four factors that may reduce confidence (downgrades). Next, factors that may increase confidence (upgrades) are discussed. The Panel decided a priori not to consider the upgrading factor large magnitude of the effect.

All studies that provided estimates of association between TRAP and active asthma in children for meta-analyses were cross-sectional assessments, except the study by Dell and colleagues (2014), which was a case-control study (also based on prevalence cases). Although approximately a fifth of the cross-sectional assessments were nested within cohort studies, only three out of seven studies were meta-analyzed. The initial rating for all studies was nonetheless set at low as the majority of studies were cross-sectional.

Downgrading Factor Risk of Bias The overview of the risk of bias ratings for each exposure–outcome pair that was meta-analyzed is presented in Table 9.12 for active asthma in children. Very few estimates from several studies were rated at high risk of bias. Thus, a formal comparison between the low to moderate and the high risk of bias subgroups was not possible. Nonetheless, subgroup analyses with respect to risk of bias for NO_2 (Appendix Figure 9B-15) shows that excluding the few estimates of association rated at high risk of bias, due to confounding because of the lack of adjustment for tobacco smoke (Appendix Figure 9B-16), had minimal influence on the meta-analytic estimate. There were only four estimates of association with PM_{10}, and they were very imprecise; thus, excluding the two studies at high risk of bias was not informative. Additionally, none of the EC and one out of three NO_x estimates of association were rated at high risk of bias, but the small number of studies did not permit stratification of the meta-analyses.

Thus, the subgroup analysis with respect to risk of bias assessment does not suggest a need to downgrade the confidence in the evidence for the pollutants included in the meta-analyses. This judgment is supported by the very small numbers of estimates that were rated as high risk of bias and the limited changes in summary estimates when excluding the studies rated as high risk of bias.

Downgrading Factor Unexplained Inconsistency The Panel observed either no (NO_x, EC) or low heterogeneity of effect estimates across studies (NO_2, PM_{10}). Therefore, the Panel did not downgrade the evidence; there were too few studies available to meaningfully investigate sources of heterogeneity for pollutants other than NO_2. Regional differences in NO_2 estimates explain some of the heterogeneity, as NO_2 estimates of association from Asian countries (all based on surface monitoring) were higher in magnitude than those from other countries. However, the evidence for NO_2 was also not downgraded because the majority of the estimates of association between NO_2 and active asthma in children were positive, and regional differences was one plausible explanation for some heterogeneity.

Other Factors That Reduce Confidence The Panel downgraded the evidence for NO_x, EC, and PM_{10} for imprecision. The sample size for these pollutants was smaller than the specified needed minimum sample size in the protocol. Confidence intervals of meta-analytic estimates for these pollutants were wide and contained unity. In contrast, the Panel did not downgrade the evidence for NO_2 for imprecision because the required sample size was met and the summary estimate did not include unity (1.12 per 10-μg/m^3; 95% CI: 1.02–1.23).

The Panel did not downgrade for publication bias. There were more than 10 studies, so funnel plots and Egger tests were produced for NO_2. The funnel plot and the Egger test did not suggest asymmetry (Appendix Figure 9B-17). Due to the small number of studies, it was not possible to assess publication bias for studies on associations with the other pollutants; as there was no evidence of bias for NO_2, the Panel chose to not downgrade the evidence for all pollutants.

Factors That Increase Confidence No study provided evidence of a plausible monotonic exposure–response function, so an upgrade was not applied. In the current body of evidence, the Panel found no clear indication that residual confounding or other factors are likely to lead to an underestimation of the associations. An upgrade was thus not considered appropriate. Regarding consistency across geographic regions, populations, or study period, the Panel decided to upgrade the evidence for NO_2. The Panel found positive associations in Europe, North America, and Asia, although the estimates were larger in Asian countries and the confidence intervals for the summary estimates for North America and Europe

Table 9.13. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and the Prevalence of Active Asthma in Children[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cross-sectional	++ (N = 12)	0	0	0	0	0	0	+	+++ (Moderate)
	Rationale	Cross-sectional analyses initially rated as low.	Few studies high RoB and robust effect estimates in low and moderate RoB studies.	Low heterogeneity (I^2 = 49%).	Sample size met, and confidence interval does not include unity.	No evidence found.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Consistent association across different geographic regions.	
NO_X	Cross-sectional	++ (N = 3)	0	0	–	0	0	0	0	+ (Very low)
	Rationale	Cross-sectional analyses initially rated as low.	1 of 3 studies at high RoB.	Low heterogeneity (I^2 = 0%). No heterogeneity to be explained.	Sample size not met, confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	
EC	Cross-sectional	++ (N = 3)	0	0	–	0	0	0	0	+ (Very low)
	Rationale	Cross-sectional analyses initially rated as low.	No studies at high RoB.	Low heterogeneity (I^2 = 0%). No heterogeneity to be explained.	Sample size not met, confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	
PM_{10}	Cross-sectional	++ (N = 4)	0	0	–	0	0	0	0	+ (Very low)
	Rationale	Cross-sectional analyses initially rated as low.	2 of 4 studies at high RoB; exclusion not informative.	Low heterogeneity (I^2 = 36%).	Sample size not met, confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor indirectness and the upgrading factor large magnitude of effect were not considered further.

included unity and were based on only three or four studies for each region. Note that most studies were published after 2008, so the Panel could not assess consistency across time periods.

Evaluation of Confidence for Combined Measures of TRAP The Panel gave one moderate (NO_2), and three very low (NO_x, EC, and PM_{10}) assessments of the confidence in the body of evidence for active asthma. The Panel's overall confidence assessment was based mostly on NO_2 because NO_2 had many more studies than the other pollutants. Moreover, most of the NO_2 studies were of high-traffic specificity. Therefore, the level of confidence in the body of evidence of the association between TRAP exposure and active asthma in children was moderate based on the modified OHAT assessment.

As described earlier, the Panel did not present separate evaluations for the prevalence of active asthma from cohort and cross-sectional studies, because the actual analyses conducted were cross-sectional in all studies, and stratification by design did not influence the summary estimates.

9.3.3.8 Overall Confidence Assessment

Based on the narrative evaluation (moderate) and the modified OHAT assessment (moderate), the overall confidence in the evidence for an association between TRAP and active asthma in children is moderate.

9.3.4 ASTHMA EXACERBATION

9.3.4.1 Study Selection and Description

Six studies explored associations between TRAP and asthma exacerbation in children with asthma, and another five solely explored associations with indirect measures of traffic exposures (Table 9.14 and Figure 9.18). Asthma exacerbation has been assessed by these 11 studies using emergency department visits, hospital admissions, or medication use among children with asthma. Combined, these studies produced 17 different effect estimates—11 for the pollutants and 6 different indirect traffic metrics. All but three studies were based in the United States, six of which were based in the state of California. Table 9.14 presents details of the studies that considered exposures with pollutants, including the effect estimates. All but one study (English et al. 1999) was published after 2008 (the end of the search date for the 2010 HEI Traffic Review). Across the six studies that considered exposures to pollutants, three effect estimates were presented for each of NO_x and EC, two for CO and NO_2, and one for $PM_{2.5}$. All 11 effect estimates were greater than one. The lower confidence interval was higher than one in six cases and borderline (0.99) in an additional three cases. In particular, the two relatively large cohorts of children with asthma reported clearly increased RRs for NO_2, NO_x, and CO (Delfino et al. 2009) and for NO_x (Urman et al. 2018).

9.3.4.2 Meta-analysis

Hasunuma and colleagues (2016), which reported NO_x and EC, could not be included in meta-analyses because indoor pollutant levels and exposures related to time–activity patterns were considered, and the exposures were therefore not comparable with the ambient exposures assessed in other studies. Therefore, no meta-analyses were conducted on asthma exacerbations in children due to the limited number of studies for each pollutant.

9.3.4.3 Associations with Indirect Traffic Measures

Studies on indirect traffic measures did not provide convincing evidence of an association with asthma exacerbation in children with asthma (Figure 9.18). Note that Huynh and colleagues (2010) used uninformative exposure categories with <2 versus >2 miles. Results from one study (Chang et al. 2009), however, did suggest some evidence of increasing risk of this outcome associated with incremental increases in distance from major roads.

9.3.4.4 Narrative and Overall Confidence Assessment

In summary, the evidence base for an assessment of associations between traffic pollutants and asthma exacerbation in children with asthma is limited, with 12 studies of mainly cross-sectional design and conducted in the United States. There was little overlap in the choice of pollutant or metric of exposure considered so meta-analysis and assessment in the confidence in the body of the evidence using the modified OHAT method could not be conducted. Most of the studies were based on relatively small sample sizes, but most of them, including the two cohorts, provided evidence of a positive association between TRAP-related pollutants and asthma exacerbation. As such, the confidence in the presence of an association between TRAP and asthma exacerbation in children is considered low based on the narrative assessment.

9.3.5 ACUTE LOWER RESPIRATORY INFECTION

9.3.5.1 Study Selection and Description

The Panel identified 27 studies that reported findings on the relationship between TRAP or indirect traffic measures and ALRI in children (Table 9.15 and Table 9.16). 17 of these studies quantified the association between ALRI and at least one of the identified pollutants, 10 studies report on indirect traffic measures, and five of the latter studies report only on indirect traffic measures. Many studies were cohort studies—including prospective birth cohorts—but there were also some cross-sectional studies and case-control studies.

In most of the study populations extensive information on potential confounders was available and considered in the analyses. This included various measures of tobacco smoke with varying levels of detail (i.e., maternal smoking during

Table 9.14. Key Study Characteristics of Articles Included in the Systematic Review for Asthma Exacerbation in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Exposure Window	Effect Measure	Effect Estimate (95% CI)	Increment
Delfino 2009	Orange County Asthmatics	Cohort	Orange County, California, United States	2000–2003	2,768	Dispersion/CTM	NO_2	About 5.5	Annual average recent year	HR	1.04 (0.99–1.10)	2.68 ppb
							NO_x	About 7.2			1.10 (1.03–1.16)	4 ppb
							CO	About 0.1			1.07 (1.01–1.14)	0.056 ppm
Hasunuma 2016	SORA	Cross sectional	Multiple cities, Japan	2006–2010	398	Personal exposure	NO_x	37.7	Cumulative average	OR	1.02 (0.99–1.06)	1 ppb
							EC	2.85			1.06 (0.99–1.14)	0.1 µg/m^3
Lovinsky-Desir 2019	NYC-NAAS	Cross sectional	New York City, New York, United States	2008–2011	190	LUR	NO_2	20	Annual average current year	PR	1.13 (1.01–1.26)	1 ppb
							EC	Not reported			1.02 (1.00–1.04)	1 µg/m^3
							$PM_{2.5}$ mass	Not reported			1.50 (0.98–2.30)	1 µg/m^3
Newman 2014	GCARS	Cohort	Cincinnati, Ohio, United States	2010–2012	621	LUR	EC	0.37	Annual average previous year	OR	1.40 (0.90–2.20)	>0.37 vs. <0.37 µg/m^3
Urman 2018	CHS	Cohort	California, United States	1993–2013	1,353	Dispersion/CTM	NO_x	18.3	Previous year annual average	OR	1.39 (1.13–1.71)	42.3 ppb
Wilhelm 2009	LA FANS	Cross sectional	Los Angeles, California, United States	2000–2002	345	Surface monitoring	CO	About 1	Annual average current year	OR	2.33 (1.03–5.25)	1 ppm

HR = hazard ratio; OR = odds ratio; PR = prevalence ratio.

[a] All studies included male and female participants.

[b] Units are in the increment column.

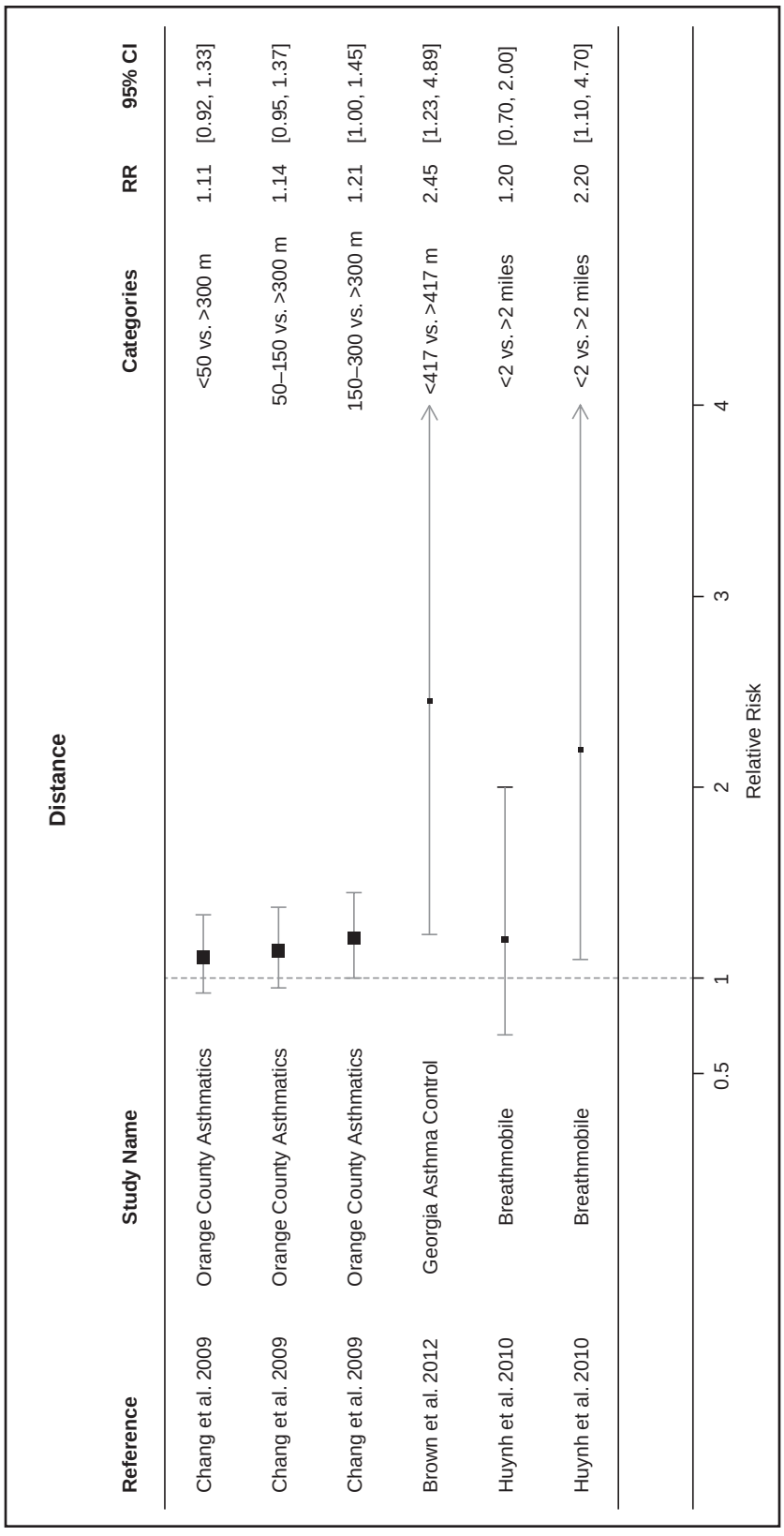

Figure 9.18. Associations between indirect traffic measures and asthma exacerbation in children. Huynh et al. 2010 was stratified by moderate to severe and intermittent mild asthma. Cook et al. 2011 and Değer et al. 2010 are not in the figure because estimates were log transformed. *Figure continues next page.*

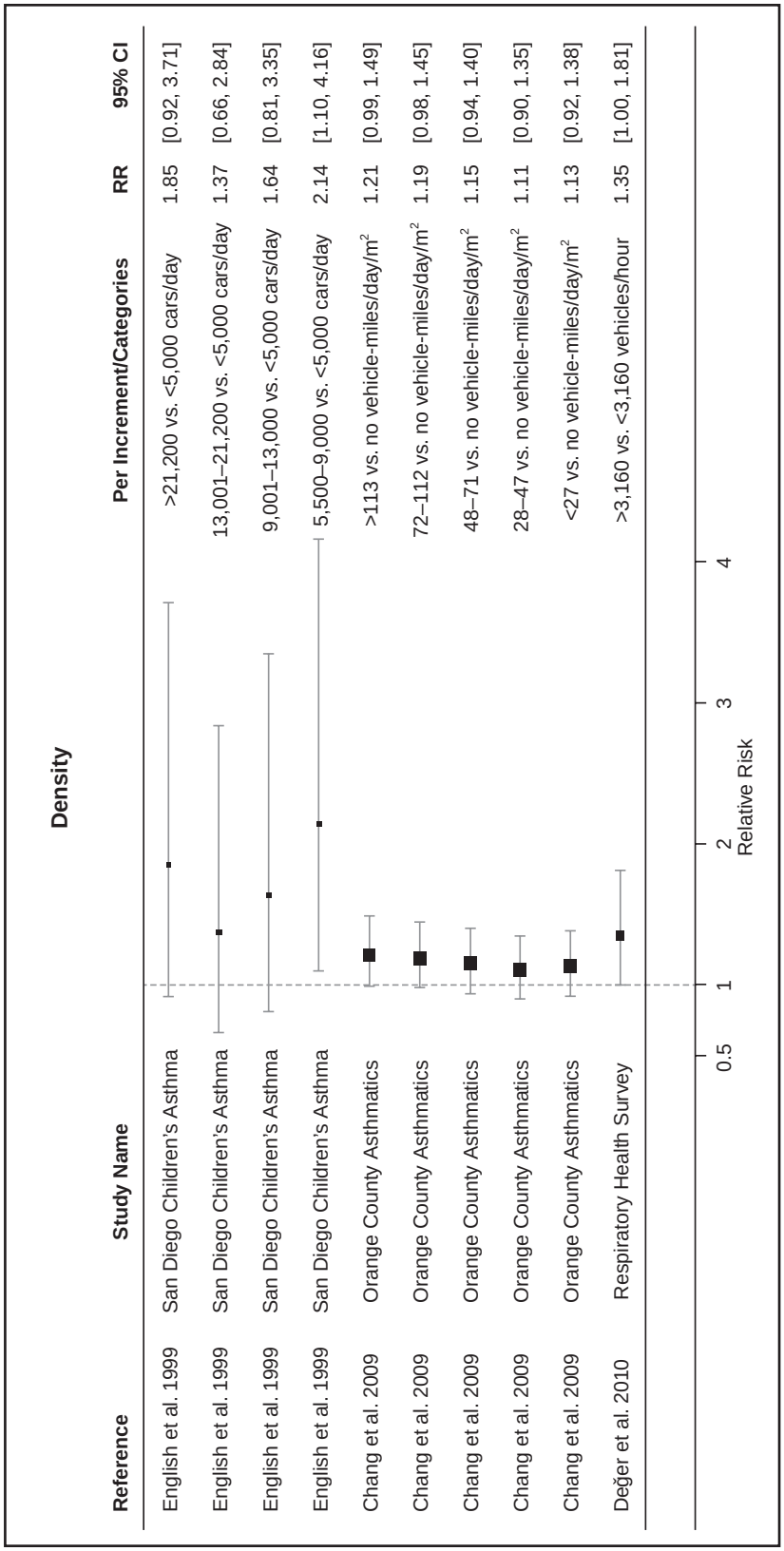

Figure 9.18. *(Continued).*

Table 9.15. Included in the Systematic Review for ALRI in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Sex	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Exposure Window	Effect Measure	Effect Estimate (95% CI)[b]	Increment
Aguilera 2013	INMA	Cohort	Multiple cities, Spain	2003–2010	2,199	Both	LUR	NO_2	17–38	Entire pregnancy	RR	**1.05 (0.98–1.12)**	10 µg/m^3
										Average first year		1.03 (0.95–1.11)	
								Benzene	0.8–1.9	Entire pregnancy		1.05 (0.96–1.14)	1 µg/m^3
										Average first year		1.02 (0.93–1.11)	
Esplugues 2011	INMA Valencia	Cohort	Valencia, Spain	2003–2006	706	Both	LUR	NO_2	36.8	Entire pregnancy	OR	1.18 (0.92–1.53)	10 µg/m^3
Fuertes 2014	ESCAPE, TRANSPHORM	Cohort	Multiple cities, multiple countries	1994–2010	14,961	Both	LUR	$PM_{2.5}$ Cu	2–13	Annual average at birth	OR	1.49 (0.90–2.46)	5 ng/m^3
								$PM_{2.5}$ Fe	44.1–252.8			1.50 (1.06–2.12)	100 ng/m^3
								$PM_{2.5}$ Zn	10.8–24.6			1.47 (1.11–1.94)	10 ng/m^3
Hirsch 1999	ISAAC Dresden	Cross sectional	Dresden, Germany	1995–1996	4,228	Both	Surface monitoring	NO_2	33.8	Annual mean	OR	**1.23 (1.11–1.38)**	10 µg/m^3
								CO	0.69			1.19 (1.11–1.27)	0.2 mg/m^3
								Benzene	4.0			1.11 (1.03–1.19)	1 µg/m^3
Janssen 2003	ISAAC Southwestern Netherlands	Cross sectional	Multiple cities, the Netherlands	1997–1998	2,037	Both	Surface monitoring	NO_2	34.8	Annual average current year	OR	**1.37 (0.60–3.12)**	17.6 µg/m^3
								BS	10.3			**1.32 (0.44–3.94)**	9.3 µg/m^3

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Table 9.15 (*Continued*). Included in the Systematic Review for ALRI in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Sex	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Exposure Window	Effect Measure	Effect Estimate (95% CI)[b]	Increment
Karr 2009	Georgia Air Basin Birth Cohort	Case-control	British Columbia, Canada	1999–2002	68,802	Both	LUR	NO_2	29.5	Cumulative average	OR	**1.04 (1.02–1.07)**	7.2 μg/m^3
								NO	33.3			1.01 (0.98–1.03)	16.4 μg/m^3
								BC	1.3			**0.99 (0.96–1.01)**	0.7 1×10^{-5}/m
								Traffic $PM_{2.5}$	4.7			1.00 (0.98–1.03)	2.9 μg/m^3
Kennedy 2018	KAPPA	Cohort	Atlanta, Georgia, United States	2000–2010	22,441	Both	Dispersion/CTM	NO_x	0.06	Average first year	HR	1.03 (1.02–1.05)	20 ppm
								CO	0.59			1.13 (1.03–1.24)	1 ppm
								Traffic $PM_{2.5}$	1.41			1.10 (1.05–1.14)	1 μg/m^3
Lindgren 2013	Scania Birth Cohort 05/11	Cohort	Scania including Malmö, Sweden	2005–2011	6,005	Both	Dispersion/CTM	NO_x	22	Annual average at birth	HR	0.5 (0.4–0.8)	>25 vs. <15 μg/m^3
												0.6 (0.5–0.8)	15–25 vs. <15 μg/m^3
										Cumulative average		0.7 (0.5–1.0)	>25 vs. <15 μg/m^3
												0.7 (0.5–0.8)	15–25 vs. <15 μg/m^3
Liu 2016	CCHH Shanghai	Cross sectional	Shanghai, China	2011–2012	3,244	Both	Surface monitoring	NO_2	55.4	Entire pregnancy	OR	**1.38 (1.13–1.67)**	20 μg/m^3
										Average first year		1.53 (1.29–1.81)	
										Cumulative average		1.50 (1.27–1.77)	

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Table 9.15 (*Continued*). Included in the Systematic Review for ALRI in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Sex	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Exposure Window	Effect Measure	Effect Estimate (95% CI)[b]	Increment
MacIntyre 2014	ESCAPE	Cohort	Multiple cities, multiple countries	1994–2011	16,208	Both	LUR	NO_2	12.4–43.2	Annual average at birth[c]	OR	**1.30 (1.02–1.65)**	10 μg/m^3
								NO_x	20.9–69.7			1.26 (1.04–1.52)	20 μg/m^3
								$PM_{2.5\ abs}$	0.6–2.5			**1.99 (1.44–2.75)**	1 1×10^{-5}/m
								PM_{10} mass	15.6–34.9			1.76 (1.00–3.09)	10 μg/m^3
								PM_{coarse} mass	6.5–15.7			1.24 (1.03–1.50)	5 μg/m^3
								$PM_{2.5}$ mass	8.1–18.8			2.58 (0.91–7.27)	5 μg/m^3
Madsen 2017	MoBa	Cohort	Multiple cities, Norway	1999–2011	13,116	Both	LUR	NO_2	13.6	Entire pregnancy	RR	0.99 (0.84–1.17) (age 0–6 months)	10 μg/m^3
					11,412							**1.05 (0.94–1.16)** (age 6–18 months)	
Morgen-stern 2007	GINI, LISA: Munich	Cohort	Multiple cities, Germany	1995–2001	3,021	Both	LUR	NO_2	35.3	Annual average at birth	OR	1.06 (0.89–1.26) (age 1)	5.7 μg/m^3
												1.08 (0.83–1.42) (age 2)	
								$PM_{2.5\ abs}$	1.7			1.03 (0.86–1.24) (age 1)	0.22 1×10^{-5}/m

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Table 9.15 (*Continued*). Included in the Systematic Review for ALRI in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Sex	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Exposure Window	Effect Measure	Effect Estimate (95% CI)[b]	Increment
												1.05 (0.79–1.27) (age 2)	
								$PM_{2.5}$ mass	12.8			1.05 (0.88–1.22) (age 1)	1.04 μg/m^3
												1.09 (0.94–1.27) (age 2)	
Pedersen 2013	EDEN	Cohort	Nancy and Poitiers, France	2003–2007	879	Both	Dispersion/ CTM	NO_2	18.8	Entire pregnancy	OR	**0.95 (0.75–1.21)**	10 μg/m^3
								PM_{10} mass	20.3			0.62 (0.32–1.20)	10 μg/m^3
Pershagen 1995	St Göran's Infant Respiratory	Case-control	Stockholm, Sweden	1986–1988	546	Female	Dispersion/ CTM	NO_2	54	Cumulative average	RR	2.7 (1.1–6.8)	>70 vs. <35 μg/m^3
												1.5 (0.6–3.6)	46–70 vs. <35 μg/m^3
												1.7 (0.6–4.4)	35–45 vs. <35 μg/m^3
						Male						0.7 (0.4–1.3)	>70 vs. <35 μg/m^3
												1.0 (0.5–1.8)	46–70 vs. <35 μg/m^3
												1.7 (0.9–3.3)	35–45 vs. <35 μg/m^3
Ranzi 2014	GASPII	Cohort	Rome, Italy	2003–2011	672	Both	LUR	NO_2	37.88	Annual average at birth	OR	**0.87 (0.69–1.08)**	10 μg/m^3
										Cumulative average		0.95 (0.77–1.18)	

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Table 9.15 (*Continued*). Included in the Systematic Review for ALRI in Children—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Sex	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Exposure Window	Effect Measure	Effect Estimate (95% CI)[b]	Increment
Svendsen 2012	El Paso Children's Health	Cross sectional	El Paso and Texas, United States	2001	4,231	Both	LUR	NO_2	20–27	Average recent	OR	**1.80 (1.10–2.93)** (Upland schools)[d] **0.87 (0.54–1.40)** (Valley schools)[d]	10 ppb
Zhang 2002	Chinese 4-City School Survey	Cross sectional	Multiple cities, China	1993–1996	7,392	Both	Surface monitoring	NO_x	90	At baseline	OR	0.90 (0.35–2.29)	64 µg/m^3

BC = black carbon; BS = black smoke; HR = hazard ratio; OR = odds ratio; RR = relative risk.

[a] Units are in the increment column.

[b] **Bold** indicates the effect estimate was included in the meta-analysis.

[c] Not extrapolated.

[d] Estimates were combined by a fixed effect meta-analysis before entering the random-effects model.

Table 9.16. Included in the Systematic Review for ALRI in Children—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
Cakmak 2012	Windsor Children's Health 05	Cross sectional	Windsor, Ontario, Canada	2005	1,570	Density	OR	1.12 (0.99–1.28)	33,787.5 vehicles/day
Janssen 2003	ISAAC Southwestern Netherlands	Cross sectional	Multiple cities, the Netherlands	1997–1998	2,037	Distance	OR	1.21 (0.87–1.68)	100 vs. 400 m
Lee 2018b	CHEER	Cohort	Multiple cities, South Korea	2005–2008	2,627	Distance	OR	1.12 (0.71–1.79)	<75 vs. >700 m
								1.17 (0.81–1.68)	75–700 vs. >700 m
Lindgren 2013	Scania Birth Cohort 05/11	Cohort	Scania including Malmö, Sweden	2005–2011	6,007	Density	HR	0.7 (0.6–0.9)	<8,640 vs. >8,640 vehicles/day
MacIntyre 2014	ESCAPE	Cohort	Multiple cities, multiple countries	1994–2011	16,208	Density	OR	1.21 (1.09–1.34)	4,000 vehicle-km/day
Morgenstern 2007	GINI, LISA: Munich	Cohort	Multiple cities, Germany	1995–2001	3,021	Distance	OR	1.03 (0.86–1.26) (age 1)	<50 vs. >50 m
								1.15 (0.87–1.53) (age 2)	<50 vs. >50 m
Ranzi 2014	GASPII	Cohort	Rome, Italy	2003–2011	672	Distance	OR	1.03 (0.72–1.48)	<86.1 vs. >86.1 m
Rice 2015	VIVA	Cohort	Boston, Massachusetts, United States	1999–2005	1,263	Density	RR	1.05 (0.98–1.13)	1,485 vehicle-km/day
						Distance		1.38 (1.11–1.63)	<100 vs. >1,000 m
van Vliet 1997	South Holland Respiratory Survey	Cross sectional	Multiple cities, the Netherlands	1995	878	Density	OR	0.76 (0.28–2.08)	High vs. low car volume
								1.43 (0.52–3.91)	High vs. low truck volume
						Distance		0.99 (0.39–2.52)	<100 vs. 100–1,000 m
Yang 2002	Kaohsiung Respiratory Survey	Cross sectional	Kaohsiung, Taiwan	1999–2000	6,190	Distance	OR	0.99 (0.88–1.12)	150 vs. 1,500 m

HR = hazard ratio; OR = odds ratio; RR = relative risk.

[a] All studies included male and female participants.

pregnancy or exposure to environmental tobacco smoke), other indoor exposures such as presence of gas stoves and mold, and indicators of individual SES. As is common in childhood respiratory health studies, risk factors such as maternal or family history of respiratory disease or allergy, siblings, attendance at daycare, ethnicity, pets, age, season of birth, sex, and physical activity or body mass index (BMI) or obesity were also considered in some of the analyses. Critically, some aspects of environmental tobacco smoke exposure and SES were included in all studies, even those relying on

administrative data. Two of the publications (Fuertes et al. 2014; MacIntyre et al. 2014) examined the data from multiple cohorts using a common exposure model and then reported the combined results among the cohorts.

The studies differed substantially in sample size from about 550 in a small study in Stockholm, Sweden (Pershagen et al. 1995) to a large retrospective, administrative cohort (N = 68,802) in British Columbia, Canada (Karr et al. 2009). The majority of them were conducted in North America and Europe, although a small number were from Asia. Related to this range of geographic locations, mean exposures covered a large range. In terms of NO_2, mean concentrations ranged from 14 μg/m³ in Norway (Madsen et al. 2017) to 55 μg/m³ in Shanghai (Liu et al. 2016). The range of mean pollutant exposure for NO_2 across the 10 cohorts in the ESCAPE multicohort analysis was 12 to 43 μg/m³ (MacIntyre et al. 2014). All studies were performed in a general population of children, although some were restricted by exposure, for example to children attending schools within 1,000 meters of a motorway (Janssen et al. 2003) or attending schools and living within a certain distance from available monitoring sites (Liu et al. 2016). The period over which the incidence of infections was assessed varied considerably across the studies. In general, in the cross-sectional studies involving recruitment in schools the time periods considered were longer; for example, Zhang and colleagues (2002) included children between 5 and 16 years in a 4-year period (1993–1996). Follow-up periods tended to focus on shorter periods among the birth cohorts; largely from the first year of life to the first few years of life. In some cases, multiple time windows for follow-up were analyzed separately, such as from 0–1 years and 1–2 years.

A range of exposure-assessment methods was applied including LUR, dispersion models, and monitoring at nearby routine monitoring sites or using measurements specifically undertaken for the study. The majority of the studies (N = 13) included NO_2. About half of them independently evaluated the associations between ALRI and several of the traffic-related pollutants), allowing for some assessment of consistency among the various traffic-related air pollutants available.

9.3.5.2 Primary Meta-analysis

A summary of the meta-analysis results for the incidence of ALRI in children is shown in Figure 9.19. 11 of the 13 studies using NO_2 as the exposure indicator were included in the meta-analysis. One small case-control study on wheezing bronchitis was excluded from the analysis, because results were available only for categories of exposure to NO_2 (Pershagen at al. 1995). The other study (Esplugues et al. 2011) was excluded because the population it reported on was also part of a larger study that used the same exposure-assessment method (Aguilera et al. 2013). As described in Chapter 5, the Panel decided to be inclusive—thus some studies (Aguilera

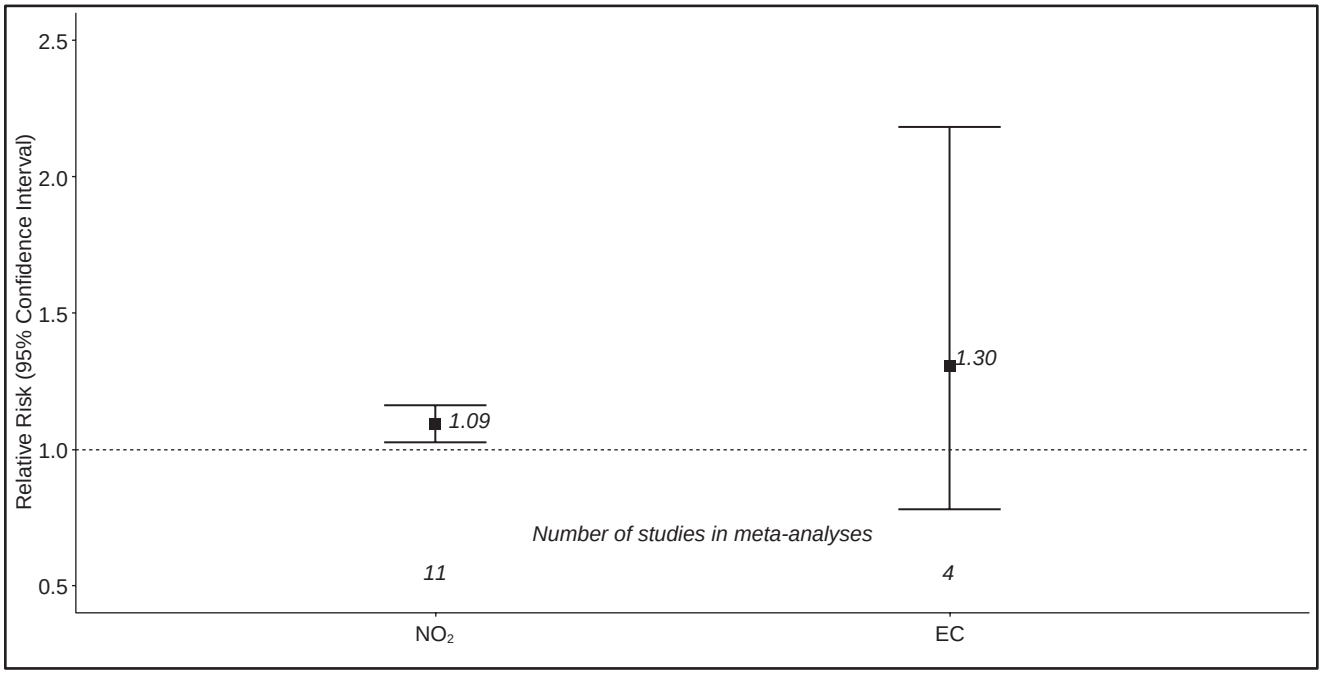

Figure 9.19. Meta-analysis of associations between traffic-related air pollutants and ALRI in children. The following increments were used: 10 μg/m³ for NO_2 and 1 μg/m³ for EC. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

et al. 2013; Morgenstern et al. 2007; Ranzi et al. 2014) were also included in the meta-analyses, even though the same cohorts were also analyzed in the ESCAPE multicohort analysis (MacIntyre et al. 2014), because they used different exposure-assessment methods. All four of the studies that used some measures of EC have been included in the summary estimate in Figure 9.19.

For both NO_2 and EC, the summary estimate was found to be positive. In terms of NO_2, the meta-analytic combination of the 11 qualifying studies on ALRI (7 based on incidence cases and 4 cross-sectional), shown in Figure 9.20 yielded an effect size of 1.09 (CI: 1.03–1.16) per 10-μg/m^3 of long-term NO_2 exposure. In the NO_2 meta-analysis, five of the studies each received ≥12% of the weight in the meta-analysis, with one study (Karr et al. 2009) receiving 22.5% of the weight. The association with NO_2 was positive in each, with confidence intervals above unity in three of them. Among the other six studies, four found positive associations between ALRI incidence and NO_2 and two found RRs less than one. The confidence intervals included unity in all but one of the studies, which itself was an analysis of 10 separate birth cohorts in a multicenter study from different European cities that included a total of 16,208 children (MacIntyre et al. 2014). The available statistical measures indicate relatively low heterogeneity (e.g., I^2 = 45%) (Figure 9.20).

The four studies that reported associations with EC are shown in Figure 9.21. The summary estimate is 1.30 (95% CI: 0.78–2.18) per 1-μg/m^3 of EC. The wide confidence intervals are due to the smaller number of studies and greater variability among these studies' results. Among the four studies based on EC exposure there was high heterogeneity (I^2 = 84%). Three of the four studies reported positive associations, whereas the fourth study (Karr et al. 2009) essentially reported null findings (RR = 0.99; 0.96–1.02).

There was an insufficient number of studies using other indicators of TRAP exposure to conduct a meta-analysis. However, the overwhelming majority of the reported effect estimates for ALRI in children were positive (Table 9.15). Only two of these studies (Lindgren et al. 2013; Zhang et al. 2002) found negative associations between TRAP exposure and ALRI in children.

9.3.5.3 Additional Meta-analyses

The more recent studies (i.e., published after 2008) tended to have smaller effect sizes (1.06; 95% CI: 1.02–1.11) than those published prior to 2008 (1.22; 1.16–1.29), as shown in Figure 9.22. Those studies published after 2008 also exhibited a slightly smaller range of effect sizes compared with the entire group of studies; consistent with this, the I^2 statistic decreased to 38% among studies published after 2008 from 45% for the whole set of studies.

Only three of the studies were conducted outside of Europe, with two in North America and one in Asia. Stratifying by these regions did not reduce heterogeneity (I^2 = 49% among those in Europe), but did differentiate effect sizes, which were slightly smaller in the two North America studies and larger in the one study from Asia (Figure 9.23). Also, grouping by study region led to confidence intervals crossing unity in the summary estimate based on European studies (1.08; 95% CI 0.97–1.20).

Stratifying the NO_2 studies according to traffic specificity resulted in two distinct and more precise (i.e., less heterogeneity) summary estimates (Figure 9.24). Although both estimates were positive with confidence intervals above unity, the summary estimate was smaller among the high specificity studies (1.05; 95% CI: 1.02–1.09) compared with those in the moderate specificity group (1.20; 1.12–1.28). On the other hand, comparing effect sizes and heterogeneity according to study design revealed that the associations were consistently larger among the cross-sectional studies (1.19; 1.12–1.26) compared with cohort studies (for cohort studies the RR was 1.05; 0.97–1.13). Within a given study design, the heterogeneity was smaller than for the analyses including all study designs (Figure 9.25). It is important to note is that there is considerable overlap in those studies classified with moderate traffic specificity and being based on a cross-sectional design (all the three studies with moderate traffic specificity were cross-sectional studies), making it difficult to determine which of the characteristics (traffic specificity or study design) led to larger effect sizes.

Another factor that may contribute to heterogeneity is a difference among the exposure time windows considered (i.e., prenatal and postnatal). Although there is potential for different exposure windows (e.g., prenatal or postnatal) to vary in their contributions to ALRI risk, there were not enough studies to separate and compare associations, and all studies on early life exposures were combined in the main meta-analysis. In the primary meta-analysis, the order of preference was to include exposure during pregnancy if available and, if not, then select the window closest to birth date followed by later time windows (e.g., average of first year, recent years, or times nearest the ARLI diagnosis). Given that it is not certain which exposure window is most biologically relevant in increasing ALRI risk, a sensitivity analysis was conducted by repeating the meta-analysis with the opposite priority order to identify the preferred exposure window (i.e., recent year's exposures were used if available, then progressing toward inclusion of the exposure earlier in life, ending with pregnancy windows if that was all that was available). In this sensitivity analysis the effect estimate included in the meta-analysis changed for five of the 11 studies (see Appendix Figure 9B-18) and consequently, the summary estimate increased slightly from 1.09 (95% CI: 1.03–1.16) to 1.10 (1.03–1.17) for NO_2. Heterogeneity increased more substantially; I^2 increased from 45% from 56%, suggesting that some of the heterogeneity in the primary meta-analysis could be due to variability in exposure window among studies. Note that results are difficult to interpret

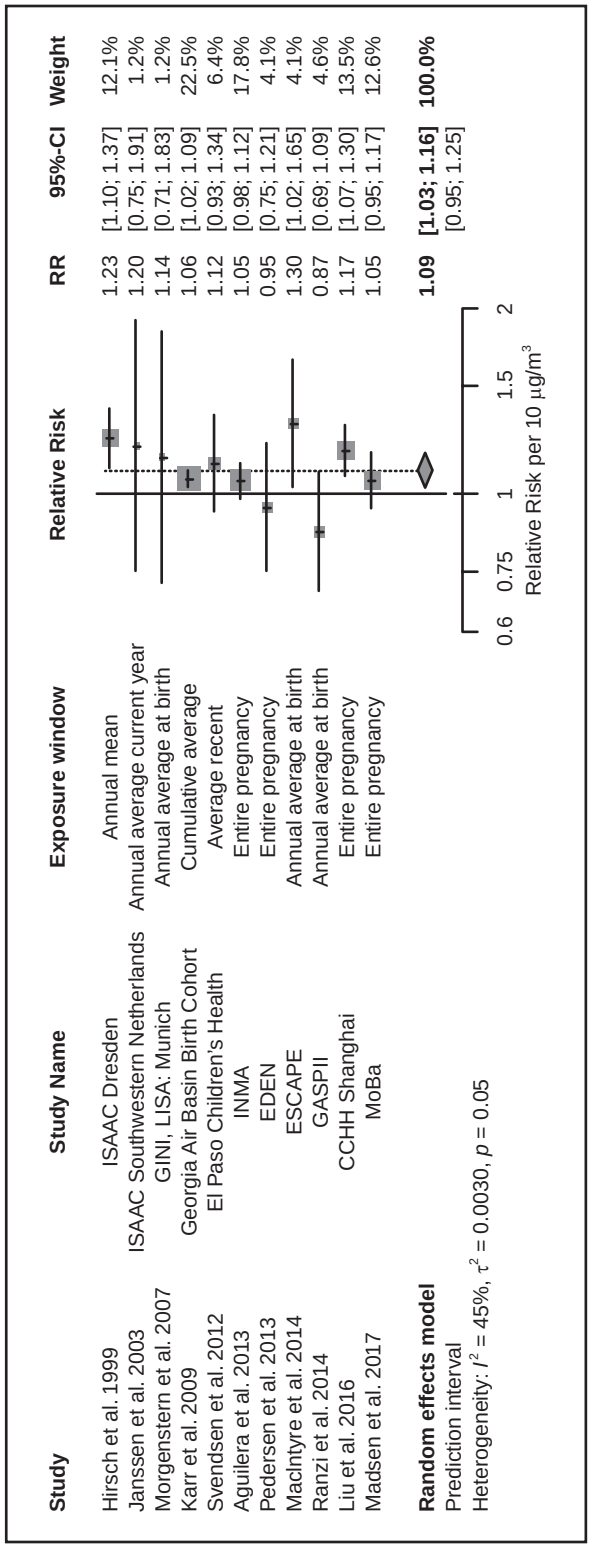

Figure 9.20. Association between NO_2 and ALRI in children: meta-analysis.

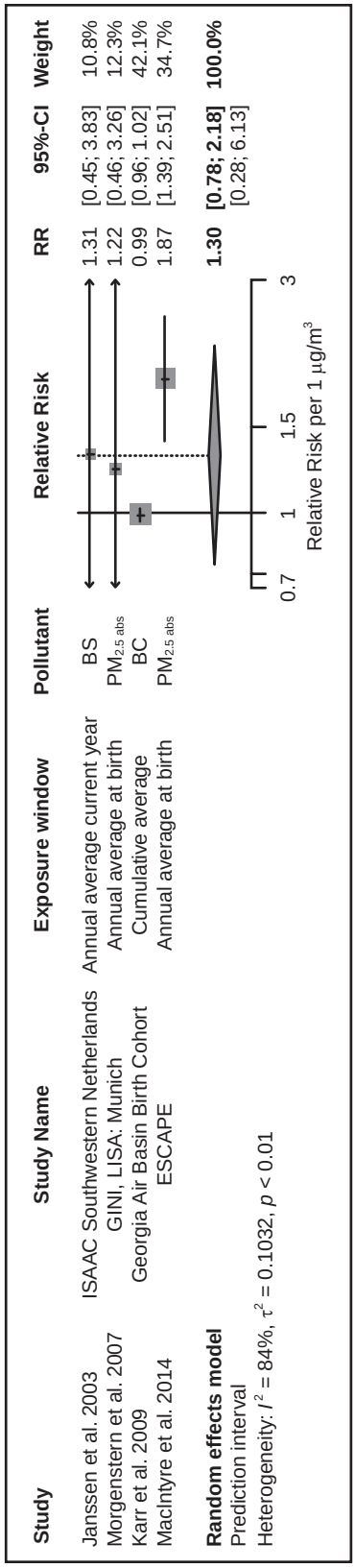

Figure 9.21. Association between EC and ALRI in children: meta-analysis.

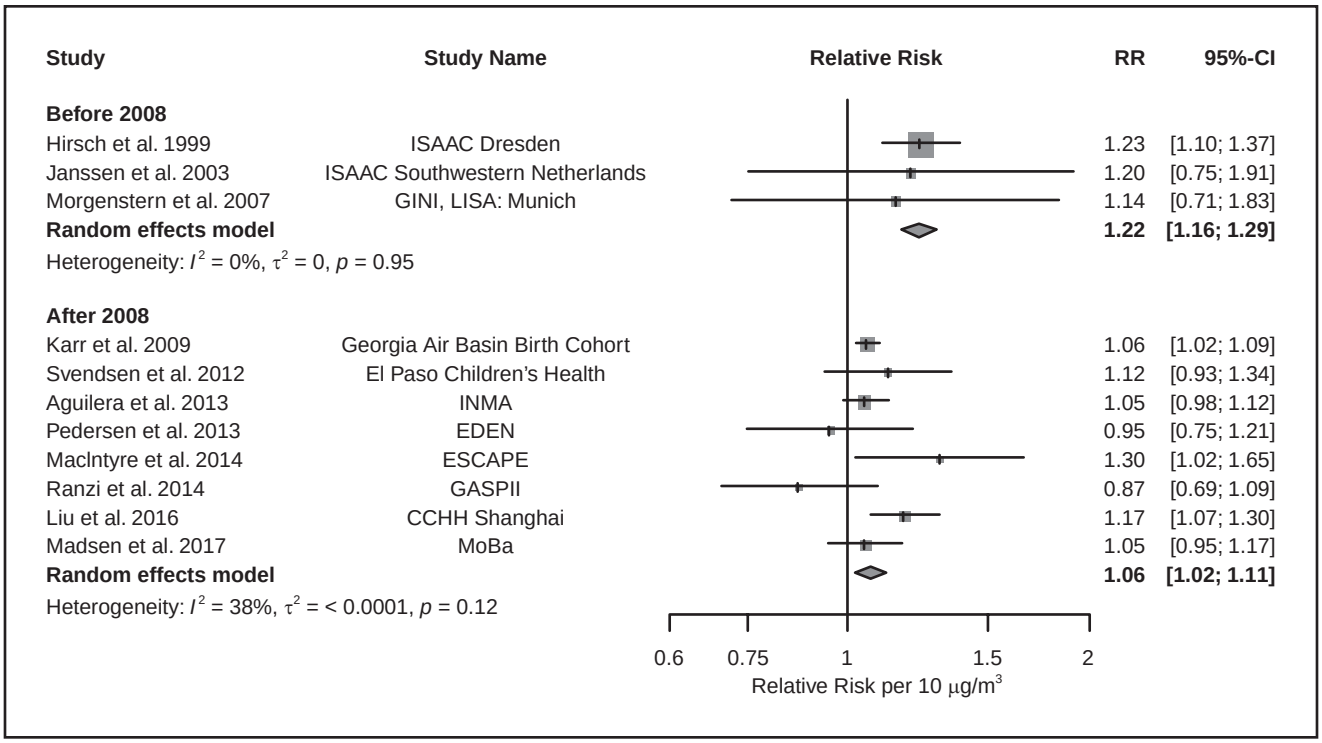

Figure 9.22. Association between NO_2 and ALRI in children: meta-analysis by publication year.

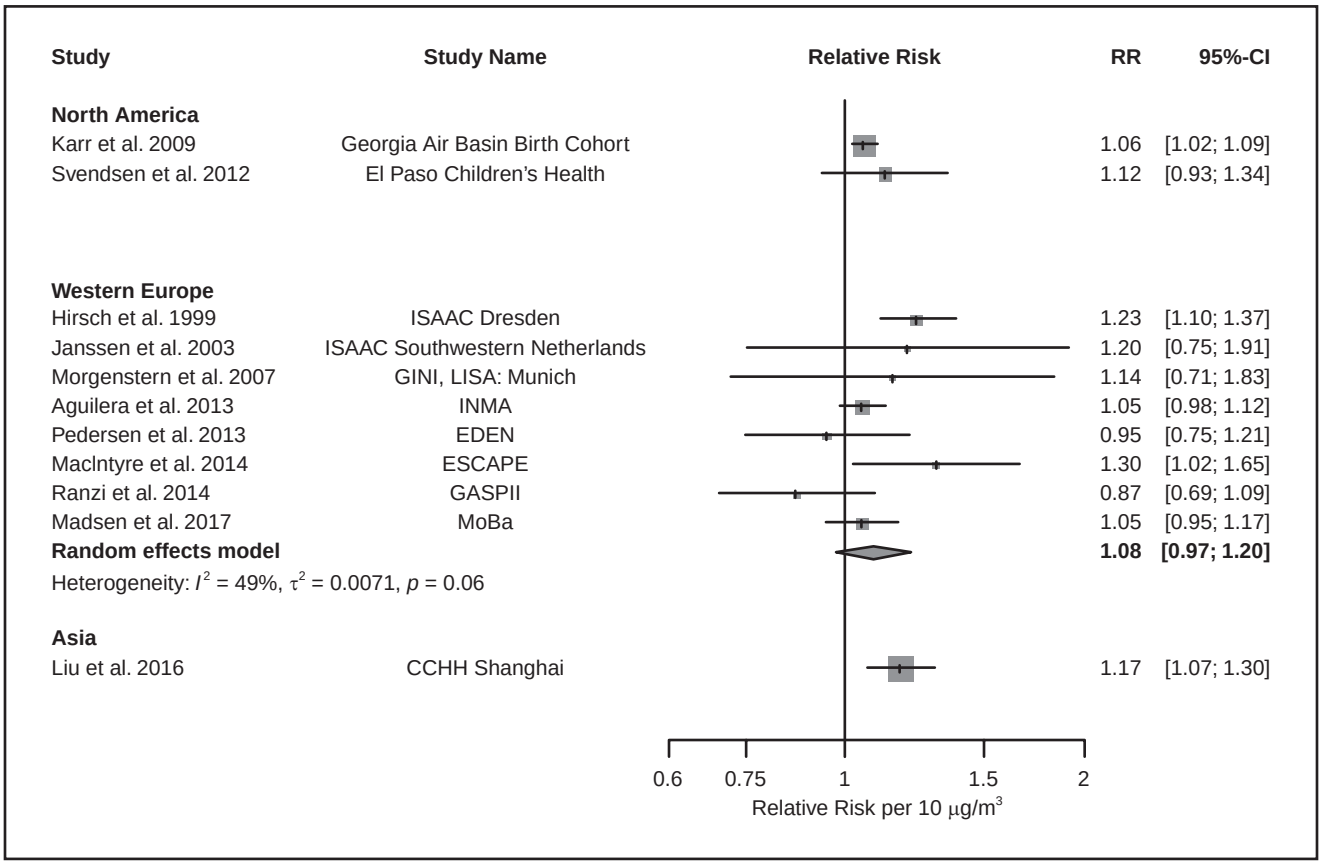

Figure 9.23. Association between NO_2 and ALRI in children: meta-analysis by region.

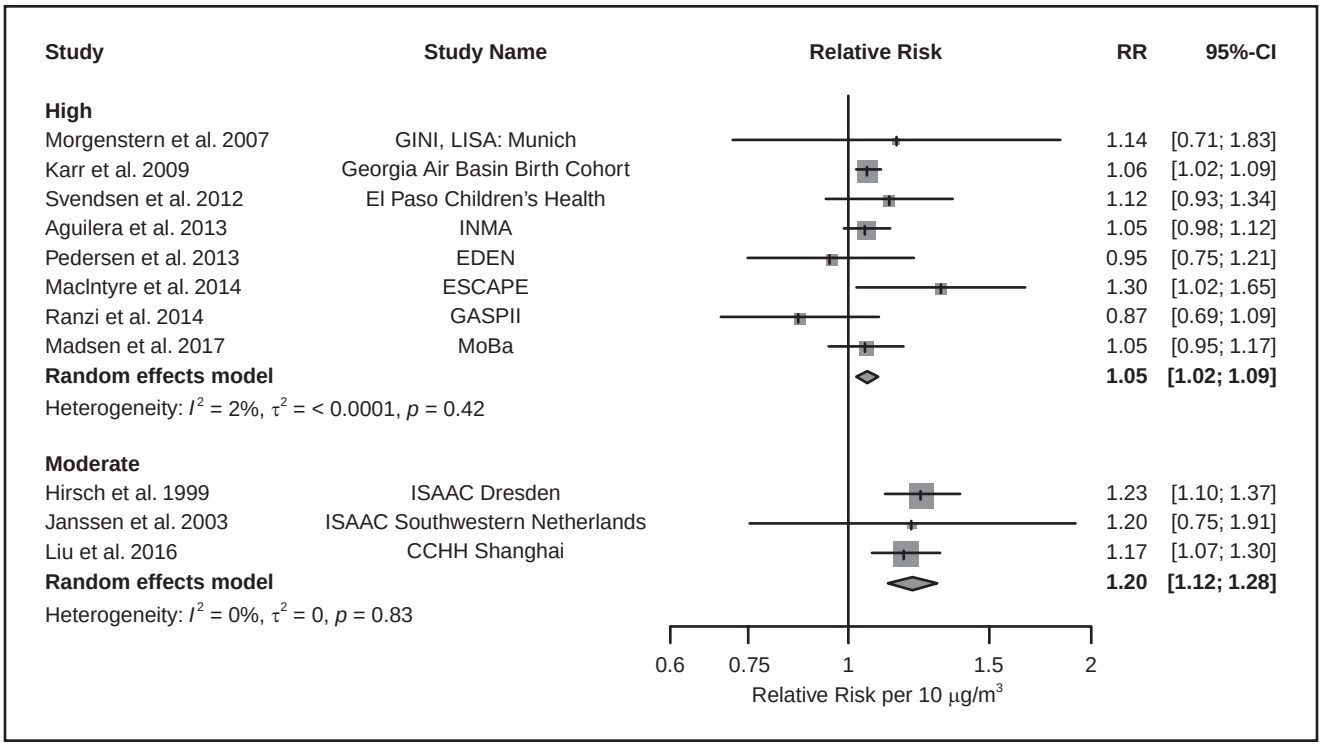

Figure 9.24. Association between NO_2 and ALRI in children: meta-analysis by traffic specificity.

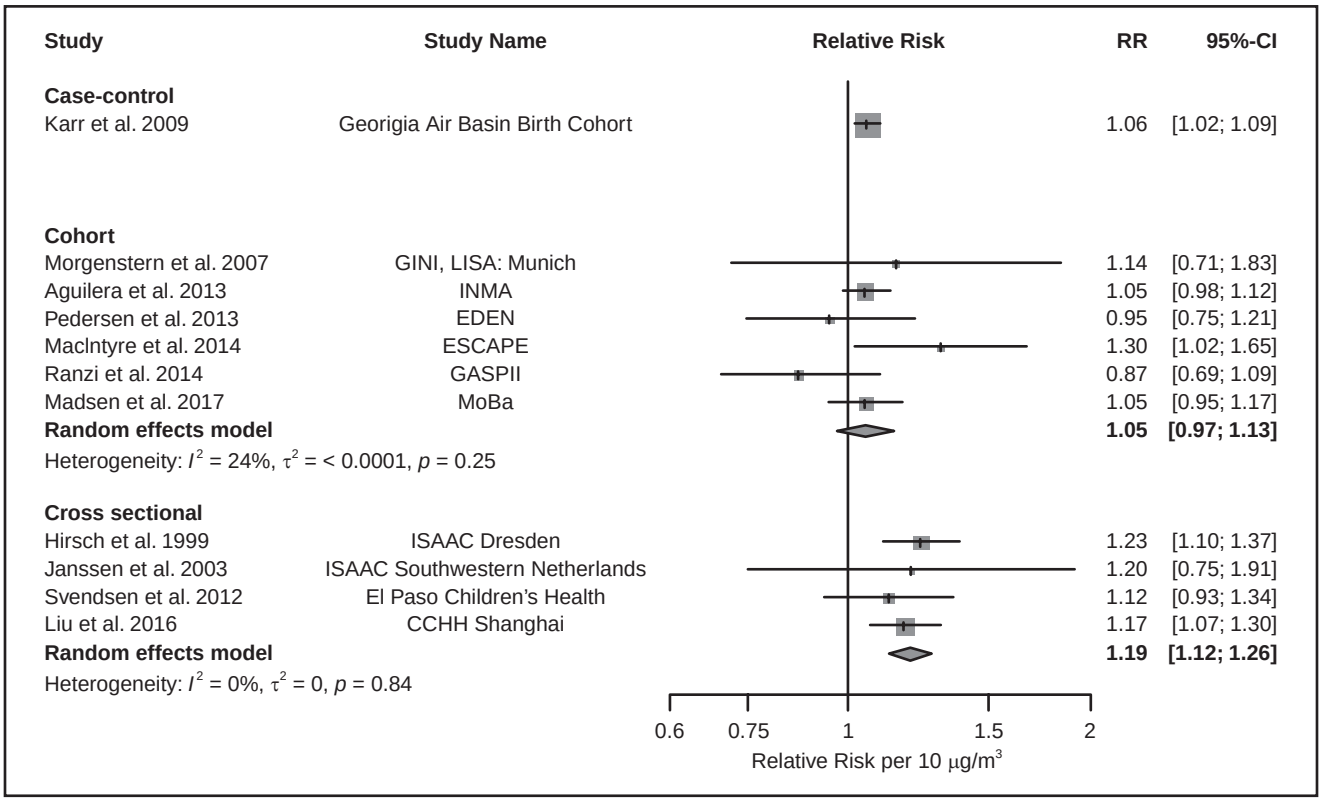

Figure 9.25. Association between NO_2 and ALRI in children: meta-analysis by study design.

because the exposures tend to be highly correlated between prenatal and postnatal periods unless residential address changes between the times and exposures are sufficiently resolved in terms of time of move and exposure differences within the cohorts involved. Therefore, the exposure window of most importance cannot be confidently ascertained from these results.

Two other underlying sources of heterogeneity to be aware of are (1) merging of infection type (e.g., bronchiolitis, pneumonia) and (2) merging of the age at which the incidence of infection was assessed. However, there were not enough studies to evaluate these possible causes of differences in effect size and hence heterogeneity.

9.3.5.4 Associations with Indirect Traffic Measures

Ten studies made use of indirect measures to classify TRAP exposure, and most point toward a positive association with ALRI (Table 9.16). Five of those studies involved only indirect measures of exposure to TRAP. Six studies were based on cohorts, and the other four were cross-sectional studies; all controlled for important potential confounders. The largest study (N = 16,208 participants, MacIntyre et al. 2014) combined separate effect estimates from multiple European cohorts and was one of only two with both a positive association and confidence intervals above unity (1.21; 95% CI: 1.09, 1.34). The other was also a cohort study examining Project VIVA participants in Boston comparing children living within 100 meters of a major road to those living >1,000 meters away (1.38; 1.11–1.63). Only two studies—both relatively large (N > 6,000)—yielded null or negative associations. These were a relatively recent cohort study in Sweden that reported a negative association (Lindgren et al. 2013) and a cross-sectional analysis in Taiwan that essentially reported no association (Yang et al. 2002). The remainder of the studies found positive associations but with confidence intervals that included unity. Of note are two separate follow-ups in the German GINI and LISA cohorts, Morgenstern and colleagues (2007), where they observed a positive association at both age 1 and age 2 with the stronger effect at the later time point, albeit imprecise.

9.3.5.5 Narrative Assessment

Twenty-seven studies were identified that met the Panel's inclusion criteria with a large majority done in Europe or North America. Most of these studies had detailed individual-level information on potential confounding factors and were well designed, including a considerable number of longitudinal cohorts (16) followed by several cross-sectional analyses (9 studies), and 2 case-control studies (one of which was based on administrative data). As ALRIs are expected to resolve and reoccur independently, there tends to be good temporal alignment between the measures of long-term exposure to TRAP (e.g., home address) and ascertainment of the outcomes, which were usually assessed through questionnaires. However, the period over which the incidence of infections was assessed tended to be longer among the cross-sectional studies, particularly the large school-based studies conducted in China.

The 27 studies assessed for ALRIs were based on a range of exposure indicators for TRAP; in some studies more than one indicator was evaluated. NO_2 from LUR or dispersion model estimates was the most commonly used indicator (10 studies) and indirect traffic measures (10 studies). Beyond EC (four studies), the other exposure indicators considered among the different studies were NO_x, NO, CO, $PM_{2.5}$, PM_{10}, PM_{coarse}, benzene, and Cu, Fe, and Zn in $PM_{2.5}$. In total, 69 separate tests for an association were reported among the 27 studies; 50 of those estimates (72%) were positive, although the number of these where the 95% CI excluded unity was considerably smaller. Five studies assessed by the Panel included three or more exposure indicators and each consistently found statistically significant, positive results across the associations examined. Thus, among a range of study designs, in different geographic locations and using different ways to characterize a TRAP exposure gradient, the evidence consistently suggested that there is an association with ALRI in children.

It was only possible to conduct a meta-analysis among the NO_2 studies and the four studies that used EC as the TRAP exposure indicator. The summary estimate was positive in each of these; 1.09 and 1.30 for NO_2 and EC, respectively, although for the latter the meta-analytic estimate was imprecise. In summary, the dominance of positive associations overall, the consistency in associations seen in the meta-analysis for NO_2, and the positive associations reported using indirect traffic measures, strongly points toward an association between TRAP and an increased risk of ALRI in children. Furthermore, as it is unlikely that any potential biases (assessed formally in a later section) have affected all estimates of association in the same direction in diverse populations from different regions, the Panel concluded that the evidence in the presence of an association between long-term exposure to TRAP and ALRI in children is high.

9.3.5.6 Risk of Bias Assessment

Table 9.17 shows an overview of the results of the risk of bias assessment for exposure–outcome pairs of studies on children's ALRI that were meta-analyzed; Appendix Table 9B-4 presents the assessment for each individual study. Notably, a large majority of the estimates were rated low risk of bias and there were no studies where risk of bias was rated high.

Blinding of outcome measurements was the domain most often reported for moderate risk of bias (13 of the 15 exposure–outcome pairs). Risk of bias due to missing data and confounding were the categories with the next largest number

Table 9.17. Summary of Risk of Bias Rating for Studies on ALRI in Children

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	10	1	0	14	1	0
	Validity of measuring of confounding factors	10	1	0	13	2	0
	Control in analysis	11	0	0	15	0	0
	Overall	9	2	0	12	3	0
2. Selection bias	Selection of participants into the study	10	1	0	14	1	0
3. Exposure assessment	Methods used for exposure assessment	11	0	0	15	0	0
	Exposure measurement methods comparable across the range of exposure	11	0	0	15	0	0
	Change in exposure status	10	1	0	13	2	0
	Overall	10	1	0	13	2	0
4. Outcome measurements	Blinding of outcome measurements	1	10	0	2	13	0
	Validity of outcome measurements	11	0	0	15	0	0
	Outcome measurements	11	0	0	15	0	0
	Overall	1	10	0	2	13	0
5. Missing data	Missing data on outcome measures	9	2	0	13	2	0
	Missing data on exposures	10	1	0	14	1	0
	Overall	8	3	0	12	3	0
6. Selective reporting	Authors reported a priori primary and secondary study aims	11	0	0	15	0	0

of pairs with a moderate risk of bias, but this amounted to only 3 of the 15 exposure–outcome pairs in each category. For confounding, two were due to the validity of the method for measuring the confounders and one was due to the lack of adjusting for an important potential confounder. For missing data, two were due to missing outcome measures data and one to missing exposure data.

9.3.5.7 Confidence Assessment of the Body of Evidence

Table 9.18 provides the Panel's confidence assessment. The table includes the pollutants with three or more studies for which a meta-analysis was conducted (NO_2 and EC). The available studies for meta-analysis were based on a range of study designs. More than half of the studies of ALRI and NO_2 were cohort studies (six), one was a case-control study, and the four remaining studies were from cross-sectional studies. For EC, three of the four ALRI studies were cohorts or case-control studies. Thus, the initial rating was moderate for both NO_2 and EC.

Factors That Reduce Confidence The overview of the risk of bias ratings for each ALRI in children exposure–outcome pair that was meta-analyzed is presented in Table 9.17. No changes in confidence rating from the initial moderate rating can be justified given there were no exposure–outcome pairs with a high risk of bias rating, an important finding for the evaluation.

The Panel did not downgrade associations of ALRI in children for unexplained inconsistency. Given the limited number of studies available for meta-analysis, possible explanations for heterogeneity can be assessed only for NO_2. Three factors seem to further reduce heterogeneity: traffic specificity, study design, and publication year. In addition, some of the heterogeneity in the primary meta-analysis of ALRI in children and NO_2 could be due to the variability in exposure window among studies. Given the dominance of positive associations and the ability to explain some of the heterogeneity, the evidence clearly suggests that no downgrading due to inconsistency is warranted for NO_2. Heterogeneity was

Table 9.18. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and ALRI in Children[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort, cross-sectional, case-control	+++ (N = 11)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Majority was of cohort and case-control design initially rated as moderate.	None were high RoB.	Low heterogeneity (I^2 = 45%). Plausible reasons to explain inconsistency.	Sample size met, and confidence interval does not include unity.	No evidence found.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Majority of studies were in Europe. Although results in other regions were also positive, differences in study design obscures determination of consistency across populations.	
EC	Cohort, cross-sectional, case-control	+++ (N = 4)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Majority was of cohort and case-control design initially rated as moderate.	None were high RoB.	High heterogeneity (I^2 = 84%) mostly due to magnitude not direction.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor indirectness and the upgrading factor large magnitude of effect were not considered further.

high for EC (I^2 = 84%) but was mostly due to magnitude not direction of effect estimates (three of four were positive, and one null). No downgrade was warranted for high heterogeneity in EC estimates as it could be explained by different time windows of exposures across the four studies and by the large positive association of the ESCAPE study (MacIntyre et al. 2014); there were too few studies to meaningfully investigate the reasons behind the variations among studies.

Regarding imprecision, the Panel downgraded the ALRI evidence only for EC, and not for NO_2. For both EC and NO_2, the sample size was larger than the specified needed minimum sample size in the protocol. For NO_2, the confidence interval for its summary estimate was above unity (95% CI: 1.03–1.16). The confidence interval for EC—albeit among only four studies—was much wider and included unity (0.78–2.18); therefore, a downgrade was applied for EC.

For NO_2, there were 11 studies, which is just enough to produce a funnel plot and conduct the Egger test to evaluate publication bias (Appendix Figure 9B-19). Neither of these suggested asymmetry, which would be a mark of potential for publication bias. Therefore, no downgrade of the evidence due to publication bias was be justified.

Factors That Increase Confidence For NO_2 and EC, none of the studies provided information of the shape of the exposure–response function. Therefore, no upgrade was justified. In the current body of evidence, the Panel found no clear indication that residual confounding or other factors are likely to lead to an underestimation of the associations. An upgrade was thus not considered appropriate.

The Panel did not upgrade associations for consistency across geographic regions, populations, or study period. For NO_2, positive associations were found in each geographical area considered, although few effect estimates were reported outside of Europe, with only two in North America and one in China. Consideration of the difference in the associations found in studies published before and after 2008 revealed that over time the finding of positive associations is quite consistent. However, the summary estimate was larger in the three studies before 2008 (RR: 1.22; CI: 1.16–1.29), compared with the summary estimate of the eight studies published after 2008 (RR: 1.06; CI: 1.02–1.11). Therefore, no upgrade of the evidence before consistency was justified for NO_2. There were not enough studies to explore this factor for EC.

Evaluation of Confidence for Combined Measures of TRAP Table 9.18 has two assessments of the level of confidence in the body of evidence for ALRI incidence, based on NO_2 and EC. For NO_2 the assessment was moderate confidence, while for EC confidence in the body of evidence was low. The low confidence assessment for EC was motivated by imprecision among the small number of available studies. However, the positive summary estimate for EC lends some additional support to the NO_2 findings that TRAP does increase the risk of children developing an ALRI. Therefore, based on the modified OHAT assessment, the Panel's overall confidence assessment in the quality of the body of evidence for TRAP and ALRI in children was moderate, which was the same as for NO_2.

9.3.5.8 Overall Confidence Assessment

The Panel found a moderate to high level of confidence in the evidence for an association of long-term exposure to TRAP with ALRI in children based on the narrative evaluation (high) and the modified OHAT assessment (moderate).

9.4 RESPIRATORY OUTCOMES IN ADULTS

The systematic review will consider the following respiratory outcomes for adults: asthma onset, prevalence of asthma ever, prevalence of active asthma, asthma exacerbations, ALRI, and COPD (incidence, prevalence, and severity). Results for wheeze ever and active wheeze are reported in Appendix 9A.

9.4.1 ASTHMA ONSET

9.4.1.1 Study Selection and Description

A total of nine studies reported associations between TRAP and asthma onset in adults (Table 9.19). Most studies were conducted in Europe (N = 7); only 1 study was conducted in Canada and 1 in Australia. All studies but one (Modig et al. 2006) were published after 2008, the end of the search date for the 2010 HEI Traffic Review.

All studies were based on a cohort design except for a case-control investigation also based on incident cases (Modig et al. 2006). As with asthma onset in children, there were traditional cohorts based on information collected from the individuals in the study and cohorts based exclusively on administrative health data. Cohort studies differed substantially in sample size, ranging from a few thousand to more than one million participants for the cohort study in Canada based on administrative data with limited information on the individual data (Weichenthal et al. 2017). All the other traditional cohorts had extensive information on individual risk factors such as educational level, smoking, and BMI. Pollutant exposure assessment was based on LUR or dispersion CTM models and only the Modig and colleagues (2006) study was based on surface monitoring. Most studies reported estimates of exposure based on the annual average concentrations at the start of the follow-up or at the end of follow-up, but the Swiss study (Künzli et al. 2009) considered an average between the start and the end of the follow-up, a Danish study (Andersen et al. 2012) used cumulative exposure, and the Canadian study (Weichenthal et al. 2017) employed a three-year moving average exposure.

Table 9.19. Key Study Characteristics of Articles Included in the Systematic Review for Asthma Onset in Adults—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Andersen 2012	DDCH	Cohort	Copenhagen and Aarhus, Denmark	1993–2006	53,143	50–78	Dispersion/ CTM	NO_2	15.2	HR	**1.10 (1.01–1.20)**	5.8 µg/m³
Fisher 2016b	DDCH	Cohort	Copenhagen and Aarhus, Denmark	1993–2012	52,572	50–84	Dispersion/ CTM	NO_2	18.8–19.3	HR	1.23 (1.04–1.47)	>21.0 vs. <14.3 µg/m³
											1.16 (0.99–1.35)	14.3–21.0 vs. <14.3 µg/m³
Jacquemin 2009b	ECRHS	Cohort	Multiple cities, multiple countries	1991–2001	4,185	28–52	LUR	NO_2	27.7	OR	**1.43 (1.02–2.01)**	10 µg/m³
Jacquemin 2015	ESCAPE	Cohort	Multiple cities, multiple countries	1985–2010	23,704	27–56	LUR	NO_2	22–31	OR	**1.10 (0.99–1.21)**	10 µg/m³
								NO_x	38–57		1.04 (0.99–1.08)	20 µg/m³
								$PM_{2.5\ abs}$	1.0–2.1		1.06 (0.95–1.19)	1 1×10^{-5}/m
								PM_{10} mass	16–27		1.04 (0.88–1.23)	10 µg/m³
								PM_{coarse} mass	6–11		0.99 (0.87–1.14)	5 µg/m³
								$PM_{2.5}$ mass	10–18		1.04 (0.88–1.23)	5 µg/m³
Künzli 2009	SAPALDIA	Cohort	Multiple cities, Switzerland	1991–2002	2,390	29–71	Dispersion/ CTM	traffic PM_{10}	2.84	HR	1.32 (1.06–1.65)	1 µg/m³
Modig 2006	Lulea Adults' Asthma Incidence	Case-control	Lulea, Sweden	1995–1999	261	20–60	Surface monitoring	NO_2	5.6	OR	**1.0 (0.9–1.1)**	1 µg/m³

Continues next page

Table 9.19 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Asthma Onset in Adults—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Modig 2009	RHINE Sweden	Cohort	Gothenburg and Uppsala and Umea, Sweden	1990–1999	3,824	26–54	Dispersion/ CTM	NO_2	17.9	OR	**1.54 (1.00–2.36)**	10 µg/m^3
Salimi 2018	45 and Up Study	Cohort	Sydney, Australia	2006–2014	84,285	46–54	LUR	NO_2	17.5	HR	**1.03 (0.88–1.19)**	5.9 µg/m^3
								$PM_{2.5}$ mass	4.5		1.10 (0.89–1.37)	0.8 µg/m^3
Weichenthal 2017	ONPHEC	Cohort	Toronto, Canada	1996–2012	1,057,722	30–100	LUR	NO_2	21.4	HR	**1.03 (1.02–1.05)**	4.1 ppb
								PNC <100 nm	24,473		1.00 (1.00–1.01)	10,097 particles/cm^3

HR = hazard ratio; OR = odds ratio; PNC = particle number concentration.

[a] Participants in all studies were adults (age ≥18) and included both males and females.

[b] Units are in the increment column.

[c] **Bold** indicates the effect estimate was included in the meta-analysis.

Follow-up periods differed across studies and extended up to more than 15 years in the European multicohort ESCAPE study (Jacquemin et al. 2015) and the DDCH cohort in Denmark (Fisher et al. 2016b). Age at asthma onset also differed between studies and it was usually between 25 and 55 years, except for the DDCH cohort (Fisher et al. 2016b), for which the age range was 50–84 years. Mean NO_2 levels were relatively low, with most studies below 20 μg/m³, except for the European ESCAPE study (Jacquemin et al. 2015) with levels within a range from 22 to 31 μg/m³. Some of the studies identified new asthma cases using hospitalization records (e.g., Andersen et al. 2012; Weichenthal et al. 2017), whereas other studies used a validated questionnaire (e.g., Jacquemin et al. 2015). In the Canadian and Australian studies, asthma onset was defined based on the first hospitalization for asthma rather than with a direct assessment using a questionnaire. Overall, the identified studies differed in size, methods, exposure levels, and populations.

9.4.1.2 Primary Meta-analysis

A total of eight studies evaluated associations between asthma onset in adults and NO_2 exposure, but one study (Fisher et al. 2016b) could not be considered for the meta-analysis as the exposure levels were reported in categories rather than as a linear continuous variable. For all the other pollutants, fewer than three effect estimates were available, and thus no meta-analysis was conducted. In fact, only three studies, including the European ESCAPE study, reported associations for several pollutants; all others reported results for only one pollutant each. On some traffic-related pollutants there was only one study: Künzli and colleagues (2009) reported results only for traffic PM_{10}, Weichenthal and colleagues (2017) reported results for UFPs, and Salimi and colleagues (2018) reported results for $PM_{2.5}$. Furthermore, the Panel did not identify studies that reported associations between asthma onset in adults and other traffic-related air pollutants such as CO, PAH, and benzene.

Figure 9.26 shows the forest plot of effect estimates for NO_2 and asthma onset in adults based on the meta-analysis. The meta-analytic summary estimate documented a positive association between NO_2 exposure and asthma onset in adults, and the summary estimate was 1.10 (95% CI: 1.01–1.21) per 10-μg/m³. Most of the individual studies reported an association between NO_2 and asthma onset, except for the small case-control study by Modig and colleagues (2006) with null findings and wide confidence intervals. The confidence intervals clearly included unity only in the case of the Australian study (Salimi et al. 2018). The results of the meta-analysis of the association with NO_2 showed a low degree of heterogeneity (I^2 = 42%) with RRs ranging from 1.00 to 1.54 per 10-μg/m³. The combined estimate was most influenced by the study in Canada (Weichenthal et al. 2017), which accounted for 44% of the weight in the meta-analysis and had one of the lowest effect estimates (1.04). In addition, the large DDCH cohort (Fisher et al. 2016b), not included in the meta-analysis, reported a statistically significant RR above unity when comparing categories of NO_2 exposure; RRs reported by Fisher and colleagues (2016b) were 1.23 (95% CI: 1.04–1.47) when comparing exposures >21.0 versus <14.3 μg/m³ NO_2, and 1.16 (0.99–1.35) when comparing exposures 14.3–21.0 versus <14.3 μg/m³ NO_2.

For the other pollutants only one or two effect estimates were available. For NO_x and $PM_{2.5}$ absorbance ($PM_{2.5\ abs}$), only the ESCAPE study provided data with RRs of 1.04 (95% CI: 0.99–1.08) per 20-μg/m³ NO_x and 1.06 (0.95–1.19) per 1×10^{-5}/m $PM_{2.5\ abs}$. For PM_{10}, two studies provided data with RRs of 1.04 (0.88–1.23) (Jacquemin et al. 2015) and 1.32 (1.06–1.65) (Künzli et al. 2009) per 10- and 1-μg/m³, respectively. For $PM_{2.5}$, two studies were available and reported RRs of 1.04 (0.88–1.23) (Jacquemin et al. 2015) and 1.10 (0.89–1.37) (Salimi et al. 2018) per 5- and 0.8-μg/m³, respectively. The only study that addressed UFPs was the Canadian study (Weichenthal et al. 2017) with null results (RR = 1.00; 1.00–1.01) per 10,097-particles/cm³.

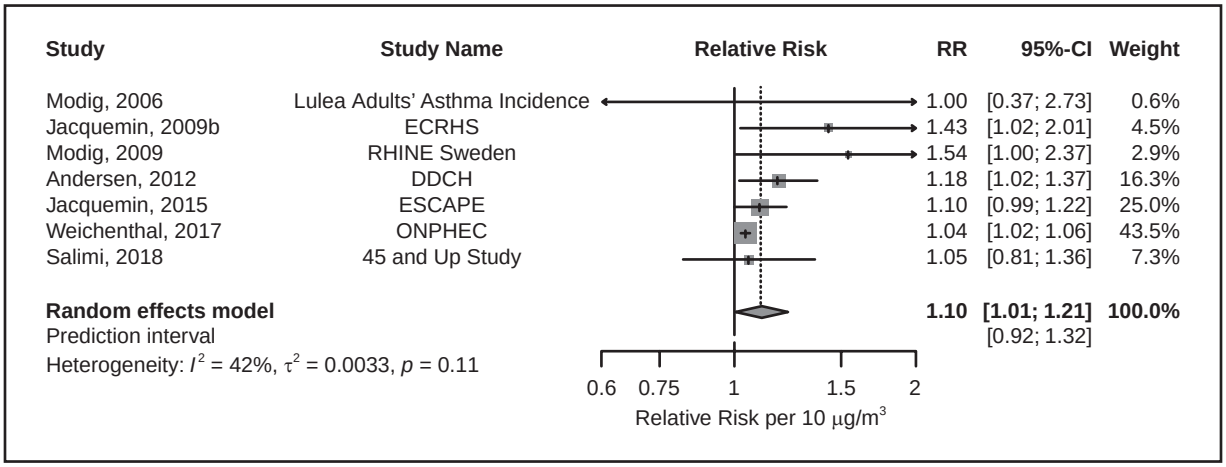

Figure 9.26. Association between NO_2 and asthma onset in adults: meta-analysis.

9.4.1.3 Additional Meta-analyses

All the studies for asthma onset in adults and NO_2 were rated as high traffic specificity except the case-control study (Modig et al. 2009). The meta-analytic effect estimates with and without the moderate traffic specificity study were similar (Appendix Figure 9B-20).

The NO_2 meta-analysis by geographic region indicates a stronger and less heterogeneous effect for Europe (five studies, I^2 = 7%; Appendix Figure 9B-21) than when studies in other locations were included. Indeed, the estimate of association from the administrative cohort in Canada (Weichenthal et al. 2017) and the large cohort in Australia (Salimi et al. 2018) were lower than estimates from European studies.

When the meta-analysis was stratified by availability of the information on smoking status, the summary estimate for the six studies that were able to adjust for smoking was larger (RR = 1.14; 95% CI: 1.04–1.26) than the overall estimate (Appendix Figure 9B-22). Only one study did not correct for smoking (Weichenthal et al. 2017), and this was the study with the largest weight in the primary meta-analysis because it had the largest study population. Only one study assessed the effect of NO_2 in a multipollutant model adjusting for general $PM_{2.5}$, and the association was similar (Weichenthal et al. 2017).

9.4.1.4 Associations with Indirect Traffic Measures

Studies on indirect traffic measures are an additional source of information for assessing the evidence of associations between TRAP exposure and asthma onset in adults. Table 9.20 lists the studies with indirect traffic measures. The indirect traffic measures were too heterogeneous in their definitions to allow meta-analysis. Estimates of association with distance measures from four studies provided little information for the overall evidence assessment; three studies reported positive associations (Bowatte et al. 2018; Fisher et al. 2016a; Modig et al. 2009), and one study reported a null association (Andersen et al. 2012). However, confidence intervals were also large and often included unity.

Only three studies reported estimates of association with traffic density measures; estimates were positive for two studies, but again the confidence intervals of the estimates were large (Jacquemin et al. 2015; Modig et al. 2006, 2009).

9.4.1.5 Narrative Assessment

In summary, the main evidence on TRAP and asthma onset in adults is based on studies examining NO_2. Studies on asthma onset in adults and NO_2 included four cohort studies from Europe with detailed individual information on potential confounding factors (in particular the large ESCAPE multicohort study with 24,000 participants), one administrative cohort in Canada with limited information for potential confounder adjustments, and one large study in Australia with adjustment for several individual lifestyle factors. The evidence base also includes a large cohort study in Denmark (Fisher et al. 2016b) that found a statistically significant association with exposure to NO_2, but the exposure was categorized so the results could not be included in the meta-analysis. In general, these studies did not have important problems regarding confounding, selection bias, and missing data. The assessment of the outcome was based on reliable methods (e.g., questionnaires or hospitalization records), and the pollutant exposure assessment was based on LUR or dispersion models. Some findings provide strong support for an association: the positive meta-analytic effect estimate between NO_2 and asthma onset in adults, the positive associations with NO_2 seen in different populations and, particularly, in studies that were able to adjust for individual smoking; and one study (Andersen et al. 2012) provided evidence of a plausible monotonic exposure–response function, thus increasing the robustness of the results. The findings are also supported by the positive (although with large confidence intervals) estimates of association with pollutants not meta-analyzed, like NO_x, EC, PM_{10}, and $PM_{2.5}$. Furthermore, all the assessed studies were carefully screened for traffic specificity, increasing the likelihood that associations found pertain to traffic emissions. Because it is unlikely that potential biases have affected all estimates of association in the same direction in diverse populations from different regions, the Panel concluded that the confidence in the presence of an association between exposure to TRAP and asthma onset in adults was high.

9.4.1.6 Risk of Bias Assessment

Table 9.21 shows an overview of the results of the risk of bias assessment for exposure–outcome pairs of studies on NO_2 and asthma onset that were meta-analyzed; Appendix Table 9B-5 presents the assessment for each individual study. Most of the estimates of association were rated low or moderate risk of bias for all the domains. There was only one study that was found at high risk of bias for lack of adjustment for important confounders (Modig et al. 2006) and two studies with high risk of bias for missing data (Jacquemin et al. 2009b; Modig et al. 2006).

9.4.1.7 Confidence Assessment of the Body of Evidence

Table 9.22 provides the Panel's confidence assessment in the body of evidence. The table includes only NO_2 for which a meta-analysis was conducted. Almost all studies used the cohort study design (only one case-control study was found); therefore the initial rating was moderate.

Factors That Reduce Confidence No downgrade in the confidence in the evidence for asthma onset in adults was warranted for risk of bias. As indicated in Table 9.21 only two exposure–outcome pairs for NO_2 were rated high risk of bias for missing data, and one of those pairs was also rated high risk of bias due to confounding. Excluding the one estimate of association with NO_2 rated at high risk of bias due

Table 9.20. Key Study Characteristics of Articles Included in the Systematic Review for Asthma Onset in Adults—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Age	Sex	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
Andersen 2012	DDCH	Cohort	Copenhagen and Aarhus, Denmark	1993–2006	37,448	50–78	Both	Density	HR	0.99 (0.79–1.14)	10,000 vehicle-km/day
								Distance		0.98 (0.81–1.19)	<100 vs. >100 m
Bowatte 2018	TAHS	Cohort	Tasmania, Australia	2005–2016	476	45–53	Both	Distance	OR	1.60 (0.71–3.60)	<200 vs. >200 m
Fisher 2016a	Nurses' Health	Cohort	United States	1992–2000	104,254	46–79	Female	Distance	HR	1.13 (0.93–1.38)	<50 vs. >200 m
										0.90 (0.77–1.07)	50–199 vs. >200 m
Jacquemin 2015	ESCAPE	Cohort	Multiple cities, multiple countries	1985–2010	23,704	27–56	Both	Density	OR	1.10 (0.93–1.30)	4,000 vehicle-km/day
Modig 2006	Lulea Adults' Asthma Incidence	Case-control	Lulea, Sweden	1995–1999	379	20–60	Both	Density	OR	1.5 (0.9–2.5)	high traffic flow vs. low traffic flow
Modig 2009	RHINE Sweden	Cohort	Gothenburg and Uppsala and Umea, Sweden	1990–1999	3,824	26–54	Both	Distance	OR	3.88 (1.93–7.82)	<50 vs. >50 m

HR = hazard ratio; OR = odds ratio.

Table 9.21. Summary of Risk of Bias Rating for Studies on Asthma Onset in Adults

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	4	2	1	4	2	1
	Validity of measuring of confounding factors	7	0	0	7	0	0
	Control in analysis	7	0	0	7	0	0
	Overall	4	2	1	4	2	1
2. Selection bias	Selection of participants into the study	7	0	0	7	0	0
3. Exposure assessment	Methods used for exposure assessment	7	0	0	7	0	0
	Exposure measurement methods comparable across the range of exposure	7	0	0	7	0	0
	Change in exposure status	2	5	0	2	5	0
	Overall	2	5	0	2	5	0
4. Outcome measurements	Blinding of outcome measurements	4	3	0	4	3	0
	Validity of outcome measurements	7	0	0	7	0	0
	Outcome measurements	7	0	0	7	0	0
	Overall	4	3	0	4	3	0
5. Missing data	Missing data on outcome measures	6	1	0	6	1	0
	Missing data on exposures	3	2	2	3	2	2
	Overall	3	2	2	3	2	2
6. Selective reporting	Authors reported a priori primary and secondary study aims	7	0	0	7	0	0

to confounding (Modig et al. 2006) did not modify the effect estimate in a meaningful way. The same was true when both this study and the other one that also had high risk of bias because of missing data (Jacquemin et al. 2009) were both excluded (Appendix Figure 9B-23). In contrast, the summary estimate increased (RR = 1.14; 95% CI: 1.04–1.26 per 10-μg/m^3) (Appendix Figure B-22) when the Panel excluded the single large (and influential) Canadian study that lacked information on individual risk factors like smoking (Weichenthal et al. 2017).

The Panel did not downgrade associations for unexplained inconsistency. The Panel observed a low degree of heterogeneity of effect estimates across studies for NO_2, and the heterogenicity was mainly explained by variability across geographical regions. In addition, when excluding the administrative study with limited control for individual confounders (Weichenthal et al. 2017), heterogenicity was reduced to zero. For these reasons, no downgrade for unexplained inconsistency was considered necessary.

Regarding imprecision, the sample size was larger than the minimum sample size required. Also, the confidence interval of the summary estimate did not include unity, so no downgrade was applied. There were fewer than 10 studies, so funnel plots and Egger tests were not produced to evaluate publication bias. The Panel decided not to downgrade for publication bias, per protocol.

Factors That Increase Confidence Only one study (Andersen et al. 2012) provided evidence of a plausible monotonic exposure–response function and so no upgrade was applied. In addition, the Panel found no clear indication that residual confounding or other factors are likely to lead to an underestimation of the associations. An upgrade was thus not considered appropriate. Regarding consistency across geographic regions, populations, or study period, the Panel observed positive associations in Europe, North America, and Australia, although the associations were smaller in the Canadian (Weichenthal et al. 2017) and Australian (Salimi et al. 2018)

Table 9.22. Confidence Rating in the Quality for the Body of Evidence for Traffic-Related Air Pollutants and Asthma Onset in Adults[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort, Case-control	+++ ($N = 7$)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Cohort and case control design initially rated as moderate.	Few studies high RoB and robust effect estimates in low and moderate RoB studies.	Low heterogeneity ($I^2 = 42\%$). Plausible reasons to explain inconsistency.	Sample size met, and confidence interval does not include unity.	No formal evaluation possible.	Evidence of plausible monotonic ERF in one study (Andersen 2012).	Confounding in both directions possible.	Consistent associations within Europe but not in comparison to North America and Australia.	

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor indirectness and the upgrading factor large magnitude of effect were not considered further.

studies. One explanation for the different effect estimates in Europe and Canada is lack of individual information of some confounders in the Canadian administrative cohort, as mentioned earlier. The Panel did not upgrade the evidence for consistency for NO_2. Also, most studies were published after 2008; so the Panel could not assess consistency across time periods.

Evaluation of Confidence for Combined Measures of TRAP Overall, the assessment for NO_2 was moderate confidence. The Panel assessed the level of confidence in the body of evidence for asthma onset in adults only for NO_2, but there were some supportive indications of increased risk of asthma onset for other pollutants ($PM_{2.5}$, PM_{10}, $PM_{2.5\ abs}$) for which the modified OHAT assessment was not possible. The studies on indirect traffic measures do not provide additional support for an association of TRAP with asthma onset, as positive, negative, and null associations were reported. The Panel's assessment of confidence in the body of evidence for TRAP and asthma onset in adults is therefore moderate because, based on the modified OHAT assessment, the highest rating was moderate and supportive evidence was provided from the results of single studies related to other pollutants.

9.4.1.8 Overall Confidence Assessment

Based on the narrative evaluation (high) and the modified OHAT assessment in the body of evidence (moderate), the overall confidence assessment between TRAP and asthma onset in adults is moderate to high.

9.4.2 PREVALENCE OF ASTHMA EVER

9.4.2.1 Study Selection and Description

Six studies reported associations between TRAP and prevalence of asthma ever in adults (Table 9.23). Five studies were conducted in European countries and one was conducted in Australia. The large majority of the studies were published after 2008 (the end of the search date for the 2010 HEI Traffic Review).

All studies were based on a cross-sectional design and differed substantially in sample size, ranging from a few hundreds to several thousand participants with the largest contribution coming from a study in the Netherlands (Cai et al. 2017) with about 56,000 participants. Two other studies included 27,000 and 21,000 participants, in Australia and Sweden, respectively (Lazarevic et al. 2015; Lindgren et al. 2010.

Pollutant exposure assessment was based on LUR or dispersion models. All studies identified asthma cases using a questionnaire; the Swedish study (Lindgren et al. 2010) divided the participants into allergic and nonallergic cases. Particularly, the large study in the northern part of the Netherlands (Lifelines) (Cai et al. 2017) was a part of a larger investigation including cohorts in other European countries (HUNT3 and U.K. Biobank); only the results of Lifelines met the inclusion criteria for this review; the HUNT3 and U.K. Biobank did not include an area correction. The Lifelines study corrected for several individual lifestyle factors, such as smoking.

Few effect estimates were available for each individual traffic-related pollutant, and no meta-analysis was conducted. In fact, only two studies were available for associations of NO_2 exposure as a continuous variable with prevalence of asthma ever in adults (Lazarevic et al. 2015 in Australia and Cai et al. 2017 in the Netherlands); Lazarevic and colleagues (2015) reported null findings and Cai and colleagues (2017) reported RR = 1.10 (95% CI: 1.04–1.16) per 10-μg/m^3 NO_2. The large study in the Netherlands (Cai et al. 2017) also examined exposure to PM_{10} and found a strong and statistically significant association (RR = 1.35; 1.13–1.61 per 10-μg/m^3), whereas a small study in Estonia (Pindus et al. 2016) examined traffic PM_{10} exposure and reported no statistically significant effect (RR = 1.09; 0.69–1.76 per 2.2-μg/m^3). A cross-sectional study in Rome (Cesaroni et al. 2008) reported inconsistent results in categorical analyses of associations of asthma ever in adults with exposure to NO_2. Similarly, Lindgren and colleagues (2009a and 2010) examined exposure to NO_x in categories with largely null results and wide confidence intervals. Overall, only one large study (Cai et al. 2017) found a strong association with prevalence of asthma ever for both NO_2 and PM_{10} exposure.

9.4.2.2 Associations with Indirect Traffic Measures

A total of five studies used indirect traffic measures to study asthma ever in adults (Table 9.24). Estimates of association with distance measures provided little information for the overall evidence assessment, as positive and null associations were reported. Confidence intervals were large and often included unity. Only two studies reported associations with traffic density measures, but the confidence intervals were wide and included unity.

9.4.2.3 Narrative and Overall Confidence Assessment

In summary, the evidence of an association between TRAP and prevalence of asthma ever in adults is limited to the results of a strong association reported in a single large study in the Netherlands (Cai et al. 2017) for both NO_2 and PM_{10}. The Dutch study (Cai et al. 2017) suggests that both long-term PM_{10} and NO_2 exposure is associated with prevalence of asthma ever in adults. The study had a much larger sample size and statistical power to detect an effect when compared with the other studies. However, all the effect estimates from the other studies had large confidence intervals and did not provide much additional support. Thus, the Panel concluded that the presence of an association between TRAP and asthma ever in adults

Table 9.23. Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Asthma Ever in Adults—Pollutants

Reference	Study Name[a]	Location	Study Period	Sample Size	Age	Sex	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Measure	Effect Estimate (95% CI)	Increment
Cai 2017	Lifelines	Northern part, the Netherlands	2006–2013	56,401	Adults (18–64)	Both	LUR	NO_2	21.2	OR	1.10 (1.04–1.16)	10 µg/m³
								PM_{10} mass	23.6		1.35 (1.13–1.61)	10 µg/m³
Cesaroni 2008	SIDRIA	Rome, Italy	1994–1995	9,488	Adults (18–64)	Both	LUR	NO_2	45.4	OR	1.11 (0.84–1.48)	50.3–62.6 vs. <37.3 µg/m³
											1.08 (0.81–1.44)	47.3–50.3 vs. <37.3 µg/m³
											1.11 (0.84–1.47)	37.3–47.3 vs. <37.3 µg/m³
Lazarevic 2015	ALSWH	Australia	2006–2011	26,991	Adults (18+)	Female	LUR	NO_2	5	RR	0.99 (0.91–1.08)	3.7 ppb
Lindgren 2009a	Scania Respiratory Survey 2000	Scania including Malmö, Sweden	2000	9,316	Adults (18+)	Both	Dispersion/ CTM	NO_x	13.5	OR	1.05 (0.83–1.34)	>19 vs. <8 µg/m³
											0.77 (0.60–1.00)	14–19 vs. <8 µg/m³
											0.85 (0.66–1.09)	11–14 vs. <8 µg/m³
											1.04 (0.82–1.32)	8–11 vs. <8 µg/m³
Lindgren 2010	Scania Health Survey 2004	Scania, Sweden	2004–2005	21,360	Adults (18–64)	Both	Dispersion/ CTM	NO_x	12	OR	1.1 (0.93–1.4)	>19 vs. <8 µg/m³
											0.84 (0.69–1.0)	14–19 vs. <8 µg/m³
											1.1 (0.93–1.3)	11–14 vs. <8 µg/m³
											0.94 (0.79–1.10)	8–11 vs. <8 µg/m³
Pindus 2016	RHINE Tartu	Tartu, Estonia	2011–2012	905	Adults (18–64)	Both	Dispersion/ CTM	Traffic PM_{10}	3.3	OR	1.09 (0.69–1.76)	2.2 µg/m³

OR = odds ratio; RR = relative risk.

[a] All were cross-sectional studies.

[b] Units are in the increment column.

Table 9.24. Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Asthma Ever in Adults—Indirect Traffic Measures

Reference	Study Name[a]	Location	Study Period	Sample Size	Age	Sex	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
Cesaroni 2008	SIDRIA	Rome, Italy	1994–1995	9,488	Adults (18–64)	Both	Distance	OR	1.01 (0.73–1.39)	<50 vs. >200 m
									1.07 (0.76–1.52)	50–100 vs. >200 m
									1.00 (0.77–1.29)	100–200 vs. >200 m
Lazarevic 2015	ALSWH	Australia	2006–2011	26,991	Adults (18+)	Female	Distance	RR	1.00 (0.98–1.03)[b]	1 km
Lindgren 2010	Scania Health Survey 2004	Scania, Sweden	2004–2005	21,360	Adults (18–64)	Both	Density	OR	1.3 (0.95–1.8)	>10 vs. no cars/minute
									1.2 (0.92–1.6)	6–10 vs. no cars/minute
									0.96 (0.81–1.1)	2–5 vs. no cars/minute
									1.1 (0.92–1.2)	<2 vs. no cars/minute
Nuvolone 2011	Tuscany Health Survey	Pisa, Tuscany, Italy	1991–1993	2,062	Children (<18) and adults (18+)	Female	Distance	OR	1.68 (0.97–2.88)	<100 vs. 250–800 m
						Male			1.59 (0.85–2.98)	<100 vs. 250–800 m
						Female			0.58 (0.30–1.15)	100–250 vs. 250–800 m
						Male			1.55 (0.83–2.87)	100–250 vs. 250–800 m
Oosterlee 1996	Haarlem Respiratory Survey	Haarlem, the Netherlands	1991	1,110	Adults (18–64)	Both	Density	OR	1.2 (0.8–1.9)	High vs. low

OR = odds ratio; RR = relative risk.

[a] All were cross-sectional studies.

[b] Log transformed.

was low. No confidence assessment of the body of evidence using OHAT was undertaken because of the lack of studies; therefore, the overall confidence assessment was also low.

9.4.3 PREVALENCE OF ACTIVE ASTHMA

9.4.3.1 Study Selection and Description

A total of four studies, all conducted in Europe, investigated the prevalence of active asthma in relation to TRAP (Table 9.25). The European ECHRS investigation addressed changes in an indicator of asthma (*asthma score*) (Jacquemin et al. 2009a). The indicator of asthma was defined using a grading scheme based on reported symptoms, and as such it was not fully comparable with the others. A small study in France included a few hundred participants (Havet et al. 2018); the other three studies included several thousand participants with the largest one being the Lifelines study in the northern part of the Netherlands with 56,000 individuals (Cai et al. 2017).

Few effect estimates were available for the individual pollutants, and no meta-analysis was conducted. Cai and colleagues (2017) in the large study in the Netherlands reported positive associations of RR = 1.16 (1.08–1.25) per 10-μg/m^3 NO_2 and 1.58 (1.23–2.02) per 10-μg/m^3 PM_{10}, respectively. A relatively small cross-sectional study in France (Havet et al. 2018) examined several pollutants (NO_2, NO_x, PM_{10}, $PM_{2.5}$) and reported null results with wide confidence intervals. Lindgren and colleagues (2009b) examined NO_x exposure in categories, also with null results and large confidence intervals. Finally, the European ECHRS (Jacquemin et al. 2009b) that used asthma score as an outcome reported a statistically significant increased risk of having a worse asthma score with higher NO_2 exposure.

9.4.3.2 Associations with Indirect Traffic Measures

Six studies addressed distance to major roads and two studies considered traffic density in relation to active asthma in adults (Table 9.26). The results were heterogeneous. A study in Tasmania (Bowatte et al. 2017a,b), as well as a follow-up of the same population (Bowatte et al. 2018), observed an association with distance to major roads. An increased risk with traffic intensity was observed in a study in Sweden but only for allergic asthma (Lindgren et al. 2009b). No associations were found in other studies (Balmes et al. 2014; Havet et al. 2018; Livingstone et al. 1996; Morris et al. 2000). Note that in three indirect traffic measures studies, asthmatic patient populations were investigated as opposed to the general population. This demonstrates the difficulty involved in classifying studies into these selected respiratory health outcomes because those studies did not quite classify as being asthma exacerbation studies (Balmes et al. 2014; Bowatte et al. 2018; Morris et al. 2000).

9.4.3.3 Narrative and Overall Confidence Assessment

In summary, similar to asthma ever in adults, the evidence base for active asthma in adults is also limited to the association seen in one large study in the Netherlands (Cai et al. 2017) for both NO_2 and PM_{10}. The results of the European ECHRS (Jacquemin et al. 2009b) between NO_2 exposure and asthma score also point toward an association. The other two pollutant studies reported null results, with wide confidence intervals and do not provide much additional information. The Panel concluded that the confidence in the presence of an association between TRAP and active asthma in adults is low. No modified OHAT assessment was undertaken to assess the confidence in the body of evidence because of the lack of studies.

9.4.4 ASTHMA EXACERBATION

9.4.4.1 Study Selection and Description

A total of three studies, all conducted in Europe, investigated exacerbation of asthma in participants with a previous diagnosis of asthma in relation to long-term exposure to TRAP (Table 9.27). Andersen and colleagues (2012) investigated the risk of hospital readmissions in relation to NO_2 exposure in 552 asthma patients enrolled in the large DDCH cohort. The work was subsequently extended by Fisher and colleagues (2016b) for the same cohort. Jacquemin and colleagues (2012) in the French EGEA study assessed uncontrolled asthma (defined by symptoms, exacerbations, and lung function) in 481 adults in relation to PM_{10} exposure. No meta-analysis was conducted because there were not at least three studies with the same pollutant. For NO_2, there was a statistically increased risk of rehospitalization in the Danish cohort (Andersen et al. 2012), RR = 1.41 (95% CI: 1.15–1.71) per 5.8-μg/m^3 NO_2, and the results were confirmed—although they were less precise—in later categorical analysis (Fisher et al. 2016b). An increased risk of uncontrolled asthma (RR = 1.33; 1.06–1.67 per 3-μg/m^3 PM_{10}) was seen in the EGEA study (Jacquemin et al. 2012).

9.4.4.2 Associations with Indirect Traffic Measures

Table 9.28 lists the studies with indirect traffic measures for asthma exacerbation. The indirect traffic measures were too heterogeneous in their definitions, precluding a meta-analysis. The two studies reporting on distance measures observed positive associations but were imprecise and provided limited information for the overall evidence assessment (Andersen et al. 2012; Lai et al. 2018). The two traffic density studies in the United States (Meng et al. 2007, 2008) showed increased risk at increasing levels of traffic density. The same was true for the Danish study (Andersen et al. 2012), although the association was imprecise.

Table 9.25. Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Active Asthma in Adults—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Measure	Effect Estimate (95% CI)	Increment
Cai 2017	Lifelines	Cross sectional	Northern part, the Netherlands	2006–2013	56,401	LUR	NO_2	21.2	OR	1.16 (1.08–1.25)	10 µg/m^3
							PM_{10} mass	23.6		1.58 (1.23–2.02)	10 µg/m^3
Havet 2018	EGEA	Cross sectional	Multiple cities, France	2003–2007	603	LUR	NO_2	25–30	OR	0.98 (0.85–1.14)	10 µg/m^3
							NO_x	40–55		1.03 (0.90–1.17)	20 µg/m^3
					435		PM_{10} mass	About 25		1.03 (0.59–1.80)	10 µg/m^3
							$PM_{2.5}$ mass	About 150		0.82 (0.49–1.39)	5 µg/m^3
Jacquemin 2009a	ECRHS	Cohort	Multiple cities, multiple countries	1991–2002	2,921	LUR	NO_2	28	RMS	1.23 (1.09–1.38)	10 µg/m^3
Lindgren 2009b	Scania Respiratory Survey 2000	Cross sectional	Scania including Malmö, Sweden	2000	8,285	Dispersion/ CTM	NO_x	About 12	OR	1.15 (0.82–1.61) (allergic asthma)	>19 vs. <8 µg/m^3
										0.73 (0.50–1.05) (allergic asthma)	14–19 vs. <8 µg/m^3
										0.74 (0.51–1.07) (allergic asthma)	11–14 vs. <8 µg/m^3
										1.04 (0.74–1.46) (allergic asthma)	8–11 vs. <8 µg/m^3
					8,110					0.91 (0.52–1.58) (nonallergic asthma)	>19 vs. <8 µg/m^3
										1.05 (0.62–1.76) (nonallergic asthma)	14–19 vs. <8 µg/m^3
										1.15 (0.69–1.94) (nonallergic asthma)	11–14 vs. <8 µg/m^3
										1.13 (0.67–1.91) (nonallergic asthma)	8–11 vs. <8 µg/m^3

OR = odds ratio; RMS = ratios of the mean asthma scores; RR = relative risk.

[a] Participants in all studies were adults (age 18–64) and included both males and females.

[b] Units are in the increment column.

Table 9.26. Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Active Asthma in Adults—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Traffic Measure	Effect Estimate (95% CI)[b]	Increment
Balmes 2014	Asthma Rhinitis Cohort, Severe Asthma Cohort	Cross sectional	California, United States	2008–2009	302	Distance	0.77 (0.47–1.26)	<131 vs. >334 m
							1.26 (0.77–2.06)	131–334 vs. >334 m
Bowatte 2017a	TAHS	Cohort	Tasmania, Australia	2005–2012	709	Distance	1.49 (1.09–2.05)	<200 vs. >200 m
Bowatte 2017b	TAHS	Cross sectional	Tasmania, Australia	2005	1,367	Distance	1.21 (0.91–1.59)	<200 vs. >200 m
Bowatte 2018	TAHS	Cohort	Tasmania, Australia	2005–2016	543	Distance	5.21 (1.54–17.6)	<200 vs. >200 m
Havet 2018	EGEA	Cross sectional	Multiple cities, France	2003–2007	603	Density	1.14 (0.94–1.37)	4,000 vehicle-km/day
Lindgren 2009b	Scania Respiratory Survey 2000	Cross sectional	Scania including Malmö, Sweden	2000	8,285	Density	1.83 (1.23–2.72) (allergic asthma)	>10 vehicles/minute vs. no heavy road
							1.34 (0.92–1.96) (allergic asthma)	6–10 vehicles/minute vs. no heavy road
							0.96 (0.69–1.33) (allergic asthma)	2–5 vehicles/minute vs. no heavy road
							1.13 (0.84–1.51) (allergic asthma)	<2 vehicles/minute vs. no heavy road
					8,110		0.96 (0.47–1.96) (nonallergic asthma)	>10 vehicles/minute vs. no heavy road
							0.95 (0.54–1.69) (nonallergic asthma)	6–10 vehicles/minute vs. no heavy road
							0.98 (0.63–1.53) (nonallergic asthma)	2–5 vehicles/minute vs. no heavy road
							0.82 (0.53–1.28) (nonallergic asthma)	<2 vehicles/minute vs. no heavy road
Livingstone 1996	Tower Hamlets GP	Case-control	London, United Kingdom	1994	5,725	Distance	1.00 (0.84–1.19)	<150 vs. >150 m
Morris 2000	Tower Hamlets Respiratory	Case-control	London, United Kingdom	1991–1992	248[c]	Distance	0.78 (0.46–1.32)	<150 vs. >150 m

[a] Participants in all studies were adults (age 18–64) and included both males and females unless indicated otherwise.

[b] The effect estimate in all studies was odds ratio.

[c] Age 15+.

Table 9.27. Key Study Characteristics of Articles Included in the Systematic Review for Asthma Exacerbation in Adults—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Measure	Effect Estimate (95% CI)	Increment
Andersen 2012	DDCH	Cohort	Copenhagen and Aarhus, Denmark	1993–2006	552	Dispersion/ CTM	NO_2	15.2	HR	1.41 (1.15–1.71)	5.8 µg/m^3
Fisher 2016b	DDCH	Cohort	Copenhagen and Aarhus, Denmark	1993–2012	541	Dispersion/ CTM	NO_2	18.8–19.3	HR	1.43 (0.91–2.24)	>21.0 vs. <14.3 µg/m^3
										1.12 (0.75–1.65)	14.3–21.0 vs. <14.3 µg/m^3
Jacquemin 2012	EGEA	Cross sectional	Multiple cities, France	2003–2007	481	LUR	PM_{10} mass	20.2	OR	1.33 (1.06–1.67)	3 µg/m^3

HR = hazard ratio; OR = odds ratio.

[a] Participants in all studies were adults (age 18–64) and included both males and females.

[b] Units are in the increment column.

Table 9.28. Key Study Characteristics of Articles Included in the Systematic Review for Asthma Exacerbation in Adults—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
Andersen 2012	DDCH	Cohort	Copenhagen and Aarhus, Denmark	1993–2006	388	Adults (18–64)	Density	HR	1.23 (0.93–1.62)	10,000 vehicle-km/day
							Distance		1.22 (0.80–1.86)	<100 vs. >100 m
Lai 2018	Thunderstorm Asthma	Case-control	Melbourne, Australia	2016	88	Adults (18–64)	Distance	OR	1.47 (0.29–7.45)	<200 vs. >200 m
Lindgren 2016	Rochester Epidemiology	Cross sectional	Olmsted County, United States	2000–2010	19,915	Children (<18) and adults (18+)	Density	OR	1.15 (1.11–1.22)[b]	10% increase in vehicle-km/m^2/day
Meng 2007	CHIS 2001	Cross sectional	Los Angeles and San Diego Counties, California, United States	2001	1,291	Adults (18+)	Density	OR	2.11 (1.38–3.23)	>200,000 vs. <20,000 vehicle-miles/day/square mile
									1.45 (0.99–2.11)	20,001–200,000 vs. <20,000 vehicle-miles/day/square mile
Meng 2008	CHIS 2001	Cross sectional	Multiple cities, United States	2000–2001	1,217	Children (<18) and adults (18+)	Density	OR	2.25 (1.40–3.62)	>200,000 vs. <20,000 vehicle-miles/day/square mile
									1.38 (0.90–2.12)	20,001–200,000 vs. <20,000 vehicle-miles/day/square mile

HR = hazard ratio; OR = odds ratio.

[a] All studies included male and female participants.

[b] Log transformed.

9.4.4.3 Narrative and Overall Confidence Assessment

In summary, an association between asthma exacerbation in adults was reported for both exposure to traffic-related pollutants (NO_2 and PM_{10}) and indirect traffic measures. However, the evidence on TRAP and asthma exacerbation is based on few studies with small study populations. Overall, the confidence in the presence of an association between TRAP and asthma exacerbation in adults was considered very low. No modified OHAT assessment was undertaken because of the lack of studies.

9.4.5 ACUTE LOWER RESPIRATORY INFECTION

9.4.5.1 Study Selection and Description

Only three studies were identified that reported associations between TRAP and ALRI in adults. These are listed in Table 9.29. Sample sizes ranged from just under 1,000 to over 200,000, and follow-up periods ranged from 3 to 8 years. Two of the three studies considered more than one traffic-related pollutant. One of the studies was particularly large (N = 207,901) and had a retrospective cohort design using administrative data from primary care reports for adults ≥40 years of age residing in London, U.K. (Carey et al. 2016). Salimi and colleagues (2018) was also large (N = 84,285) and used a prospective design for adults ≥45 years old residing in New South Wales, Australia. The third study was a case-control study in which pneumonia was identified from the emergency department records of four hospitals in Hamilton, Ontario, Canada, but it was small (859 cases among adults ≥65 years of age) compared with the other two studies (Neupane et al. 2010). NO_2 exposures were assessed with LUR by Neupane and colleagues (2010) and Salimi and colleagues (2018); both NO_2 and NO_x were predicted with a dispersion model by Carey and colleagues (2016). Two of the studies also assessed the association between $PM_{2.5}$ and respiratory infections (Carey et al. 2016; Salimi et al. 2018). Carey and colleagues (2016) refined the $PM_{2.5}$ exposure assessment into traffic and nontraffic sources and also considered indirect measures of traffic exposure in their analyses.

9.4.5.2 Primary Meta-analysis and Associations with Indirect Traffic Measures

A meta-analysis was conducted based on the three NO_2 studies reporting associations with ALRI in adults (Figure 9.27). The range of RRs was large (from 0.95 to 1.42), suggesting moderate heterogeneity (I^2 = 71%). Consequently, the summary estimate was 1.07 per 10-μg/m^3 increase in NO_2 concentrations, but with a wide confidence interval (95% CI: 0.71–1.61).

The two largest studies reported mixed evidence, with associations of 1.08 (95% CI: 0.98–1.20) (Carey et al. 2016) and 0.95 (0.86–1.05) (Salimi et al. 2018) per 10-μg/m^3. The third much smaller study (Neupane et al. 2010) reported a large positive association with NO_2 but with a wide confidence interval (1.42; 1.0–2.02 per 10-μg/m^3).

There was very limited evidence for an association with $PM_{2.5}$. Carey and colleagues (2016) reported a positive association of 1.04 (95% CI: 0.95–1.15) per 1-μg/m^3 and Salimi and colleagues (2018) reported null results.

The largest of the three studies, Carey and colleagues (2016) also considered indirect traffic measures and reported positive associations with confidence intervals crossing unity (Table 9.30). For the distance measures there was a logical increase in the effect estimate of 1.03 (95% CI: 0.96–1.11) for 100 to 250 meters versus <100 meters and 1.06 (0.98–1.14) for >250 meters versus <100 meters. However, for the traffic density measures the comparison of lower intensity of heavy vehicle traffic to no heavy vehicle traffic had a larger effect estimate (1.03; 0.95–1.12) than the comparison of higher intensity of heavy vehicle traffic to no heavy vehicle traffic (1.01; 0.91–1.11).

9.4.5.3 Narrative Assessment

Due to the very small number of studies, the available evidence regarding an association between TRAP and ALRI in adults is low. Two of the three studies found positive associations with NO_2, but there were large differences in the effect estimates. In all three studies the confidence intervals included unity. There was only limited evidence for an association with $PM_{2.5}$ and indirect measures of traffic exposure. Collectively the evidence of the presence of an association between TRAP and adult ALRI remains low due to the limited number of studies.

9.4.5.4 Risk of Bias and Confidence Assessment of the Body of Evidence

The three studies included were of low or moderate risk of bias with appropriate confounder adjustments, suggesting limited risk of bias (Appendix Table 9B-6). A modified OHAT assessment was attempted for NO_2. The results of the confidence assessment are summarized in Table 9.31. Due to imprecision in the summary estimate and the large differences in the effect sizes between studies, the initial rating of moderate confidence was downgraded to very low. Therefore, the Panel judged that the confidence in the body of evidence between TRAP and ALRI in adults is very low.

9.4.5.5 Overall Confidence Assessment

Because the level of confidence in the evidence in the narrative assessment was considered low and the confidence in the body of evidence was very low, the overall confidence assessment of the association between TRAP and ALRI in adults is very low to low.

Table 9.29. Key Study Characteristics of Articles Included in the Systematic Review for ALRI in Adults—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Carey 2016	CPRD London	Cohort	London, United Kingdom	2005–2011	207,901	Adults (18+)	Dispersion/ CTM	NO_2	37.4	HR	**1.08 (0.98–1.20)**	10 µg/m^3
								NO_x	63.0		1.06 (0.98–1.14)	20 µg/m^3
								Traffic $PM_{2.5}$	1.45		1.04 (0.95–1.15)	1 µg/m^3
Neupane 2010	Hamilton Pneumonia	Case-control	Hamilton, Ontario, Canada	2003–2005	859	Older adults (65+)	LUR	NO_2	15	OR	**1.70 (1.00–2.89)**	8.04 ppb
Salimi 2018	45 and Up Study	Cohort	Sydney, Australia	2006–2014	84,285	Adults (18–64)	LUR	NO_2	17.5	HR	**0.97 (0.92–1.03)**	5.9 µg/m^3
							Dispersion/ CTM	$PM_{2.5}$ mass	4.5		0.96 (0.88–1.05)	0.8 µg/m^3

HR = hazard ratio; OR = odds ratio.

[a] All studies included male and female participants.

[b] Units are in the increment column.

[c] **Bold** indicates the effect estimate was included in the meta-analysis.

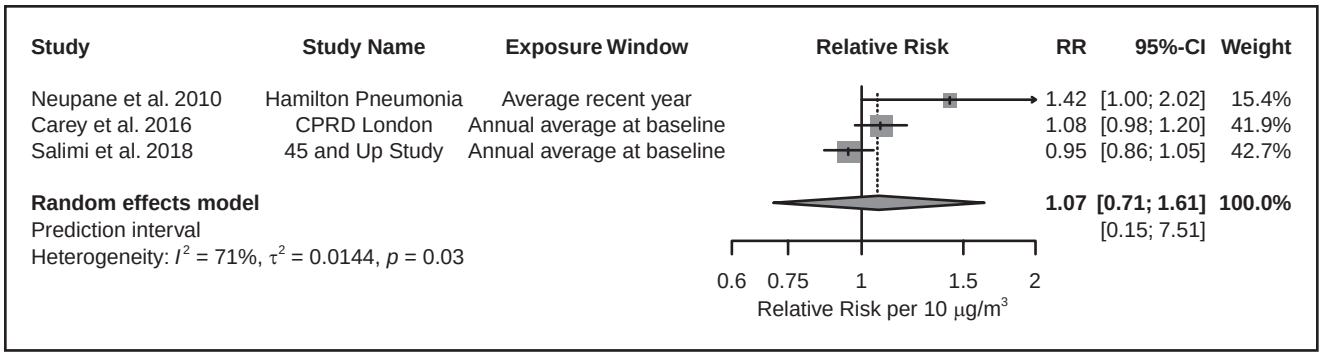

Figure 9.27. Association between NO_2 and ALRI in adults: meta-analysis.

Table 9.30. Key Study Characteristics of Articles Included in the Systematic Review for ALRI in Adults—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Traffic Measure	Effect Estimate (95% CI)[b]	Increment
Carey 2016	CPRD London	Cohort	London, United Kingdom	2005–2011	207,901	Adults (18+)	Density	1.01 (0.91–1.11)	>100,000 heavy vehicle-km/year vs. none
								1.03 (0.95–1.12)	<100,000 heavy vehicle-km/year vs. none
							Distance	1.06 (0.98–1.14)	<100 vs. >250 m
								1.03 (0.96–1.11)	100–250 vs. >250 m

[a] All studies included male and female participants.

[b] The effect estimate was hazard ratio.

9.4.6 INCIDENCE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

9.4.6.1 Study Selection and Description

Eight studies reported associations between TRAP and the incidence of COPD in adults. Their key study characteristics are given in Table 9.32. All studies were of a cohort design and conducted in either Canada (Gan et al. 2013; Weichenthal et al. 2017), Europe (Andersen et al. 2011; Atkinson et al. 2015; Carey et al. 2016; Fisher et al. 2016b; Schikowski et al. 2014) or Australia (Salimi et al. 2018) and varied in size from a few thousand to over 1.1 million participants. All were conducted in adults over the age of 18 years and included both male and female participants. All studies were published after the search end date (2008) for the 2010 HEI Traffic Review. One study reported results for categories of pollutant exposures, rather than continuous increments (Fisher et al. 2016b). Results for NO_2 and $PM_{2.5}$ mass were reported most frequently. Both LUR and dispersion air pollution models were used to estimate pollutant concentrations assigned to study participants. Three of the studies also report on indirect traffic measures.

9.4.6.2 Primary Meta-analysis

Meta-analysis was possible for NO_2 (seven studies), NO_x (three studies) and $PM_{2.5}$ (four studies). The results are shown in Figure 9.28. For each pollutant, the meta-analytical summary estimate confidence intervals included unity.

Meta-analysis of seven NO_2 studies showed a high level of heterogeneity (I^2 = 79%) with RRs in the range 0.84 to 1.14 per 10-μg/m³. The summary estimate was 1.03 (95% CI: 0.94–1.13) per 10-μg/m³ increase in NO_2 concentrations. Three studies were available for meta-analysis for NO_x resulting in a summary estimate of 1.03 (0.88–1.20). Four studies provided estimates for the $PM_{2.5}$ meta-analysis. Heterogeneity was moderate (I^2 = 60%), and the summary estimate was 0.91 (0.62–1.36) per 5-μg/m³ increase in $PM_{2.5}$ concentrations (Figure 9.29).

For the other pollutants, few studies reported results for NO and PM_{10} and further meta-analyses were not possible. One study (Weichenthal et al. 2017) reported a positive association with UFPs measured as particle number concentration <100 nm. Details of these studies are given in Table 9.32.

Table 9.31. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and ALRI in Adults[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort, case-control	+++ ($N = 3$)	0	–	–	0	0	0	0	+ (Very low)
	Rationale	Cohorts and case-control studies start with moderate.	No high RoB studies.	Moderate heterogeneity ($I^2 = 71\%$), one positive, two large null findings.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

Table 9.32. Key Study Characteristics of Articles Included in the Systematic Review for Incidence of COPD in Adults—Pollutants

Reference	Study Name[a]	Location	Study Period	Sample Size[b]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[c]	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Andersen 2011	DDCH	Copenhagen and Aarhus, Denmark	1993–2006	52,799	Adults (18–64)	Dispersion/ CTM	NO_2	17	HR	**1.08 (1.02–1.14)**	5.8 µg/m^3
							NO_x	28.2		**1.05 (1.01–1.10)**	12.4 µg/m^3
Atkinson 2015	CPRD	England	2003–2007	807,000	Adults (18+)	Dispersion/ CTM	NO_2	22.5	HR	**1.03 (0.96–1.10)** (GP diagnosed)	10 µg/m^3
								22.5		1.06 (0.98–1.14) (hospital)	
							PM_{10} mass	19.7		0.97 (0.79–1.18) (GP diagnosed)	10 µg/m^3
										1.17 (0.93–1.46) (hospital)	
							$PM_{2.5}$ mass	12.9		**0.97 (0.71–1.34)** (GP diagnosed)	10 µg/m^3
										1.31 (0.92–1.86) (hospital)	
Carey 2016	CPRD London	London, United Kingdom	2005–2011	207,236	Adults (18+)	Dispersion/ CTM	NO_2	37.4	HR	**0.98 (0.82–1.18)**	10 µg/m^3
							NO_x	63.0		**0.99 (0.86–1.13)**	20 µg/m^3
							Traffic $PM_{2.5}$	1.45		0.98 (0.81–1.18)	1 µg/m^3
Fisher 2016b	DDCH	Copenhagen and Aarhus, Denmark	1993–2012	52,674	Adults (18–64)	Dispersion/ CTM	NO_2	18.8–19.3	HR	1.15 (1.03–1.27)	>21.0 vs. <14.3 µg/m^3
										1.18 (1.08–1.30)	14.3–21.0 vs. <14.3 µg/m^3
Gan 2013	Vancouver Adminis-trative	Vancouver, British Columbia, Canada	1999–2002	467,994	Adults (18+)	LUR	NO_2	32.2	RR	**1.00 (0.96–1.05)**	8.40 µg/m^3
							NO	32.1		1.03 (0.98–1.08)	13.2 µg/m^3
							$PM_{2.5\ abs}$	1.50		1.06 (1.02–1.09)	0.97 1×10^{-5}/m
							$PM_{2.5}$ mass	4.10		**1.02 (0.98–1.06)**	1.58 µg/m^3

Continues next page

Table 9.32 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Incidence of COPD in Adults—Pollutants

Reference	Study Name[a]	Location	Study Period	Sample Size[b]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[c]	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Salimi 2018	45 and Up Study	Sydney, Australia	2006–2014	84,285	Adults (18–64)	LUR	NO_2	17.5	HR	**0.90 (0.82–0.98)**	5.9 µg/m^3
						Dispersion/ CTM	$PM_{2.5}$ mass	4.5		**0.89 (0.79–1.01)**	0.8 µg/m^3
Schikowski 2014	ESCAPE	Multiple cities, multiple countries	1985–2010	6,382	Adults (18–64)	LUR	NO_2	22.39–28.95	OR	**0.99 (0.87–1.14)**	10 µg/m^3
							NO_x	37.54–50.51		**0.97 (0.86–1.11)**	20 µg/m^3
				3,643			$PM_{2.5\ abs}$	1.05–2.01		0.71 (0.49–1.02)	1 1×10^{-5}/m
							PM_{10} mass	15.73–26.72		0.85 (0.55–1.30)	10 µg/m^3
							PM_{coarse} mass	6.37–10.2		0.47 (0.14–1.57)	5 µg/m^3
							$PM_{2.5}$ mass	9.52–17.76		**0.73 (0.51–1.03)**	5 µg/m^3
Weichenthal 2017	ONPHEC	Toronto, Canada	1996–2012	1,105,258	Adults (18+)	LUR	NO_2	21.4	HR	**1.11 (1.07–1.15)**	4.1 ppb
							PNC <100 nm	24,473		1.06 (1.04–1.08)	10,097 particles/ cm^3

GP = general practitioner; HR = hazard ratio; OR = odds ratio; PNC = particle number concentration; RR = relative risk.

[a] All were cohort studies.

[b] All studies included male and female participants.

[c] Units are in the increment column.

[d] **Bold** indicates the effect estimate was included in the meta-analysis.

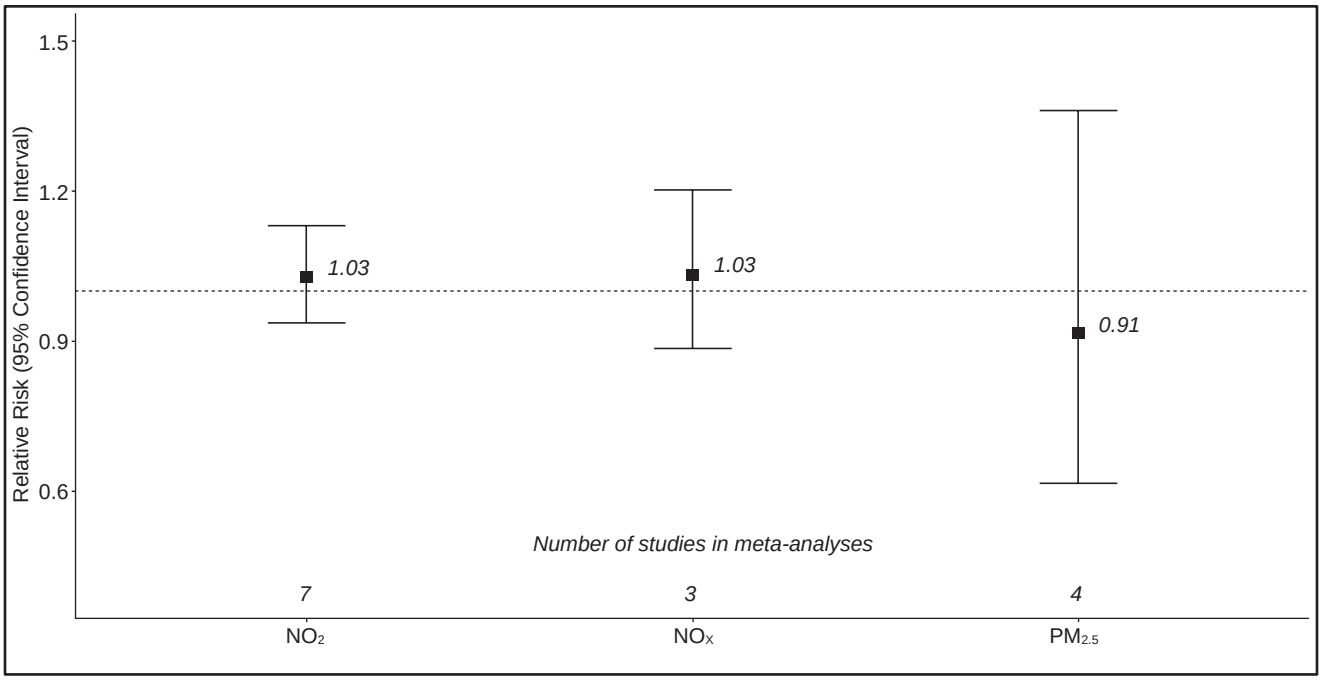

Figure 9.28. Meta-analysis of associations between traffic-related air pollutants and incidence of COPD in adults. The following increments were used: 10 μg/m³ for NO_2, 20 μg/m³ for NO_x, and 5 μg/m³ for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

One study (Weichenthal et al. 2017) reported results from two-pollutant models, adjusted for general $PM_{2.5}$ mass concentrations. The study assessed NO_2 and reported statistically significant associations with minimal changes in the associations after adjustment for $PM_{2.5}$.

9.4.6.3 Additional Meta-analyses

Due to the relatively small number of studies, subgroup and sensitivity analyses were performed for NO_2 only. Selecting only studies that were able to perform adjustment for some measure of smoking indicated a null finding (RR = 1.00; 95% CI: 0.87–1.15 per 10-μg/m³) (Figure 9.30). Exclusion of the single study rated moderate for traffic specificity (Atkinson et al. 2015) altered the summary estimate slightly, RR = 1.02 (0.91–1.15; Appendix Figure 9B-24).

9.4.6.4 Associations with Indirect Traffic Measures

Table 9.33 presents key study characteristics and results for the four studies that included traffic distance and density measures. Only the Nurses' Health study reports solely on indirect traffic measures (Fisher et al. 2016a); the traffic-related pollutants in that study did not make the exposure framework requirements. There was no evidence for associations between indirect traffic measures and incidence of COPD. RRs were imprecisely estimated with confidence intervals including unity in most studies.

9.4.6.5 Narrative Assessment

In summary, the evidence base for assessment of associations between TRAP and the incidence of COPD is based on nine cohort studies, the majority conducted in Western European or North American populations. All studies used LUR or dispersion models to estimate TRAP and were published since the 2010 HEI Traffic Review. Although some large studies showed a higher risk for some traffic-related air pollutants, the summary estimates for the three traffic pollutants with three or more estimates available (NO_2, NO_x, and $PM_{2.5}$) were close to unity with confidence intervals encompassing unity. Levels of heterogeneity were high for NO_2, low for NO_x, and moderate for $PM_{2.5}$. In conclusion, the evidence for the presence of an association between TRAP and incidence of COPD in adults is low.

9.4.6.6 Risk of Bias Assessment

Overviews of the risk of bias assessments for the pollutants meta-analyzed for COPD incidence in adults are presented in Table 9.34 and Appendix Table 9B-7. All but one of the included studies were rated as low or moderate risk of bias for each domain. A single study was rated high risk of bias for confounding (Gan et al. 2013) for both NO_2 and $PM_{2.5}$ as it did not adjust directly for smoking and BMI, although it did correct for comorbidity conditions, such as asthma, diabetes, and coronary heart disease. For NO_2, the impact of exclusion

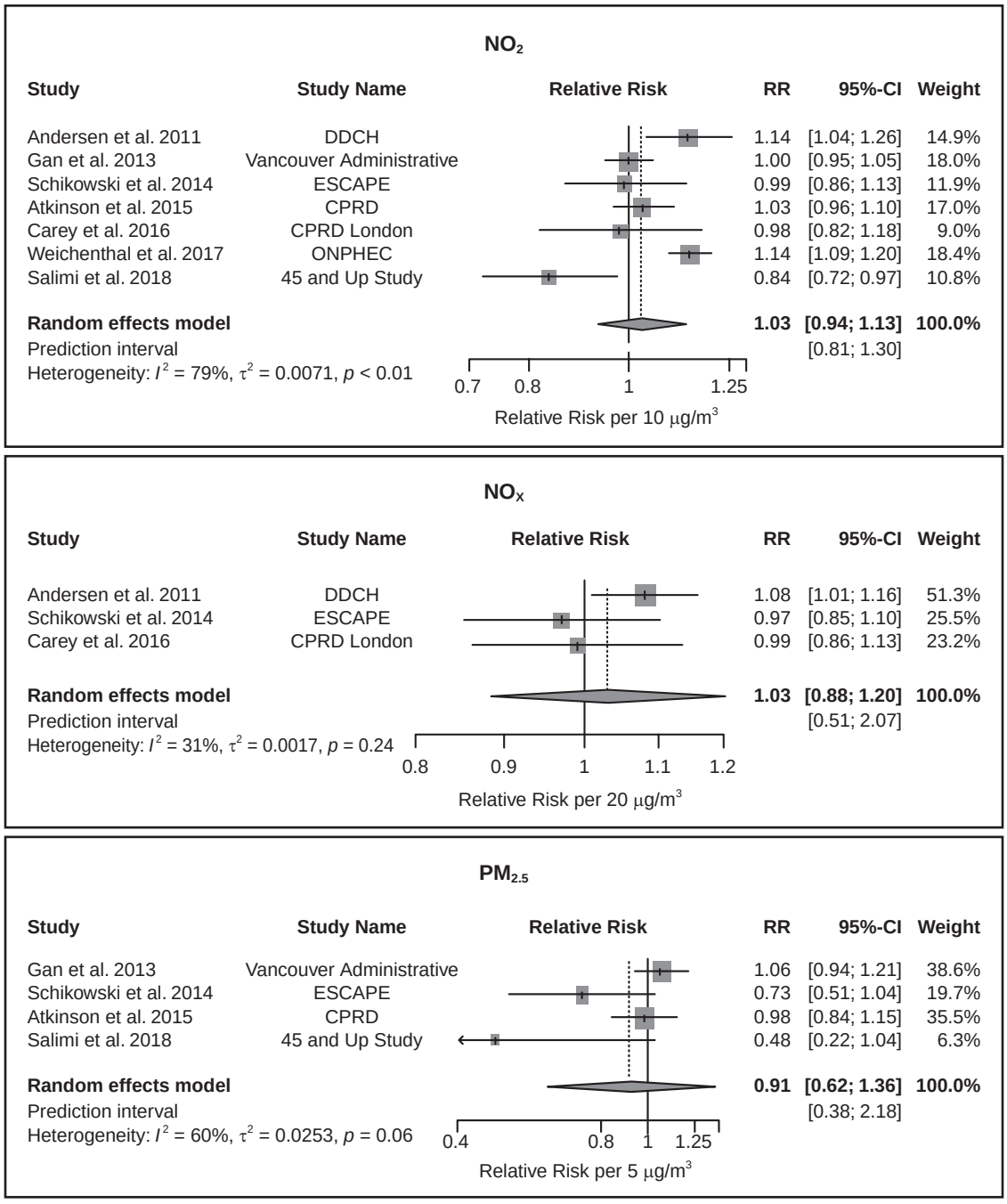

Figure 9.29. Association between NO_2, NO_x, and $PM_{2.5}$ and incidence of COPD in adults: meta-analysis.

of this study from the meta-analysis had little impact on the overall summary of the evidence whereas for $PM_{2.5}$, the summary estimate—and its precision—decreased substantially.

9.4.6.7 Confidence Assessment of the Body of Evidence

Table 9.35 provides the assessment of the evidence for the pollutants for which a meta-analysis was conducted (NO_2, NO_x, and $PM_{2.5}$). Only cohort studies were used, thus the initial starting point was moderate and no combined assessment across study designs was needed.

Factors That Reduce Confidence Regarding the downgrading factor risk of bias for studies on associations of COPD incidence in adults, the NO_2 summary estimate was

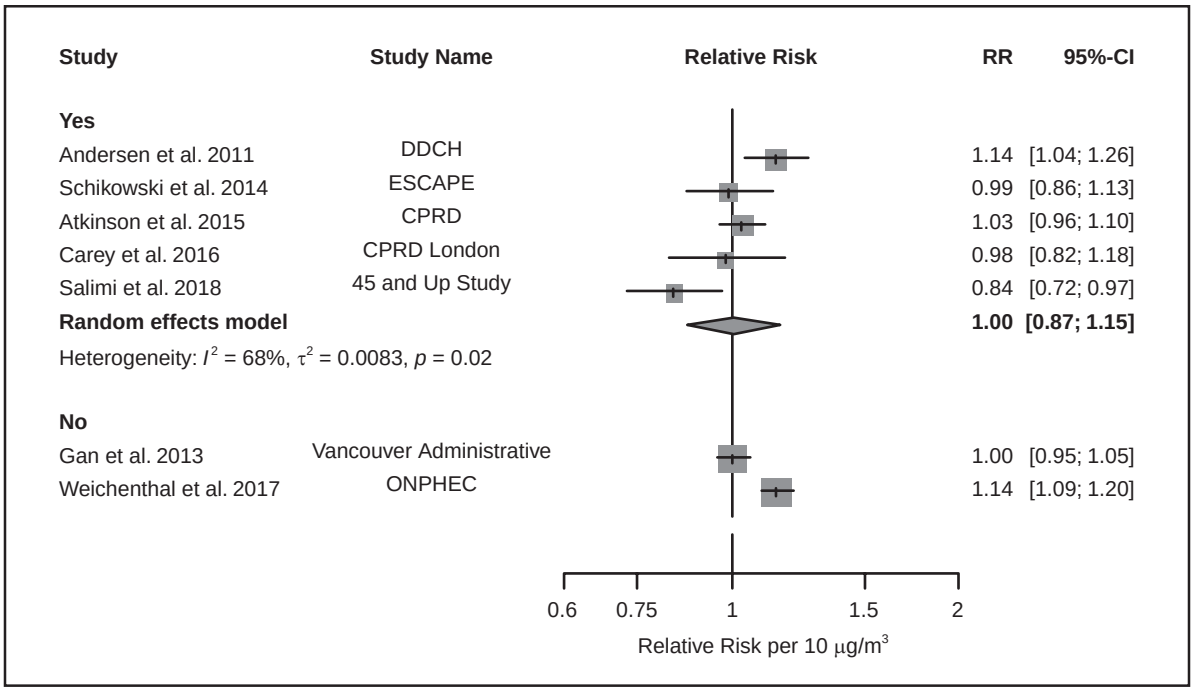

Figure 9.30. Association between NO_2 and incidence of COPD in adults: meta-analysis by smoking adjustment.

unaltered, but the precision was decreased from 1.03 (95% CI: 0.94–1.13) to 1.03 (0.91–1.16) per 10-μg/m³ after exclusion of the single study on NO_2 at high risk of bias in the confounding domain (Gan et al. 2013) (see Appendix Figure 9B-25). This increased the confidence that the findings were not unduly affected by this study; thus, no downgrading was applied for risk of bias in studies of COPD incidence in adults and NO_2. None of the three studies reporting results for NO_x were at high risk of bias, so no downgrade was applied. Exclusion from the meta-analysis of the single $PM_{2.5}$ study at high risk of bias in the confounding domains (Gan et al. 2013) led to a reduction in the summary estimate and reduced the precision of the estimate; from 0.91 (0.62–1.36) to 0.80 (0.38–1.70) per 5-μg/m³ (see Appendix Figure 9B-26). However, the summary estimate was already null, thus no downgrade was applied for risk of bias.

The Panel did downgrade NO_2 associations for unexplained inconsistency. There was a high degree of heterogeneity of effect estimates among studies for NO_2 (Figure 9.29). The estimates were not consistent in direction or magnitude and were not explained by subgroup analyses. Therefore, a downgrade was applied. Heterogeneity was low (I^2 = 31%) for NO_x. The individual summary estimates were not consistent in direction, but confidence intervals overlapped. Subgroup analysis was not possible due to the small number of studies. No downgrade was applied for NO_x. A moderate degree of heterogeneity (I^2 = 60%) was observed for $PM_{2.5}$ (Figure 9.29). Three of the four studies on COPD incidence in adults and $PM_{2.5}$ reported estimates below unity, and there was a large variation in both the magnitude and direction; therefore a downgrade was applied.

With respect to imprecision, sample sizes were sufficient to meet the specified minimum sample size in the protocol for all three pollutants. However, confidence intervals for summary estimates included unity and therefore a downgrade was applied for each pollutant. The Panel did not downgrade for publication bias, per protocol, because too few studies on each pollutant were available for evaluating this potential bias.

Factors That Increase Confidence Two studies investigated the shape of the exposure–response functions. Gan and colleagues (2013) investigated the exposure–response function using natural cubic spline models and found no discernible exposure–response trends for $PM_{2.5}$, NO_2, or NO with COPD. Salimi and colleagues (2018) investigated both the shape of the relationships between $PM_{2.5}$ or NO_2 and COPD incidence using splines and also evidence for a threshold. They observed no evidence that the relationships deviated from linearity nor evidence for a threshold and reported negative associations between NO_2 or $PM_{2.5}$ and incidence of COPD. The remaining included studies did not report the shape of the exposure–response functions. Thus, the two studies that assessed the exposure–response function for NO_2 and $PM_{2.5}$ did not find evidence to reject the assumption of linearity. The summary estimates were

Table 9.33. Key Study Characteristics of Articles Included in the Systematic Review for Incidence of COPD in Adults—Indirect Traffic Measures

Reference	Study Name[a]	Location	Study Period	Sample Size	Age	Sex	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
Andersen 2011	DDCH	Copenhagen and Aarhus, Denmark	1993–2006	52,799	Adults (18–64)	Both	Density	HR	1.01 (0.97–1.05)	5,800 vehicle-km/day
							Distance		1.04 (0.89–1.21)	<50 vs. >50 m
Carey 2016	CPRD London	London, United Kingdom	2005–2011	207,236	Adults (18+)	Both	Density	HR	0.94 (0.86–1.03)	>100,000 heavy vehicle-km/year vs. none
									0.96 (0.89–1.03)	<100,000 heavy vehicle-km/year vs. none
							Distance		0.90 (0.81–0.99)	<100 vs. >250 m
									0.92 (0.84–1.01)	100–250 vs. >250 m
Fisher 2016a	Nurses' Health	United States	1992–2000	103,838	Adults (18–64)	Female	Distance	HR	0.96 (0.69–1.32)	<50 vs. >200 m
									0.98 (0.76–1.27)	50–199 vs. >200 m
Schikowski 2014	ESCAPE	Multiple cities, multiple countries	1985–2010	3,576	Adults (18–64)	Both	Density	OR	1.26 (0.96–1.67)	4,000 vehicle-km/day

[a] All were cohort studies.

close to unity (NO_2) or below unity ($PM_{2.5}$) with wide confidence intervals. Therefore, no upgrades were applied for exposure–response functions.

The Panel did not upgrade the evidence on any of the pollutant–COPD incidence associations on the basis of residual confounding or other factors potentially biasing toward the null. Finally, consistency was difficult to assess because of the small number of studies. NO_2 associations were of comparable magnitude in North America (two studies) and Western Europe (three studies) but not consistent with the single study in Australia. Therefore, no upgrade was applied.

Evaluation of Confidence for Combined Measures of TRAP Confidence assessments were very low (NO_2, $PM_{2.5}$) or low (NO_x). Because the highest rating was low, the Panel's assessment of confidence in the body of evidence of TRAP and COPD incidence in adults is low.

9.4.6.8 Overall Confidence Assessment

Because the level of confidence in the evidence was considered low in the narrative assessment and the confidence in the body of evidence was low, the overall confidence assessment of TRAP and COPD incidence in adults is low.

9.4.7 PREVALENCE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

9.4.7.1 Study Selection and Description

Four studies reported associations between TRAP and the prevalence of COPD. Their key study characteristics are given in Table 9.36. Three studies were conducted in Europe and one in South Korea. Study size varied from 252 to over six thousand participants. All studies were conducted in adults over the age of 18 years and included both male and female participants. Three of the four studies were published after

Table 9.34. Summary of Risk of Bias Rating for Studies on Incidence of COPD in Adults

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	4	2	1	9	3	2
	Validity of measuring of confounding factors	5	2	0	10	4	0
	Control in analysis	7	0	0	14	0	0
	Overall	2	4	1	5	7	2
2. Selection bias	Selection of participants into the study	7	0	0	14	0	0
3. Exposure assessment	Methods used for exposure assessment	7	0	0	14	0	0
	Exposure measurement methods comparable across the range of exposure	7	0	0	14	0	0
	Change in exposure status	3	4	0	6	8	0
	Overall	3	4	0	6	8	0
4. Outcome measurements	Blinding of outcome measurements	7	0	0	14	0	0
	Validity of outcome measurements	7	0	0	14	0	0
	Outcome measurements	7	0	0	14	0	0
	Overall	7	0	0	14	0	0
5. Missing data	Missing data on outcome measures	7	0	0	14	0	0
	Missing data on exposures	6	1	0	13	1	0
	Overall	6	1	0	13	1	0
6. Selective reporting	Authors reported a priori primary and secondary study aims	7	0	0	14	0	0

the search end date (2008) for the 2010 HEI Traffic Review. Two studies reporting results for NO_2 did not provide sufficient information to enable standardization of the estimates (Karakatsani et al. 2003; Pujades-Rodríguez et al. 2009b). There were insufficient numbers of studies for meta-analysis for any of the pollutants. Confidence intervals for all but one estimate included unity.

9.4.7.2 Associations with Indirect Traffic Measures

Key study characteristics and results for indirect traffic measures are given in Table 9.37. Two of the three studies reported results for distance measures and a single study reported results for density measures. One study reported an association for participants living <100 meters from a major road compared with those living >100 meters from a major road; the associated 95% CI excluded unity (Schikowski et al. 2005).

Other studies did not suggest associations between either of the traffic metrics and the prevalence of COPD (Pujades-Rodríguez et al. 2009b; Schikowski et al. 2014).

9.4.7.3 Narrative and Overall Confidence Assessment

The evidence base for assessment of associations between traffic pollutants and indirect traffic measures and the prevalence of COPD is limited. Associations varied in direction with confidence intervals that generally included unity. The evidence for the presence of an association between TRAP and prevalence of COPD in adults is very low. No confidence assessment of the body of evidence using OHAT was undertaken because of the lack of studies; therefore, the overall confidence assessment was also very low.

9.4.8 SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

A single study reported associations of severity of COPD in adults with exposure to traffic (Fisher et al. 2016b). This study presented positive associations with categories of increasing NO_2 and confidence intervals including unity. Therefore, the confidence in the evidence for an association between TRAP and severity of COPD is very low.

Table 9.35. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Incidence of COPD in Adults[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ (N = 7)	0	–	–	0	0	0	0	+ (Very low)
	Rationale	Cohort design initially rated as moderate.	Single study at high RoB in confounding domain. Exclusion did not alter substantially the summary RR.	High heterogeneity (I^2 = 79%) due to magnitude and direction of estimates, and not explained by subgroup analysis.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	Evidence of linear ERF in two studies (Gan 2013, Salimi 2018), however 95% CI for summary risk estimate includes 1.	Confounding in both direction possible.	Too few studies to assess consistency.	
NO_X	Cohort	+++ (N = 3)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	No studies at high RoB.	Low heterogeneity (I^2 = 31%).	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	
$PM_{2.5}$	Cohort	+++ (N = 4)	0	–	–	0	0	0	0	+ (Very low)
	Rationale	Cohort design initially rated as moderate.	Single study at high RoB in confounding domain.	Moderate heterogeneity (I^2 = 60%), due to magnitude and direction, and not explained by subgroup analysis.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor indirectness and the upgrading factor large magnitude of effect were not considered further.

Table 9.36. Key Study Characteristics of Articles Included in the Systematic Review on Prevalence of COPD in Adults—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Age	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Estimate (95% CI)[c]	Increment
Karakatsani 2003	EPIC Athens	Case-control	Athens, Greece	1998	252	Adults (18+)	Surface monitoring	NO_2	50–80	1.37 (1.05–1.79)	Per quartile (units unspecified)
Lamichhane 2018	Korea COPD Survey	Cross sectional	Seoul and Incheon, South Korea	2014–2015	1,264	Adults (18+)	LUR	NO_2	44.64	1.34 (0.89–2.02)	10 μg/m^3
								PM_{10} mass	50.98	1.39 (0.85–2.25)	10 μg/m^3
								$PM_{2.5}$ mass	33.83	1.14 (1.00–1.30)	10 μg/m^3
Pujades-Rodríguez 2009b	Nottingham Cohort	Cross sectional	Nottingham, United Kingdom	1991	2,599	Adults (18+)	Dispersion/ CTM	NO_2	34.5	1.07 (0.68–1.68)	>36.79 μg/m^3
										0.91 (0.57–1.45)	34.73–36.79 μg/m^3
										0.95 (0.60–1.52)	34.23–34.73 μg/m^3
										1.09 (0.68–1.73)	33.92–34.23 μg/m^3
Schikowski 2014	ESCAPE	Cohort	Multiple cities, multiple countries	1985–2010	6,382	Adults (18–64)	LUR	NO_2	22.39–28.95	1.07 (0.95–1.20)	10 μg/m^3
								NO_x	37.54–50.51	1.05 (0.94–1.16)	20 μg/m^3
					3,643			$PM_{2.5\ abs}$	1.05–2.01	0.97 (0.63–1.49)	1 1×10^{-5}/m
								PM_{10} mass	15.73–26.72	1.03 (0.74–1.43)	10 μg/m^3
								PM_{coarse} mass	6.37–10.2	0.55 (0.16–1.89)	5 μg/m^3
								$PM_{2.5}$ mass	9.52–17.76	0.85 (0.58–1.24)	5 μg/m^3

[a] All studies included male and female participants.

[b] Units are in the increment column.

[c] The effect estimate in all studies was odds ratio.

Table 9.37. Key Study Characteristics of Articles Included in the Systematic Review on Prevalence of COPD in Adults—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size	Age	Sex	Traffic Measure	Effect Estimate (95% CI)[a]	Increment
Pujades-Rodríguez 2009b	Nottingham Cohort	Cross sectional	Nottingham, United Kingdom	1991	2,599	Adults (18+)	Both	Distance	1.54 (0.69–3.45)	<50 vs. >100–150 m
									1.67 (0.79–3.49)	50–100 vs. 100–150 m
Schikowski 2005	SALIA	Cross sectional	North Rhine-Westphalia, Germany	1985–1994	2,314	Adults (18–64)	Female	Distance	1.79 (1.06–3.02)	<100 vs. >100 m
Schikowski 2014	ESCAPE	Cohort	Multiple cities, multiple countries	1985–2010	3,576	Adults (18–64)	Both	Density	1.25 (0.96–1.62)	4,000 vehicle-km/day

[a] The effect estimate in all studies was odds ratio.

9.5 OVERALL DISCUSSION

9.5.1 SUMMARY OF MAIN FINDINGS

The overall evaluation of the association between TRAP exposure and some important respiratory outcomes—asthma onset in children and adults, as well as the occurrence of ALRI in children—based on the narrative and modified OHAT assessment, was moderate to high (Table 9.38). Although the narrative assessment and the modified OHAT assessment were focused on complementary aspects—to assess the confidence in the presence of an association for the former, and to assess the confidence in the quality of the evidence for the latter—there were no large differences in the findings.

Overall, the Panel found an association between TRAP and asthma onset in both children and adults, as well as ALRI in children. The associations were similar in different parts of the world, among different populations, using different study designs (cohorts, case-control, and cross-sectional studies), different ways of assessing the outcomes (interview and use of health care), and with different exposure-assessment approaches with a high traffic specificity. Most studies had a low or moderate risk of bias. Moreover, they reflected no evidence of publication bias, suggested a monotonic exposure–response relationships in some cases, and, collectively, showed associations with multiple pollutants, either in meta-analyses or in single large studies. Studies examining exposure to NO_2 have made the greatest contribution to this evaluation. The NO_2 associations were also strong in individual studies where meta-analyses were not possible, such as the prevalence of asthma ever and active asthma in children, which lent further support to the moderate to high confidence in the presence of the observed associations with asthma onset in children. The magnitude of those associations was in fact higher than the corresponding summary estimate for asthma onset—for the same unit of increase in NO_2 (Table 9.1). The findings may indicate both an association of TRAP in inducing the onset of a new disease and, in parallel, an association to sustain its duration and severity.

For other respiratory outcomes in children, namely prevalence of ever and active asthma, as well as ever and active wheeze (see Appendix 9A for results for wheeze outcomes in both children and adults), the available evidence was based mainly on cross-sectional studies and was less compelling. For several respiratory outcomes, including COPD and ALRI in adults together with exacerbation of asthma and COPD, the confidence in the evidence was considered low, mainly because the results were conflicting, too few studies were available, and the modified OHAT assessment could not be conducted. The COPD findings illustrate the difficulties in performing valid longitudinal studies assessing the incidence of this condition. Some evidence of an association between TRAP exposure and COPD incidence has been reported, especially for NO_2, but the evidence was weak and inconsistent, and the overall confidence assessment was low. The evidence for COPD prevalence and exacerbation was even weaker. The epidemiological findings are in contrast with strong toxicological evidence of a clear inflammatory effect of both NO_2 and PM on the airways (see Chapter 3 on mechanisms) but are in line with the low evidence that TRAP is related to COPD mortality (see Chapter 11 on mortality).

Table 9.38. Summary of the Confidence Assessments of TRAP and Respiratory Outcomes in Children and Adults

Respiratory Outcome	Narrative Assessment	Confidence Assessment of the Body of Evidence	Overall Assessment
Children			
Asthma onset	Moderate	High	Moderate to high
Asthma ever	Moderate	Moderate	Moderate
Active asthma	Moderate	Moderate	Moderate
Asthma exacerbation	Low	Fewer than three studies	Low
ALRI	High	Moderate	Moderate to high
Wheeze ever	Low	Very low	Very low to low
Active wheeze	Low	Low	Low
Adults			
Asthma onset	High	Moderate	Moderate to high
Asthma ever	Low	Fewer than three studies	Low
Active asthma	Low	Fewer than three studies	Low
Asthma exacerbation	Very low	Fewer than three studies	Very low
ALRI	Low	Very low	Very low to low
COPD incidence	Low	Low	Low
COPD prevalence	Very low	Fewer than three studies	Very low
COPD exacerbation	Very low	Fewer than three studies	Very low
Wheeze ever	Low	Fewer than three studies	Low
Active wheeze	Low	Fewer than three studies	Low

9.5.2 FINDINGS IN RELATION TO OTHER ASSESSMENTS AND STUDIES

The 2010 HEI Traffic Review (HEI 2010) concluded that for children, the evidence was sufficient to infer a causal role for TRAP in the exacerbation of asthma. In addition, the 2010 review indicated that there was suggestive, but not sufficient, evidence to infer a causal role for traffic in the onset of asthma in children and in the exacerbation of symptoms in adults; the evidence was inadequate for understanding the contribution of TRAP exposure to the onset of adult asthma. A comparison of the present results with those in the 2010 review is difficult because the methodology differs between the two reviews and the overall database of studies has increased considerably for some outcomes since October 2008, the last publication date for inclusion in the 2010 review. Regarding the exacerbation of asthma in children, the 2010 review was based primarily on indirect traffic measures and some long-term NO_2 studies. In addition, most studies in the 2010 review on exacerbations of asthma have been categorized either as active or asthma ever in the current HEI Traffic Review, and asthma exacerbation in the current review (low confidence) was limited to participants with asthma. This may explain the difference in conclusions. Moreover, the exposure framework in the current review has been changed to include both studies in the near-road and neighborhood environment and an in-depth analysis of the high-traffic specificity studies. Nonetheless, the overall judgment of a moderate-to-high level of confidence in an association between TRAP and asthma onset (both in children and adults) represents a substantial increase in the confidence compared with what had been reported in the 2010 review (HEI 2010). The assessment of a moderate to high level of confidence in the evidence for ALRI in children represents a new finding for an outcome that was not included in the earlier review.

The Panel's assessments agree partially with other recent assessments of the evidence for health effects of pollutants that did not consider the exposure's direct relationship to traffic or

the level of specificity. Regarding NO_2, both the Health Canada (2016) and the U.S. Environmental Protection Agency (U.S. EPA 2016) assessments were available. The Health Canada (2016) report indicated that the epidemiological associations of NO_2 with respiratory health endpoints exhibit consistency, strength of association, and coherence across disciplines, as well as some indication of robustness and biological plausibility. However, considering the questions surrounding the possible role of copollutants, the overall evidence indicated that there is "likely a causal" relationship between long-term exposures to current levels of ambient NO_2 and respiratory outcomes related to the development of asthma. In addition, the Health Canada report emphasized that the evidence was stronger for children than for adults. In the U.S. EPA (2016) assessment, there was a likely causal relationship between long-term NO_2 exposure and respiratory outcomes based on evidence for the development of asthma; the evaluation was reached based on the results of epidemiological studies and experimental studies that characterize a potential mode of action for NO_2. Similarly, the U.S. EPA (2019) evaluation on $PM_{2.5}$ indicated a likely to be causal relationship between long-term $PM_{2.5}$ exposure and respiratory outcomes, with the strongest evidence for asthma development and less certain evidence for respiratory infections and COPD development. The agreement between the assessment of the individual pollutants (NO_2 and $PM_{2.5}$) on respiratory diseases, in particular asthma onset in children, and the current independent evaluation provides a strong support of the current findings.

Similarly, support for the Panel's evaluation is provided from the reported results of an official ATS Workshop on air pollution and the outcomes asthma onset and COPD incidence (Thurston et al. 2020). The Workshop found that long-term exposure to air pollution, especially metrics of TRAP such as NO_2 and BC, is associated with the onset of childhood asthma. However, they reported that the evidence for a causal role in adult-onset asthma or COPD incidence was insufficient. The conclusion in Thurston and colleagues on asthma incidence in children was based on two earlier systematic reviews conducted in 2017 (Hehua et al. 2017; Khreis et al. 2017) and on the results of the large Children's Health Study in California (Garcia et al. 2019) where decreases in ambient NO_2 and $PM_{2.5}$ between 1993 and 2014 were significantly associated with lower asthma incidence.

The results from animal toxicological studies and especially from controlled human exposure studies are relevant and provide insights on results from epidemiological studies, particularly with respect to pathophysiological mechanisms underlying the observed associations (see Chapter 3). For example, NO_2 in ambient air is recognized as a reactive gas that rapidly reacts with antioxidants and other constituents of the epithelial lining fluid of the respiratory tract (U.S. EPA 2016). Reactions with NO_2 lead to the formation of secondary oxidation products that can induce oxidative stress, inflammation, allergic responses, and altered immune function, all of which are events in the mode of action proposed for asthma development and exacerbation. For $PM_{2.5}$, the U.S. EPA (2019) assessment describes two pathways that provide biological plausibility for epidemiological evidence of respiratory health effects. One pathway involves respiratory tract injury, inflammation, and oxidative stress that may lead to morphological changes and lung function decrements, which are linked to asthma and COPD exacerbations. Respiratory tract inflammation may also lead to altered host defense, which is linked to increased respiratory infections. Short-term health effect studies have reported associations between TRAP and ALRI hospital admissions or emergency department visits in children (Chapter 4). The second pathway described in the U.S. EPA assessment on $PM_{2.5}$ involves the activation of sensory nerves in the respiratory tract leading to lung function decrements, which are linked to asthma and COPD exacerbations. Other co-emitted pollutants, such as UFPs may also enhance the inflammatory processes of the airways. Finally, panel studies, particularly those that employed a crossover design with real-world traffic exposure, have reported associations between short-term TRAP exposures and biomarkers for lung inflammation and lung function (Chapter 4).

The findings of the current HEI Traffic Review in relation to incidence of asthma in children agree with a recent report from Health Canada (2020), which considered the evidence regarding TRAP exposure and asthma, allergies, and lung function. Health Canada (2020) concluded that there is sufficient evidence of a causal relationship between TRAP exposure and asthma incidence and prevalence in children on the basis of different lines of evidence: (i) the results of the existing systematic reviews of epidemiological studies; (ii) the fact that the strongest associations were observed for NO_2 and BC, given that NO_2 is considered to be the most direct measure of TRAP and BC is a marker for diesel vehicle traffic; and (iii) supporting experimental evidence that TRAP or its components can induce airway inflammation and oxidative stress, and airway hyperresponsiveness in controlled human exposure studies and in experimental animal studies. On the basis of similar considerations, but less available human evidence, Health Canada concluded that the evidence was inadequate or suggestive of, but not sufficient to infer, a causal relationship between TRAP exposure and asthma incidence and prevalence, respectively, in adults. The Panel's assessment on TRAP and asthma incidence in adults was moderate to high, an upgrade of the Health Canada (2020) position that was motivated by the consistency of the effects, mainly NO_2, across many well-designed cohort studies.

After the completion of the systematic review, the Panel identified a few recently published high-quality studies that are also worth mentioning, as they help in the interpretation of the findings. Han and colleagues (2020) conducted a systematic review of the role of various pollutants on the development of childhood asthma. They found 27 studies for inclusion in the meta-analysis; the results showed that

exposure to air pollution increased the risk of asthma among children with statistically significant effect estimates for: $PM_{2.5}$, NO_2, benzene, and total volatile organic compounds. Although their criteria for study selection and traffic specificity were different from those employed here, leading to inclusion of more studies, their findings support the conclusions presented here. A long follow-up of the Dutch PIAMA birth cohort until 20 years of age (Gehring et al. 2020) reported a higher incidence of asthma with higher exposure to traffic-related pollutants at the birth address that was persistent with age (RR [95% CI] 1.12 [1.03–1.22] per 0.3-1×10^{-5}/m $PM_{2.5\ abs}$ to 1.20 [1.10–1.32] per 9.2-μg/m^3 NO_2). The Panel's assessment of the evidence for adult asthma is also well supported by the results from the large European ELAPSE study (Effects of Low-Level Air Pollution: A Study in Europe, on the incidence of asthma (Liu et al. 2020) in a pooled cohort of 98,326 participants with 1,965 new asthma cases during a follow-up of about 16 years. The authors reported strong associations with hazard ratios of 1.22 (95% CI: 1.04–1.43) per 5-μg/m^3 for $PM_{2.5}$, 1.17 (1.10–1.25) per 10-μg/m^3 for NO_2, and 1.15 (1.08–1.23) per 0.5-1×10^{-5}/m for BC. Furthermore, investigators from the same study reported on COPD incidence (hospital discharge diagnoses) from the same cohort (4,928 new cases; Liu et al. 2021). The adjusted hazard ratios for associations with COPD incidence were 1.17 (1.06–1.29) per 5-μg/m^3 for $PM_{2.5}$, 1.11 (1.06–1.16) per 10-μg/m^3 for NO_2, and 1.11 (1.06–1.15) per 0.5-1×10^{-5}/m for BC.

9.5.3 STRENGTHS AND LIMITATIONS

The review covers a wide range of conditions (from onset to exacerbations) in children and adults without restriction by geography or publication date. Several distinct outcomes were considered to assess the role of TRAP on incidence, prevalence, and exacerbations of the respiratory conditions. This provides a thorough, up-to-date assessment of the evidence of an association of respiratory outcomes with TRAP. The application of both a narrative assessment and a modified OHAT assessment is another strength of the review, as it allows one to integrate several pieces of the evidence into a unified picture, while considering the complexities of the studies and study quality.

The main limitations in the assessment were related to outcome definitions and limited numbers of studies. One challenge was defining and selecting appropriate outcomes for the analyses (e.g., regarding multiplicity of outcomes, outcome misclassification, and nonindependence of studies with regards to outcomes) for different study designs and windows of exposure. The Panel acknowledges that a closer examination of the differential effects of the TRAP indicators on childhood asthma by specific subgroups (e.g., by age, sex, or specific phenotypes such atopic status) could have provided additional insights, but the information was not always available, and the effort was outside the scope of the systematic review.

There were issues related to both the narrative assessment and the confidence assessment for the body of evidence; these points are summarized later. First, it was necessary to consider individual studies, as in several instances a meta-analysis was not possible. An example was the assessment of asthma onset in adults where, except for NO_2, only individual studies were available for other pollutants. Second, the Panel was more inclined in the narrative assessment to give a high confidence rating to cohort (and case-control) studies investigating incidence measures than to (cross-sectional) studies investigating prevalence measures. Third, there were questions about the need to downgrade confidence based on unexplained inconsistency. Following the study protocol, the Panel downgraded the evidence if there was high heterogeneity and considered the direction of the effect estimate rather than its magnitude. Moreover, the Panel considered the degree of unexplained inconsistency extensively in the evaluation. Several reasons that could explain heterogeneity were considered, including risk of bias, particular aspects of the study design, and geography, but it remained difficult to truly isolate which of these factors may have led to variations among studies. The Panel judged this to be a more insightful approach than automatically downgrading based on statistical tests for heterogeneity, given their well-known limitations. Fourth, in several instances a downgrade for imprecision was necessary because of the limited sample size or because of wide confidence intervals, with summary estimates that clearly included unity. Fifth, there was a possibility for an upgrade because of consistency of the summary estimates for NO_2 and $PM_{2.5}$ and asthma onset in children, but the estimates varied substantially, and the confidence intervals were wide. Finally, many of the studies in the current HEI Traffic Review reported associations of the same outcome with multiple traffic-related air pollutants (e.g., EC, NO_2). As such, the assessments are not fully independent. Despite the difficulties of the confidence assessment of the body of evidence, the Panel noted that the conclusion from the narrative assessment and the modified OHAT assessment broadly agree.

9.5.4 UNANSWERED QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The results of the Panel's assessment indicate additional areas of research related to the relationship of respiratory effects with TRAP exposure. For the respiratory outcomes for which there are some suggestions of an association with TRAP, but for which the evidence is still limited, the Panel identified the following future research needs:

1. Although combined toxicological and epidemiological evidence supports the hypothesis that long-term TRAP is related to COPD incidence in adults, further research is needed to evaluate the extent of the association.
2. Given the strong association found between TRAP and the occurrence of ALRI in children, and because this

outcome is particularly common in older adults, more studies are needed to understand the role of TRAP in ALRI occurrence in adult populations.

3. There is strong evidence that short-term exposure to some traffic-related air pollutants, particularly for NO_2 and CO, are related to exacerbation of asthma and COPD (see Chapter 4) but the evidence for long-term exposure needs to be further studied.

For the respiratory outcomes for which there was a moderate to high confidence in the evidence for an association, the Panel identified the following future research needs:

1. A robust association has been found between TRAP and asthma onset in children and corroborated by the results for asthma ever and active asthma. However, the relevant period of exposure (prenatal, first years of life, later childhood) is not well established, and more research is warranted into the relevant exposure windows for asthma onset in children (Lu et al. 2020).
2. Studies have provided conflicting evidence regarding the specific age at which air pollution-related asthma initiates. In other words, studies have found that the association between childhood asthma and TRAP is affected by the timing of the assessment of asthma. In a review of seven studies, TRAP exposure appeared to be associated with both transient and persistent asthma or wheezing phenotypes, but there was little evidence to suggest a relationship between TRAP exposure and late-onset asthma or wheezing (Lau et al. 2018, 2020). On the other hand, a long follow-up of the PIAMA cohort (Gehring et al. 2020) indicated that the associations of NO_2 and $PM_{2.5\ abs}$ at the birth address were rather stable from the age of four years onward and did not decrease in early adulthood.
3. NO_2 was the pollutant most commonly studied, and few studies have used TRAP indicators such as EC and UFPs; future studies should carefully assess associations with these pollutants to increase understanding of whether the epidemiological associations found for TRAP are due to direct effects of NO_2, to another component of TRAP, or to the broader mixture of correlated components indicative of TRAP. This research need has also been identified by others (e.g., Thurston et al. 2020).
4. Substantial heterogeneity was observed in many meta-analyses. Further research is required to understand the reasons for the heterogeneity and to assess the consequences for the magnitude and precision of the summary estimates and the characteristics of the populations to which they apply.
5. New research on TRAP and respiratory outcomes will benefit from advanced exposure methods (Caplin et al. 2019), including personal-level exposure assessment to assess the effects of mobility, exercise, and home characteristics on the individual exposure profiles. These new methods can be extremely useful for investigating mechanistic pathways and health outcomes at both the individual and molecular levels, including epigenetic changes (Cosín-Tomás et al. 2021).

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MATERIALS AVAILABLE ON THE HEI WEBSITE

Appendices A to C and Additional Materials 9.1 to 9.8 contain supplemental material not included in the main report. They are available on the HEI website at *www.healtheffects.org/publications*.

Appendices

9A Wheeze Outcomes in Children and Adults

9B Additional Figures and Tables

9C References for Studies Included in the Systematic Review of Respiratory Outcomes

Additional Materials

9.1 Asthma Onset

9.2 Prevalence of Asthma Ever

9.3 Prevalence of Active Asthma

9.4 Acute Lower Respiratory Infections (ALRI)

9.5 Incidence of Chronic Obstructive Pulmonary Disease (COPD)

9.6 Prevalence of Active Wheeze

9.7 Prevalence of Wheeze Ever

9.8 Risk of Bias Rationales for Studies Included in Meta-analyses

ABBREVIATIONS

ALRI	acute lower respiratory infection
ATS	American Thoracic Society
BC	black carbon
BMI	body mass index
BS	black smoke
CI	confidence interval
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
EC	elemental carbon
ERF	exposure–response function
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
HR	hazard ratio
IgE	Immunoglobulin E
ISAAC	International Study on Asthma and Allergy in Children
LUR	land use regression
NO	nitric oxide
NO_2	nitrogen dioxide
NO_x	nitrogen oxides

OHAT	Office of Health Assessment and Translation
OR	odds ratio
PAH	polycyclic aromatic hydrocarbons
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
$PM_{2.5\ abs}$	$PM_{2.5}$ absorbance
PM_{coarse}	particulate matter with aerodynamic diameter between 10 μm and 2.5 μm
PM_{10}	particulate matter ≤10 μm in aerodynamic diameter
PNC	particle number concentration
RR	relative risk
RoB	risk of bias
SES	socioeconomic status
TRAP	traffic-related air pollution
UFPs	ultrafine particles
U.S. EPA	U.S. Environmental Protection Agency

PART C: FINDINGS FROM SYSTEMATIC LITERATURE REVIEWS OF EPIDEMIOLOGICAL STUDIES

Chapter 10

Traffic-Related Air Pollution and Cardiometabolic Outcomes

CONTENTS

CHAPTER 10

Traffic-Related Air Pollution and Cardiometabolic Outcomes

10.1 SUMMARY

The 2010 HEI Traffic Review concluded that the evidence was "suggestive, but not sufficient" to infer a causal relationship between exposure to traffic-related air pollution (TRAP*) and cardiovascular morbidity, which was mainly due to the very small number of long-term studies. As of 2010, only three studies of ischemic heart disease (IHD) and coronary events, a subgroup of IHD, were available. Importantly, diabetes and stroke were not covered in the 2010 review due to a lack of studies. Since then, a substantial number of studies have been published on TRAP and cardiometabolic morbidity, which increased the evidence substantially, although a direct comparison with the earlier HEI traffic review is difficult because of the difference in scope and methods.

In the current review, the Panel investigated IHD, coronary events, stroke, and diabetes. Overall, 57 studies were identified that met the predefined inclusion criteria for this review. Most studies on IHD, coronary events, and stroke were cohort or case-control studies based on incident cases. Studies of diabetes examined both incident diabetes, mostly using data from cohorts, and prevalent diabetes, using a cross-sectional design. The studies varied in size and measurement detail, from a few large-scale administrative cohorts, often based in registry or hospital discharge datasets for outcome assessment, to several smaller studies with detailed information on individual health status, health-related behaviors, and socioeconomic status (SES), and with an elaborate outcome assessment based on clinical examinations and adjudication with medical records. Exposure assessment was primarily based on land use regression (LUR) models or on dispersion or chemical transport models (CTMs) with only very few studies using surface monitoring by fixed or mobile monitors. Nitrogen dioxide (NO_2), elemental carbon (EC) (which includes related metrics such as black carbon, black smoke and PM absorbance, $PM_{2.5}$, and PM_{10} (PM ≤2.5 and ≤10 μm in aerodynamic diameter, respectively) were the most studied

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* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

Highlights

- A total of 57 studies in adult populations from mainly North America and Europe were included in the evaluation of selected cardiometabolic outcomes, the majority of which were also included in meta-analyses.
- Most studies on ischemic heart disease, coronary events, and stroke were cohort or case-control studies, based on incident cases. For diabetes, analyses were conducted on both incidence, mostly using data from cohorts, and prevalence measures, using a cross-sectional study design. Studies were quite diverse, including smaller cohort and case-control studies with well-characterized study populations as well as very large studies based on administrative data that typically lacked individual lifestyle information. The overwhelming majority of studies were published after the 2010 HEI Traffic Review, demonstrating the large increase in the evidence base within the past decade.
- The overall confidence in the evidence was considered moderate for an association of traffic-related air pollution with ischemic heart disease and diabetes, low to moderate for an association of traffic-related air pollution with stroke, and low for the association of traffic-related air pollution with coronary events. The meta-analytic estimates were consistent with a positive association of NO_2 with diabetes prevalence, and EC and PM_{10} with ischemic heart disease. The meta-analytic estimates of EC, PM_{10}, and $PM_{2.5}$ with stroke were positive, though imprecise, but the evidence was strengthened by several high-quality studies with monotonic exposure–response functions or subset analyses indicating stable associations across levels of exposure. For coronary events, the number of studies was smaller and insufficient to conduct meta-analyses, except for NO_2, which yielded a positive, though imprecise, association. Additional evidence was available from indirect traffic measures for all four health outcomes, as well as from studies using diverse metrics of traffic exposure, for example, ultrafine particle concentrations, which were not included in the meta-analysis.
- Because cardiometabolic outcomes are likely influenced by traffic noise, some studies investigated possible confounding or effect modification by noise with mostly similar results after adjustment for co-exposure to noise.
- There is a need to strengthen this evidence in other areas of the world with different exposure levels and to conduct studies with specific attention to outcome assessment and confounder control.

pollutants. Most studies were conducted in North America and Europe during the last two decades with exposure periods ranging from the 1970s through 2015, and a few identified studies were conducted in Asia. The Panel's assessment is primarily based on studies of general population samples of adults; however, a few studies included selected subgroups of adults at higher risk.

Table 10.1 summarizes the evidence for associations between TRAP and the selected cardiometabolic outcomes. In the narrative assessment, the Panel found a moderate level of confidence in the presence of an association between exposure to TRAP and IHD incidence. The moderate assessment was based on four high-quality studies from different regions across Europe, yielding a positive meta-analytic estimate for PM_{10}, two studies with monotonic exposure–response relationships, and on several high-quality studies for EC and $PM_{2.5}$ in different populations from North America and Europe, including the multicohort analysis of 11 cohorts within the ESCAPE study. Moreover, the consistent associations of NO_2, nitric oxide (NO), EC, and $PM_{2.5}$ with fatal IHD in the by far largest study representative of the general population lends further support to this assessment. Additional support of an association was provided by a small number of studies showing consistent associations across several different pollutants, and a reasonable possibility that the positive findings are not explained by confounding or chance. Further support is supplied by a small number of studies showing associations to other highly traffic-specific pollutants that were not meta-analysed, and from a small number of studies investigating indirect measures of traffic exposure. Nevertheless, the results were not entirely consistent across all exposure indicators; most notably the Panel observed null findings for NO_2 and nitrogen oxides (NO_x) in the meta-analyses. Also, the PM_{10} studies had only a moderate degree of traffic specificity, but showed the most robust associations, making the evidence less compelling.

The Panel found a low level of confidence in the presence of an association of TRAP with coronary events due to the small number of high-quality studies per pollutant. Chance, confounding, and other biases cannot be ruled out with appropriate certainty. For NO_2, where the body of evidence is larger, the evidence from the studies was generally supportive but not entirely consistent, with one large study reporting a negative association.

The Panel found a moderate level of confidence in the presence of an association of TRAP with stroke incidence. The assessment is based on mostly consistent evidence for EC, PM_{10}, and $PM_{2.5}$ associations with stroke from a moderately large number of studies. Several high-quality studies from different regions across Europe and in North America yielded positive meta-analytic estimates for EC, PM_{10}, and $PM_{2.5}$ in different populations, albeit imprecise and with confidence intervals (CI) that included unity. The assessment is supported by limited evidence from studies not included in meta-analyses, indirect traffic measures, and by the relative stability in noise-adjusted models. What makes the evidence less compelling is the absence of evidence for the gaseous pollutants, yielding null findings in the meta-analyses. The Panel refrained from giving a higher rating because the overall number of studies was still rather limited, because the traffic specificity of the PM_{10} and $PM_{2.5}$ exposures was only moderate, and because of the null results in the analyses of the gaseous pollutants NO_2 and NO_x, which are thought to be more traffic specific.

The Panel rated the confidence in the presence of an association between TRAP and diabetes as moderate. The positive meta-analytic summary estimate for NO_2 and diabetes prevalence in adults in a moderately large number of studies conducted in different populations provides evidence for an association. This finding is supported by the fact that all studies except one provided positive estimates for traffic-related particulate matter (PM) and the incidence or prevalence of diabetes. Further supporting evidence includes the higher effect estimates in those studies with a more valid outcome assessment and more detailed confounder control. In addition, all of the seven studies that analyzed indirect traffic measures found associations with at least one measure. It is unlikely that potential biases have affected all estimates of association in the same direction in diverse populations from different regions or that the observed associations can be explained by concurrent traffic noise exposure.

The results of the modified Office of Health Assessment and Translation (OHAT) assessment to assess the confidence in the quality of the body of evidence yielded moderate ratings for TRAP and IHD and diabetes. The assessment yielded a low rating for TRAP and coronary events and stroke. Initial confidence ratings for most pollutant–outcome pairs started as moderate because most studies were based on cohort and case-control studies. Imprecision often resulted in downgrading. By contrast, the Panel upgraded the confidence ratings of selected pollutant–outcome pairs based on a few large and high-quality studies with monotonic exposure–response functions or, in the case of the ESCAPE studies, a subset analysis censoring participants at higher concentrations. Other reasons for down- or upgrades were large and unexplained heterogeneity and the potential for bias toward the null in a few pollutant–outcome pairs.

In conclusion, the overall confidence assessment combining the narrative assessment and the modified OHAT assessment was considered moderate for an association of TRAP with IHD and diabetes, low to moderate for an association of TRAP with stroke, and low for the association of TRAP with coronary events. Due to the uncertainties related to the assessment of potential confounders and the potential for outcome misclassification, there is a need to strengthen the

Table 10.1. Summary of the Confidence in the Evidence for an Association Between TRAP and Cardiometabolic Outcomes[a]

Pollutant	IHD Incidence	Coronary Events Incidence	Stroke Incidence	Diabetes
Meta-analytic Summary Estimate and Narrative Assessment to Assess Confidence in the Presence of an Association with TRAP				
NO_2	0.99 (0.94–1.05) *N* = 5	1.03 (0.95–1.11) *N* = 7	0.98 (0.92–1.05) *N* = 7	1.04 (0.96–1.13) *N* = 7 (incidence) 1.09 (1.02–1.17) *N* = 7 (prevalence)
NO_x	0.99 (0.96–1.03) *N* = 4	Fewer than three studies	0.99 (0.94–1.04) *N* = 8	1.02 (0.96–1.10) *N* = 4 (incidence)
EC	1.01 (0.99–1.03) *N* = 5	Fewer than three studies	1.03 (0.98–1.09) *N* = 6	1.16 (0.57–2.36) *N* = 3 (incidence)
PM_{10}	1.14 (0.99–1.31) *N* = 4	Fewer than three studies	1.09 (0.96–1.23) *N* = 5	1.19 (0.87–1.63) *N* = 4 (prevalence)
$PM_{2.5}$	1.09 (0.86–1.39) *N* = 4	Fewer than three studies	1.08 (0.89–1.32) *N* = 4	1.05 (0.96–1.15) *N* = 4 (incidence) 1.08 (0.70–1.67) *N* = 3 (prevalence)
Narrative assessment	Positive summary estimate with marginal overlap of the null for PM_{10} and evidence suggesting a monotonic exposure–response function. Evidence available for other meta-analyzed TRAP was suggestive for EC and $PM_{2.5}$, but overall less consistent. No evidence for an association of gaseous pollutants.	Positive but imprecise summary estimate for NO_2 and some evidence suggesting a monotonic exposure–response function for NO_2. Limited evidence for other pollutants from a small number of studies. Absence of consistent confounding by noise. Limited evidence from indirect traffic measures.	Positive but imprecise summary estimates for three particulate pollutants and evidence suggesting a monotonic exposure–response function for EC, PM_{10}, and $PM_{2.5}$. Additional evidence from indirect traffic measures. Absence of consistent confounding by noise. No evidence for an association of gaseous pollutants.	Positive summary estimate for NO_2 and diabetes prevalence, supported by consistent positive but imprecise meta-analytic estimates for the other meta-analysed pollutant–outcome pairs. Higher effect estimates in studies with more valid outcome assessment and more comprehensive confounder control. Indirect traffic measures positive in most studies.
	Moderate	**Low**	**Moderate**	**Moderate**
Modified OHAT Assessment to Assess Confidence in the Quality of the Body of Evidence				
NO_2	Low	Moderate	Low	Moderate
NO_x	Moderate	Fewer than three studies	Moderate	Low
EC	Moderate	Fewer than three studies	Low	Low
PM_{10}	High	Fewer than three studies	Moderate	Very low
$PM_{2.5}$	Moderate	Fewer than three studies	Moderate	Low
TRAP	**Moderate**	**Low**	**Low**	**Moderate**
Overall Assessment Combining the Narrative Assessment and Modified OHAT Assessment				
TRAP	**Moderate**	**Low**	**Low to moderate**	**Moderate**

N = number of studies; OHAT = Office of Health Assessment and Translation.

[a] The table presents only the five pollutants most widely used. The individual pollutants are considered as indicators of the TRAP mixture. Relative risks (RRs) and 95% confidence intervals are expressed per 10-, 20-, 1- and 5-μg/m^3 increments for NO_2, NO_x, EC, and $PM_{2.5}$, respectively.

evidence with specific attention to confounder control and outcome assessment. Moreover, more studies in other areas of the world with different exposure levels and baseline disease risks are needed.

10.2 INTRODUCTION

The 2010 HEI Traffic Review concluded that the evidence for traffic-related exposure and cardiovascular morbidity was "suggestive, but not sufficient" to infer a causal relationship, due to a low number of studies. The current review on cardiometabolic outcomes describes and evaluates the evidence for four outcomes: (1) IHD, including angina, acute or repeated myocardial infarction, complications after acute myocardial infarction, coronary atherosclerosis and other forms of chronic IHD (International Classification of Diseases [ICD]-10 I20-25); (2) coronary events, defined as incident acute myocardial infarction, cardiac arrest, or sudden cardiac death (ICD-10 I21, I46); (3) stroke, which includes both ischemic and hemorrhagic strokes (ICD-10 I60-69); and (4) diabetes (ICD-10 E10-14). The Panel analyzed IHD and coronary events separately, because of their differences in breadth of definition and due to their differences in pathology. IHD was defined as a relatively broad category of acute and chronic forms of IHD with different pathologies, whereas the outcome coronary events focused on the elicitation of acute thromboembolic events. The same study could contribute to both outcomes if different estimates were available. As exact definitions for the chosen endpoints vary over time due to changes in diagnostic criteria, as well as between studies, outcomes were broadly categorized into these outcome groups. Although congestive heart failure is a frequent complication of IHD, it was not included in the current review, because it is an unspecific syndrome related to multiple other etiologies besides IHD.

The description of the evidence includes a summary of the identified studies, results of meta-analyses for each pollutant–outcome pair with a sufficient number of studies, and additional sensitivity analyses according to geographic region, traffic specificity, and evaluation of potential biases. In the narrative assessment, the findings are discussed and interpreted in connection with evidence from other studies identified in the systematic review, but not included in the meta-analysis, including studies using indirect traffic measures. In addition, a confidence assessment using modified OHAT methods was conducted for each health outcome and was ultimately combined with the narrative assessment into an overall confidence assessment. Finally, results are discussed and compared with other research, and questions for future research are identified.

Most studies reviewed in this chapter were cohort studies examining incident cardiometabolic disease. Only a few publications reported results from case-control or cross-sectional studies. Because case-control studies based on incident cases were also given an initial rating of moderate in addition to cohort studies in the modified OHAT assessment, we analyzed these two study designs together in the main meta-analyses.

The included analyses of cohort studies restricted the baseline population to participants without a history of the respective disease. Individuals with a history of the disease at baseline were usually identified by either self-report or linkage with hospital discharge data or disease-specific registries. This sets the incidence analysis apart from the analyses of cause-specific mortality in the general population, which includes persons with a history of prior disease (Chapter 11 TRAP and Mortality). Interpretation of these two analyses differ, as the investigation of incidence specifically targets the development of the disease, while the investigation of cause-specific mortality cannot directly inform about the process of disease development.

The studies included in this chapter varied substantially in design and methods, including smaller studies with several hundred participants and large or very large studies with up to a few million participants in administrative cohort studies. Notably, the design of the study and size of the study population determined the method of outcome assessment. Because the underlying cardiometabolic diseases investigated in this chapter often have a long asymptomatic or oligosymptomatic phase, the correct classification of individual study participants regarding disease status is difficult (Sidebar 10.1). The gold standard diagnosis is an in-depth, in-person interview and physical examination coupled with an adjudication of cases based on medical records by trained personnel. Consequently, this can only be done in smaller studies with a limited number of participants, as this process is resource-intensive. Most often, the presence of IHD, coronary events, or stroke was therefore operationalized by identifying a first documented distinct event such as a first hospitalization for acute myocardial infarction or stroke from administrative records, disease registries, or death certificates with variable sensitivity and specificity. Undetected events, which range from 5% to 62% for stroke in the general population (Fanning et al. 2014), or undetected diabetes, approximately 40% of cases in North America and Europe (IDF 2019) remain problematic, specifically because there are several pathways through which probability of diagnosis can be related to exposure. These include differential access to and making use of health care due to differences in SES, which in turn might be related to TRAP exposure. Moreover, misclassification across subtypes of cardiovascular disease is common, specifically in primary care (Remes et al. 1991).

The incidence studies targeting IHD, coronary events, or stroke reported results for different combinations of fatal (usually defined as death within 30 days of the event) and nonfatal events. Therefore, results were reported as a combined outcome of fatal and nonfatal events and also as separate outcomes of fatal and nonfatal events, where available. When a study reported separate effect estimates for fatal and

SIDEBAR 10.1 SUMMARY OF CRITICAL CONSIDERATIONS REGARDING THE ROLE OF TRAP AND THE SELECTED CARDIOMETABOLIC OUTCOMES

To help in the interpretation of the results, we summarize below major considerations and challenges in assessing the role of TRAP in the development of selected cardiometabolic health outcomes.

- **Validity of Outcome Assessment** The methods of outcome assessment varied substantially—from dedicated clinical examinations in a study center and adjudication of cases based on an independent comprehensive medical records review to linkage with disease registries, medical records, self-reported disease, and death certificates—leading to different sensitivity and specificity of disease-status classification (Coady et al. 2001). Validity of diagnoses for cardiovascular disease has been shown to be lower in older compared with younger ages, in specific subtypes of disease compared with others, and on death certificates compared with hospital-based diagnoses (Davidson et al. 2020; Lloyd-Jones et al. 1998; McCormick et al. 2014). IHD can be misclassified as congestive heart failure, particularly in primary health care settings (Davidson et al. 2020; Hobbs 2000; Verdú-Rotellar et al. 2017). Moreover, diagnostic criteria for the classification of acute events and access to diagnostic tests (i.e. availability of computed tomography scan and magnetic resonance imaging for diagnosis of stroke) have changed during the period covered in this review, leading to differences in case definition and methods of detection during this time span. For diabetes, a disease with a long oligosymptomatic prediagnostic phase, reliance on self-report or documented disease will typically miss 40% of cases in North America or Europe (low sensitivity), while in-depth study center examinations will have a much higher sensitivity (IDF 2019).
- **Role of Individual-Level SES** An array of socioeconomic conditions contributes to the development of cardiometabolic outcomes. Socioeconomic conditions also affect the probability that a person who has any of these conditions is diagnosed, which is relevant to the many studies included in this review that relied on health care system data for disease classification. Furthermore, because SES factors influence where people live, exposure to TRAP may vary by SES (Hajat et al. 2015). Thus, SES is a key potential source of confounding in estimating the effects of TRAP and may also contribute to differential outcome misclassification. The degree to which SES is an important potential confounder and to which SES contributes to differential outcome misclassification likely differs by location and over time.
- **Adjustment for Potential Mediators** Several studies on IHD, coronary events, or stroke were adjusted for preexisting comorbidities, such as hypertension and diabetes. Those preexisting comorbidities may be mediators and on the causal pathway between exposure and outcome and can distort the results when they are treated as covariates in analyses of TRAP effects. In general, such adjustments would tend to attenuate the association.
- **Restriction to Survivors** Some studies included only short- or long-term survivors of IHD, coronary events, or stroke in the analysis. Survival is a common effect of the exposure and the outcome of interest. Investigations only within the stratum of surviving individuals may result in collider stratification bias, which can lead to bias in either direction.
- **Confounding by Traffic Noise or Other Spatially Related Factors** The analysis of TRAP with cardiometabolic disease is potentially confounded by traffic noise, a co-exposure that has been shown to be related to cardiovascular disease (World Health Organization [WHO] 2018), or by other contextual characteristics (e.g., small-area level SES or green space). Only few studies included an evaluation of these co-exposures. On the other hand, depending on the correlation of contextual factors with TRAP and their respective measurement errors, it is possible that inclusion of contextual factors such as small-area level SES removes part of the effect of the exposure.
- **Critical Exposure Windows** Whereas high exposures to TRAP over the course of hours or days have been consistently associated with acute myocardial infarction and stroke (Mustafic et al. 2012; Shah et al. 2015), the most relevant time period of long-term TRAP exposure for the elicitation of a cardiometabolic health effect is unclear. The Panel evaluated long-term exposure estimates, mostly defined as a mean exposure over several years before the onset of disease. However, long-term exposure during early life, adolescence or young adulthood may also play a role. Specifically for cardiometabolic disease, evidence suggests that underlying pathology may be developed as early as childhood and adolescence and may result in preclinical changes (Raghuveer et al. 2016), which, however, fell outside of the report's focus on clinical outcomes. In the studies investigating overt clinical disease during adulthood, earlier exposure windows were explored in only a very few studies. These analyses are hampered by exposure misclassification due to instability of exposure models back in time over periods of several decades, lack of availability of accurate residential histories, and selective survival, among other things. It is therefore possible that the studies in the current review did not include the biologically most critical exposure estimates.

nonfatal events, and also for fatal or nonfatal events combined, the combined estimate was used in the meta-analysis because it was based on the maximum number of outcomes. The estimate for nonfatal events was used if an estimate for this combined outcome was not available. If neither was available, the estimate for fatal events was used. In addition, separate additional meta-analyses were conducted for fatal and nonfatal outcomes, including all available estimates. Additional details can be found in the General Methods chapter (Chapter 5). The distinction by fatality is important due to the devastating nature of these outcomes (fatality), but also because of the possibility of misclassification if events occur outside a health care setting. Acute myocardial infarction and stroke are associated with a relatively high case fatality rate of about 30%, and about 50% of fatal acute myocardial infarction cases occur outside the hospital. Of note, fatality from acute myocardial infarction and stroke has decreased substantially during the past 20 to 30 years. Over that period, diagnostic criteria have changed and the availability of diagnostic tests has increased in many parts of the world (Levine et al. 2016; Powers et al. 2019; Thygesen et al. 2018).

Most investigations of diabetes classified participants' disease status at a specific point in time (for example at the time of a dedicated examination during a study center visit), the exact time of onset is usually not available. A few mostly smaller to medium-sized studies conducted in-depth physical examinations with elaborate diagnostic methods, such as measurement of fasting glucose or oral glucose tolerance testing, being able to diagnose heretofore undiagnosed cases. Other mainly larger studies used administrative data or disease registry data of already diagnosed disease.

10.3 ISCHEMIC HEART DISEASE

10.3.1 STUDY SELECTION AND DESCRIPTION

The identified studies reported on the association of a wide range of traffic-related air pollutants and indirect traffic measures with IHD, including angina, acute or repeated myocardial infarction, complications after acute myocardial infarction, coronary atherosclerosis, and other forms of chronic IHD (ICD-10 I20-25) (Table 10.2 and Table 10.3). Three papers evaluated this association within the same cohort (Gan et al. 2010, 2011, 2012), one paper reported results separately for two cohorts (Stockfelt et al. 2017), and two papers were set within the ESCAPE analysis of 11 European cohorts (Cesaroni et al. 2014; Wolf et al. 2015). The Panel chose to analyze the individual cohorts within the ESCAPE publications as one study because the cohorts' characteristics and study's methodologies were sufficiently similar and standardized to consider it as one large study for this review. All studies except one (Hoffmann et al. 2006) were published after the HEI 2010 review (HEI 2010).

Some large studies did not enter this review of TRAP and IHD morbidity because their exposure assessments did not fulfill the requirements of the exposure framework. These included investigations within the Women's Health Initiative (Miller et al. 2007), the pollutant analysis in the Nurses' Health Study and the Health Professionals Study (Puett et al. 2009), and the California Teachers Cohort Study (Lipsett et al. 2011). Also, this review does not include studies investigating preliminary endpoints such as the development and progression of atherosclerosis, the most important underlying pathology for IHD events, or studies evaluating the influence of long-term traffic-related air pollution on survival after such an event has taken place.

In most included studies, the measured exposure period started in the 1990s. The identified study locations were limited to Europe and North America. Most studies investigated traffic pollutants, and four included indirect measures such as distance to traffic or traffic density. NO_2, NO_x, and EC were the TRAP exposure indicators used most often in the epidemiological studies. Mean long-term exposure of NO_2 varied across publications from 19 µg/m³ (Alexeeff et al. 2018) to 53 µg/m³ (Katsoulis et al. 2014). Mean long-term exposure of NO_x ranged from 13 µg/m³ (Bodin et al. 2016) to 63 µg/m³ (Carey et al. 2016). Mean long-term exposure of $PM_{2.5}$ ranged from 4 µg/m³ (Gan et al. 2011) to 9 µg/m³ (Stockfelt et al. 2017). The range of mean pollutant exposure was wider across the 11 cohorts in the ESCAPE multicohort analysis (NO_2: 8–60 µg/m³; NO_x: 14–107 µg/m³; $PM_{2.5}$: 7–31 µg/m³). Four studies, among them the ESCAPE multicohort analysis of 11 cohorts, estimated the health effects of traffic-related air pollutants with adjustments for concurrent traffic noise exposure.

All studies, except one, followed the design of capturing incident events from a cohort at risk at baseline. The exception was a study that investigated distance to roadways and the prevalence of IHD (Hoffmann et al. 2006). One cohort study investigated contrasts in TRAP exposure and IHD risk in participants that changed their residential address compared with those that did not (Gan et al. 2010). The smallest studies were set in Athens, Greece (2,752 participants; Katsoulis et al. 2014) and the Ruhr area of Germany (3,399 participants; Hoffmann et al. 2006). Most studies included more than 30,000 participants, with the largest involving 452,735 participants in Vancouver, Canada (Gan et al. 2011). All study populations included adult men and women, except for the PPS cohort, which included only men (Stockfelt et al. 2017).

Six studies reported on investigations set in population-based cohorts that featured data on individual-level SES and health-related behaviors such as smoking. Four of these publications identified incident IHD events primarily via linkage with ambulatory medical records, hospital discharge records, disease registries, and death certificates

Table 10.2. Key Study Characteristics of Articles Included in the Systematic Review for IHD—Pollutants

Reference	Study Name[a]	Location	Study Period	Sample Size[b]	Exposure Assessment	Pollutant	Mean or Median Exposure[c]	Fatality	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Alexeeff 2018	KPNC Oakland	Oakland, California, United States	2010–2015	41,869	Surface monitoring	NO_2	9.9	Fatal and nonfatal	HR	**1.05 (0.94–1.18)**	3.8 ppb
								Fatal		1.09 (0.89–1.34)	
						NO	4.9	Fatal and nonfatal		1.06 (0.95–1.17)	3.8 ppb
								Fatal		1.05 (0.88–1.25)	
						BC	0.36	Fatal and nonfatal		**1.05 (0.95–1.16)**	0.17 μg/m^3
								Fatal		1.12 (0.94–1.33)	
Bodin 2016	Scania Public Health Cohort	Scania, Sweden	2000–2010	117,178	Dispersion/ CTM	NO_x	13	Fatal and nonfatal	IRR	0.72 (0.39–1.34)	>30 vs. <10 μg/m^3
										1.05 (0.83–1.33)	20–30 vs. <10 μg/m^3
										0.77 (0.65–0.91)	10–20 vs. <10 μg/m^3
Carey 2016	CPRD London	London, United Kingdom	2005–2011	200,457	Dispersion/ CTM	NO_2	37.4	Fatal and nonfatal	HR	**0.97 (0.91–1.02)**	10 μg/m^3
						NO_x	63.0			**0.97 (0.93–1.01)**	20 μg/m^3
						Traffic $PM_{2.5}$	1.45			0.96 (0.91–1.02)	1 μg/m^3
Cesaroni 2014	ESCAPE	Multiple cities, multiple countries	1992–2010	100,166	LUR	NO_2	8–60	Fatal and nonfatal	HR	**1.03 (0.97–1.08)**	10 μg/m^3
						NO_x	14–107			**1.01 (0.98–1.05)**	20 μg/m^3
						$PM_{2.5\ abs}$	0.6–3.2			**1.10 (0.98–1.24)**	1 1×10^{-5}/m
						PM_{10} mass	14–48			**1.12 (1.01–1.25)**	10 μg/m^3
						PM_{coarse} mass	6–17			1.06 (0.98–1.15)	5 μg/m^3
						$PM_{2.5}$ mass	7–31			**1.13 (0.98–1.30)**	5 μg/m^3

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Table 10.2 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for IHD—Pollutants

Reference	Study Name[a]	Location	Study Period	Sample Size[b]	Exposure Assessment	Pollutant	Mean or Median Exposure[c]	Fatality	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Gan 2011	Vancouver Administrative	Vancouver, British Columbia, Canada	1999–2002	452,735	LUR	NO_2	32.1	Fatal and nonfatal	RR	**0.97 (0.95–0.99)**	8.4 μg/m^3
								Fatal		1.04 (1.01–1.08)	
						NO	32.0	Fatal and nonfatal		0.96 (0.94–0.98)	13.2 μg/m^3
								Fatal		1.06 (1.02–1.10)	
						$PM_{2.5\ abs}$	1.49	Fatal and nonfatal		**1.01 (1.00–1.03)**	0.94 1×10^{-5}/m
								Fatal		1.06 (1.03–1.09)	
						$PM_{2.5}$ mass	4.08	Fatal and nonfatal		**1.00 (0.98–1.02)**	1.58 μg/m^3
								Fatal		1.01 (0.98–1.05)	
Gan 2012	Vancouver Administrative	Vancouver, British Columbia, Canada	1999–2002	445,868	LUR	$PM_{2.5\ abs}$	1.5	Fatal	HR	1.06 (1.03–1.09)	0.97 1×10^{-5}/m
Katsoulis 2014	EPIC Athens	Athens, Greece	1994–2011	2,752	LUR	NO_2	53.1	Fatal and nonfatal	HR	**1.10 (0.90–1.36)**	10 μg/m^3
						PM_{10} mass	39.4			**1.41 (0.91–2.17)**	10 μg/m^3
Stockfelt 2017	GOT-MON	Gothenburg, Sweden	1990–2011	4,500	Dispersion/ CTM	NO_x	33	Fatal and nonfatal	HR	**1.00 (0.90–1.12)**	20 μg/m^3
						BC	0.8			**1.03 (0.78–1.36)**	1 μg/m^3
						PM_{10} mass	13			**0.91 (0.6–1.38)**	10 μg/m^3
						$PM_{2.5}$ mass	8.5			**0.92 (0.61–1.37)**	5 μg/m^3
						PM_{10} exhaust	0.3			1.00 (0.89–1.12)	0.29 μg/m^3
						Nontailpipe PM_{10}	1.7			1.01 (0.91–1.12)	1.48 μg/m^3
						Traffic PM_{10}	1.41			1.01 (0.91–1.12)	1.77 μg/m^3

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Table 10.2 (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for IHD—Pollutants

Reference	Study Name[a]	Location	Study Period	Sample Size[b]	Exposure Assessment	Pollutant	Mean or Median Exposure[c]	Fatality	Effect Measure	Effect Estimate (95% CI)[d]	Increment
	PPS	Gothenburg, Sweden	1990–2011	5,850[e]	Dispersion/ CTM	NO_x	42	Fatal and nonfatal	HR	**0.98 (0.92–1.05)**	20 μg/m^3
						BC	0.9			**0.94 (0.80–1.11)**	1 μg/m^3
						PM_{10} mass	13			**1.24 (0.98–1.59)**	10 μg/m^3
						$PM_{2.5}$ mass	9.3			**1.38 (1.08–1.77)**	5 μg/m^3
						PM_{10} exhaust	0.4			0.98 (0.92–1.05)	0.29 μg/m^3
						Nontailpipe PM_{10}	2.0			0.98 (0.92–1.04)	1.41 μg/m^3
						Traffic PM_{10}	2.4			0.98 (0.92–1.04)	1.7 μg/m^3
Wolf 2015	ESCAPE	Multiple cities, multiple countries	1992–2010	100,166	LUR	$PM_{2.5}$ Cu	0.5–11.8	Fatal and nonfatal	HR	1.05 (0.94–1.17)	5 ng/m^3
						$PM_{2.5}$ Fe	49–319.7			1.07 (1.01–1.13)	100 ng/m^3
						$PM_{2.5}$ Zn	10.1–39.2			1.14 (0.96–1.36)	10 ng/m^3

HR = hazard ratio; IRR = incidence rate ratio; RR = relative risk.

[a] All were cohort studies.

[b] All were studies in adults (age 18+).

[c] Units are in the increment column.

[d] No log transformations. **Bold** indicates the effect estimate was included in the meta-analysis.

[e] Male population.

Table 10.3. Key Study Characteristics of Articles Included in the Systematic Review for IHD—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Fatality	Traffic Measure	Effect Measure	Effect Estimate (95% CI)[b]	Increment
Carey 2016	CPRD London	Cohort	London, United Kingdom	2005–2011	200,457	Fatal and nonfatal	Density	HR	1.05 (0.98–1.13)	>100,000 heavy vehicle-km/year vs. none
									0.95 (0.90–1.00)	<100,000 heavy vehicle-km/year vs. none
							Distance		1.02 (0.95–1.09)	<100 vs. >250 m
									1.00 (0.94–1.07)	100–250 vs. >250 m
Cesaroni 2014	ESCAPE	Cohort	Multiple cities, multiple countries	1997–2010	100,166	Fatal and nonfatal	Density	HR	1.00 (0.95–1.06)	4,000 vehicle-km/day
Gan 2010	Vancouver Administrative	Cohort	Vancouver, British Columbia, Canada	1999–2002	328,609	Fatal	Distance	RR	1.29 (1.18–1.41)	<50 from major road or <150 m from highway vs. higher
Hoffmann 2006	HNR	Cross-sectional	Ruhr Areas, Germany	2000–2003	3,399	Nonfatal	Distance	OR	1.75 (1.16–2.62)	<150 vs. >150 m

HR = hazard ratio; IRR = incidence rate ratio; OR = odds ratio; RR = relative risk.

[a] All adult studies (age 18+) with both males and females.

[b] No log transformations.

(Bodin et al. 2016; Cesaroni et al. 2014; Stockfelt et al. 2017; Wolf et al. 2015). One study identified events in these sources in response to self and proxy reports during follow-up (Katsoulis et al. 2014). Another study identified events based on participant reports at enrollment (Hoffmann et al. 2006).

Health care administration databases formed the basis of very large cohorts in five studies. These studies typically do not have detailed and standardized information on health-related behaviors. The cohorts comprised members of a private health maintenance organization in the United States (Alexeeff et al. 2018), patients of the subset of general practitioners in the greater London area with linked primary care and hospital admissions records (Carey et al. 2016), and residents of metropolitan Vancouver covered by British Columbia's universal health insurance (Gan et al. 2010, 2011, 2012). Events in these studies were identified via ambulatory care and hospital records, as well as death registries (except Carey et al. 2016, which was not linked with the death registry). From the three publications for the Vancouver cohort, only the study by Gan and colleagues (2011) was used in the meta-analysis, since this was the main study; Gan and colleagues (2010) only reported indirect traffic measures that were not meta-analyzed and Gan and colleagues (2012) was an additional analysis investigating the influence of traffic noise on fatal IHD.

10.3.2 META-ANALYSES

Meta-analyses were conducted for NO_2, NO_x, EC, PM_{10}, and $PM_{2.5}$ in relation to IHD (Figure 10.1). One NO_x study was not included (Bodin et al. 2016), because its results were estimated for categories of exposure rather than treating the pollutant as a continuous variable. Estimates were also reported for NO, PM with aerodynamic diameter between 10 µm and 2.5 µm (PM_{coarse}), exhaust-specific PM_{10}, nonexhaust-specific PM_{10}, traffic-specific PM_{10}, traffic-specific $PM_{2.5}$, and Cu, Fe, and Zn content of $PM_{2.5}$ (Table 10.2). Meta-analyses were not conducted for these pollutants, because the estimates came from fewer than three studies. Four studies estimated

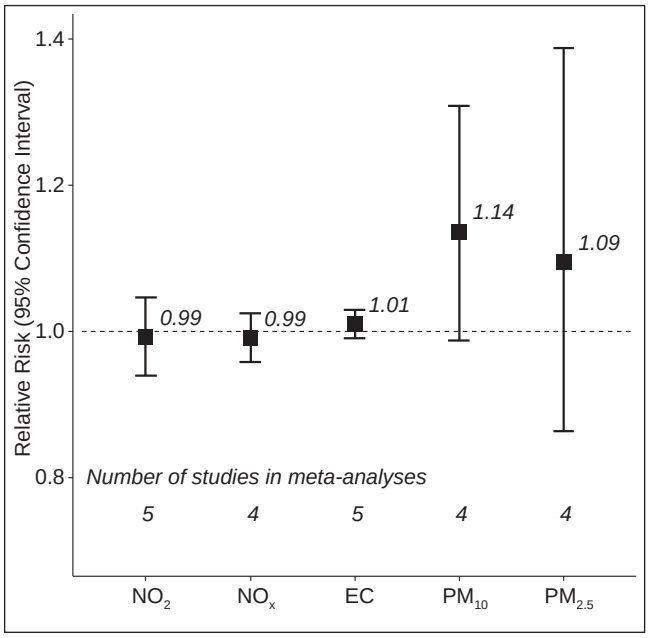

Figure 10.1. Meta-analysis of associations between traffic-related air pollutants and incidence of IHD. The following increments were used: 10 μg/m³ for NO_2, 20 μg/m³ for NO_x, 1 μg/m³ for EC, 10 μg/m³ for PM_{10}, and 5 μg/m³ for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

associations with indirect measures of traffic exposure such as residential proximity to major roadways.

The meta-analytic estimates for NO_2 and NO_x were effectively null (Figure 10.2). The estimate for PM_{10}, based on four studies, was greater than 1, with the lower boundary of the 95% CI at 0.99. The meta-analytic estimates for EC and $PM_{2.5}$, based on five and four studies, respectively, were also greater than 1, but far less precise and not inconsistent with the null (Figure 10.3). Note that the Panel used the term relative risk (RR) to describe effect estimates, as it is easier to communicate, although the exact effect measure is listed in the tables.

Three of the five studies included in the meta-analysis of NO_2 and incidence of IHD reported a positive association (Alexeeff et al. 2018; Cesaroni et al. 2014; Katsoulis et al. 2014), while two studies reported a negative association (Carey et al. 2016; Gan et al. 2011), yielding a meta-analytic estimate of 0.99 (95% CI: 0.94–1.05) with low heterogeneity (I^2 = 46%) (Figure 10.2). Overall, the analysis was dominated by the negative association from the very large administrative cohort study from Vancouver (41% of overall weight), which adjusted for preexisting comorbidities including diabetes, chronic obstructive pulmonary disease, and hypertensive heart disease (Gan et al. 2011). Those preexisting comorbidities may be mediators and may be on the causal pathway between exposure and outcome. They can distort the results when treated as confounders in the health analyses. Individual-level SES and lifestyle variables such as smoking were not available in this large Vancouver administrative cohort (Gan et al. 2011). In sensitivity analyses, exclusion of this study from the meta-analysis due to missing potential important confounders reduced the heterogeneity in the remaining estimates (I^2 = 17%) but did not change the effect estimate much (1.01; 0.94–1.09) (Appendix Figure 10A-1; available on the HEI website). Two European studies contributed equally with about 25% each of the overall weight: the multicohort analysis of 11 European cohorts within ESCAPE with a positive estimate (Cesaroni et al. 2014) and the CPRD London study which reported negative associations for IHD, myocardial infarction, and stroke (Carey et al. 2016) (Section 10.4). On the other hand, a consistent positive association was observed for congestive heart failure in this study, a common, but very unspecific consequence of IHD. Two studies with little weight, both with positive, but imprecise estimates, also adjusted for potential mediators (Alexeeff et al. 2018; Katsoulis et al. 2014). In general, such adjustments would tend to attenuate the association.

Estimates for fatal IHD were reported in two studies (Alexeeff et al. 2018; Gan et al. 2011) and were larger than the corresponding estimates for nonfatal and fatal events combined, most notably in the Vancouver administrative cohort, where the estimate for fatal IHD was significantly positive (Appendix Figure 10A-2). All except one study (Alexeeff et al. 2018) were categorized as high traffic specificity for NO_2; excluding this study did not change the effect estimate (0.98; 95% CI: 0.94–1.03) (Additional Materials to Chapter 10; available on the HEI website). Further analyses according to region did not result in notable differences.

A monotonic exposure–response function was identified in the KPNC Oakland cohort in the United States (Alexeeff et al. 2018), but it was analyzed with respect to the combined endpoint of all cardiovascular and cerebrovascular outcomes rather than IHD alone. In the Vancouver administrative cohort, investigators found a monotonic exposure–response function with respect to IHD mortality, but no such pattern was present in analyses of IHD hospitalization (Gan et al. 2011).

The four estimates included in the meta-analysis of NO_x and IHD incidence were all close to the null, yielding a meta-analytic estimate of 0.99 (95% CI: 0.96–1.03) with no heterogeneity (I^2 = 0%) (Figure 10.2). The most influential observation (RR = 1.01; 0.98–1.05) was from the ESCAPE multicohort study (Cesaroni et al. 2014), representing 11 regions across Europe, followed by the London CPRD study which reported a negative association (Carey et al. 2016). This cohort was constructed from medical records of general practitioners in the Greater London area and was a follow-up study of an England-wide analysis (Atkinson et al. 2013) but using a higher-resolution exposure model. In Carey et al. 2016, the variability of air

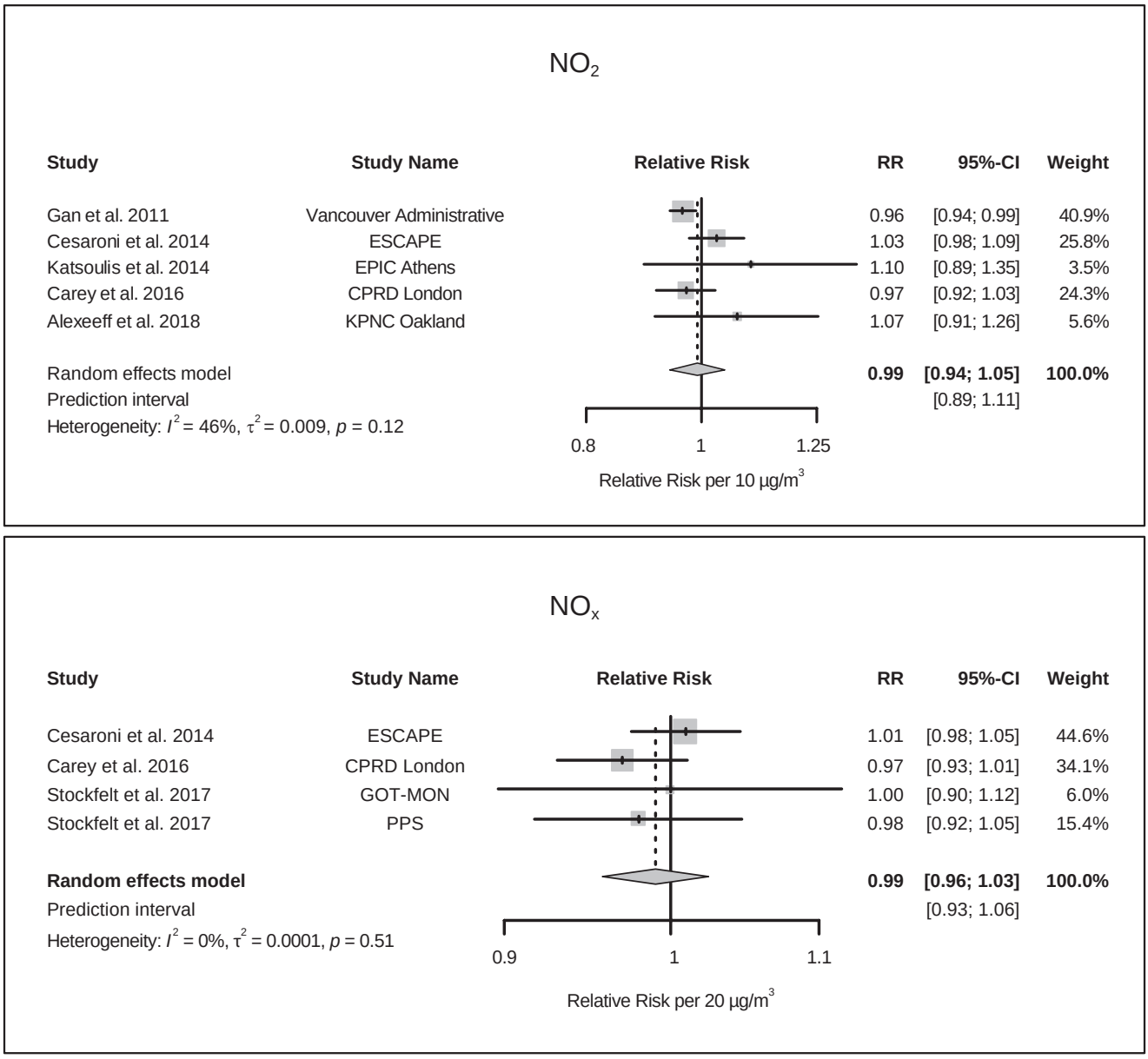

Figure 10.2. Association between NO_2 and NO_x and incidence of IHD: meta-analysis. All estimates combined fatal and nonfatal IHD.

pollution concentrations was dominated by variation among areas of Greater London (Inner London versus the rest) rather than by variation within smaller areas, which was confirmed when the overall estimate was partitioned into between-practice and within-practice effects. This analysis revealed a negative association for between-practice NO_x differences, while the within-practice association was null (Carey et al. 2016). An additional study not included in the meta-analysis was the Scania Public Health Cohort (Bodin et al. 2016). Bodin and colleagues evaluated this association across 10-µg/m^3 categories of NO_x, generating imprecise estimates that were directionally inconsistent and thus were not indicative of an exposure–response function. Separate estimates of fatal IHD, which were stronger in analyses of other pollutants, were not available for NO_x. All estimates were generated using European populations and measures of NO_x, and they were considered to be highly specific to traffic.

Four of the five effect estimates contributing to the meta-analysis of EC and IHD incidence were positive, and one was negative, yielding a meta-analytic estimate of 1.01 (95% CI: 0.99–1.03) with no heterogeneity (I^2 = 0%) (Figure 10.3). The meta-analysis was driven by the borderline association of the large Vancouver administrative cohort, carrying more than

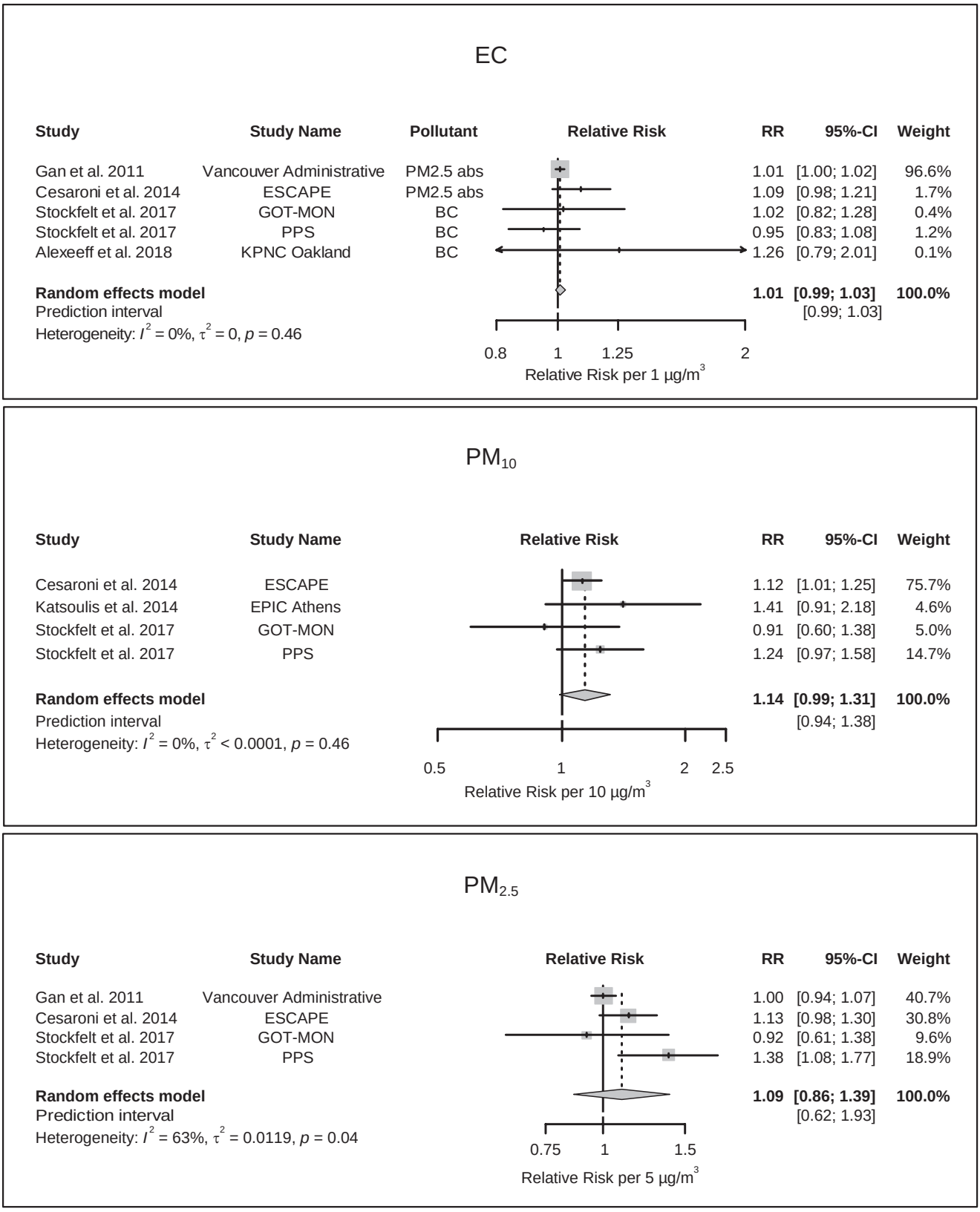

Figure 10.3. Association between EC, PM_{10}, and $PM_{2.5}$ and incidence of IHD: meta-analysis. All estimates combined fatal and nonfatal IHD.

96% of the overall weight (Gan et al. 2011). Adjustment for potentially intermediate variables in the Vancouver administrative cohort (Gan et al. 2011) makes an underestimation of the association possible (Sidebar 10.1). In contrast, the multicohort analysis within ESCAPE of more than 100,000 participants from 11 cohorts with in-depth confounder control yielded an estimate of 1.09 (0.98–1.21) but contributed only 1.7% of the overall weight. The other three studies displayed mixed results with very little weight in the overall meta-analysis. In the two studies with separate estimates for fatal IHD, the associations were substantially stronger than for fatal and nonfatal events combined (Alexeeff et al. 2018; Gan et al. 2011) (Appendix Figure 10A-2). In sensitivity analyses restricted to studies with adjustment for lifestyle factors (all studies except Gan et al. 2011), the meta-analytic estimate was higher, but imprecise (1.04 [0.91–1.18]) (Appendix Figure 10A-1). Except for one study (Alexeeff et al. 2018), all EC exposures were deemed highly traffic specific and yielded the same meta-analytic estimate as the complete group of studies. Researchers for the Vancouver administrative cohort evaluated the linearity of the association between black carbon (the measure of EC used) and IHD hospitalization, finding increased risks in the two highest quintiles of exposure, but only when further adjusting for $PM_{2.5}$, and a monotonic exposure–response function for fatal IHD (Gan et al. 2011). In contrast, an analysis of the exposure–response function in the KPNC-Oakland cohort found no indication of increasing risk with progressively higher exposure levels (Alexeeff et al. 2018). As with NO_2, this assessment pertained to the combined endpoint of all cardiovascular and cerebrovascular outcomes rather than to IHD alone.

Three of the four estimates included in the meta-analysis of PM_{10} and IHD incidence were positive, and one estimate was negative, yielding a meta-analytic estimate of 1.14 (95% CI: 0.99–1.31) with low heterogeneity (I^2 = 0%) (Figure 10.3). The analysis was dominated by the ESCAPE analysis of 11 European cohorts, a positive association that comprised more than 75% of the overall weight (Cesaroni et al. 2014). Subset analyses censoring participants at higher concentrations in this study revealed slightly stronger and statistically significant associations if exposures were restricted to PM_{10} levels below 40, 30, and 20 μg/m^3. A linear association was identified in the Swedish PPS cohort (Stockfelt et al. 2017), which was the second most influential study (15% of weight). The ESCAPE multicohort analyses were also among the few studies overall to evaluate the influence of likely confounders on the estimates for PM_{10} and $PM_{2.5}$. Data on physical activity, body mass index (BMI), and alcohol consumption were available in 8 of the 11 cohorts, and analyses of PM_{10} that were restricted to these cohorts showed results that changed little with or without adjustment for these variables (Cesaroni et al. 2014). Analyses in the EPIC-Athens study included potential mediating variables; although its effect estimate remained the largest reported for this pollutant with, however, very little weight in the meta-analysis (Katsoulis et al. 2014). Meta-analysis stratified by fatality of the outcome was not possible, as separate estimates were not available in the original publications. All included studies of PM_{10} and IHD were generated using European populations using measures of PM_{10} a priori judged to be moderately specific to traffic.

Two of the estimates included in the meta-analysis of $PM_{2.5}$ and IHD incidence were positive; the other two were negative or unity, yielding a meta-analytic estimate of 1.09 (95% CI: 0.86–1.39) with moderate heterogeneity (I^2 = 63%) (Figure 10.3). The most influential study was the administrative cohort from Vancouver (41%) (Gan et al. 2011). The Gan study observed a null association of $PM_{2.5}$ with the combined nonfatal and fatal outcome, and a small positive association with fatal events (Figure 10A-2), both with no evidence for a monotonic exposure–response function. As with analyses of other pollutants in this study, the covariate set excluded key potential confounding variables and included potential mediating variables. Exclusion of the Gan et al. 2011 study from the meta-analysis due to lack of lifestyle variables reduced the heterogeneity in the remaining estimates (I^2 = 39%) and increased the magnitude of the summary estimate (1.17; 0.79–1.73). Positive associations were observed in the PPS cohort (Stockfelt et al. 2017) and the ESCAPE study (Cesaroni et al. 2014), contributing altogether 50% of overall weight. Similar to the findings on PM_{10}, there was evidence for a monotonically increasing association in both the PPS cohort (Stockfelt et al. 2017) and the ESCAPE study (via restricting analyses to progressively lower exposures of $PM_{2.5}$) (Cesaroni et al. 2014). Similar to PM_{10}, the associations in the ESCAPE multicohort analyses changed very little with further adjustment for physical activity, BMI, and alcohol consumption among the 8 cohorts that had these data (Cesaroni et al. 2014). Meta-analysis stratified by fatality of the outcome was not possible, as separate estimates were not available in the original publications. All estimates were generated using measures of $PM_{2.5}$ judged to be moderately specific to traffic. As with the meta-analyses of the other pollutants, the analyses of $PM_{2.5}$ are constrained by a small number of studies.

For several other pollutants, fewer than the required three studies were available and therefore no meta-analyses were conducted (Table 10.2). Evaluations of NO in association with IHD were conducted in two cohorts, the KPNC-Oakland and Vancouver administrative cohort (Alexeeff et al. 2018; Gan et al. 2011). In Gan and colleagues (2011), NO was positively related to fatal IHD (RR = 1.06; 95% CI: 1.02–1.10, per 13.2-μg/m^3) but negatively related to IHD hospitalization. In addition, the exposure–response relationship identified

across quintiles of exposure was attenuated with adjustment for covariates (Gan et al. 2011). NO was also positively associated with IHD in the KPNC-Oakland cohort (RR = 1.06; 0.95–1.17 per 3.8-ppb), with more pronounced associations among participants ages 65 years and older (RR = 1.17; 1.06–1.29), and in relation to myocardial infarction only (a subset of IHD) (Alexeeff et al. 2018). In both populations, the findings on NO largely followed those on NO_2.

Investigators for the CPRD London study estimated $PM_{2.5}$ from exhaust and nonexhaust traffic sources. This exposure, expressed as a percentage of total $PM_{2.5}$, was not associated with IHD and was also negatively associated with myocardial infarction, but it was positively associated with congestive heart failure (Carey et al. 2016). Similar to the results for NO_x from this study, partitioning the effect into between- and within-area effects revealed a negative association of between-area exposure differences, while the within-area association was effectively null. PM_{10} from traffic-related exhaust, traffic-related wear, and total traffic sources were evaluated in the PPS and GOT-MONICA cohorts, and none of these exposures was positively associated with IHD incidence in either cohort (range of RRs: 0.98 [95% CI: 0.92–1.04] for both wear-related and total traffic PM_{10} in PPS, to 1.01 [0.91–1.12] for both wear-related and total traffic PM_{10} in GOT-MONICA) (Stockfelt et al. 2017). PM_{coarse} exposure was positively associated with IHD incidence in the ESCAPE analyses of 11 studies (Cesaroni et al. 2014). Finally, a second publication based on the ESCAPE study populations investigated elemental constituents of $PM_{2.5}$, including Cu, Fe, and Zn, which all have predominant traffic sources (e.g., brake and tire wear). Exposure of all three metals were positively associated with IHD risk, particularly Fe and Zn (Wolf et al. 2015). There were no studies investigating ultrafine particles (UFPs).

10.3.3 ASSOCIATIONS WITH INDIRECT TRAFFIC MEASURES

In addition to the pollutant-specific evidence above, associations of indirect traffic measures with IHD risk were estimated within four cohorts (Table 10.3 and Figure 10.4), three of which are also represented in the pollutant-specific evidence. Two of three studies investigating distance measures, namely the large Vancouver administrative study (Gan et al. 2010) and the medium-sized cross-sectional analysis of the German HNR study (Hoffmann et al. 2006), observed positive associations between dichotomized measures of residential roadway proximity (e.g., distance to busy road) and IHD. For traffic-density measures, the results were inconsistent. The ESCAPE meta-analysis (Cesaroni et al. 2014) found no association while the London CPRD study (Carey et al. 2016) observed a positive estimate in the highest exposure category and a negative association in the middle category.

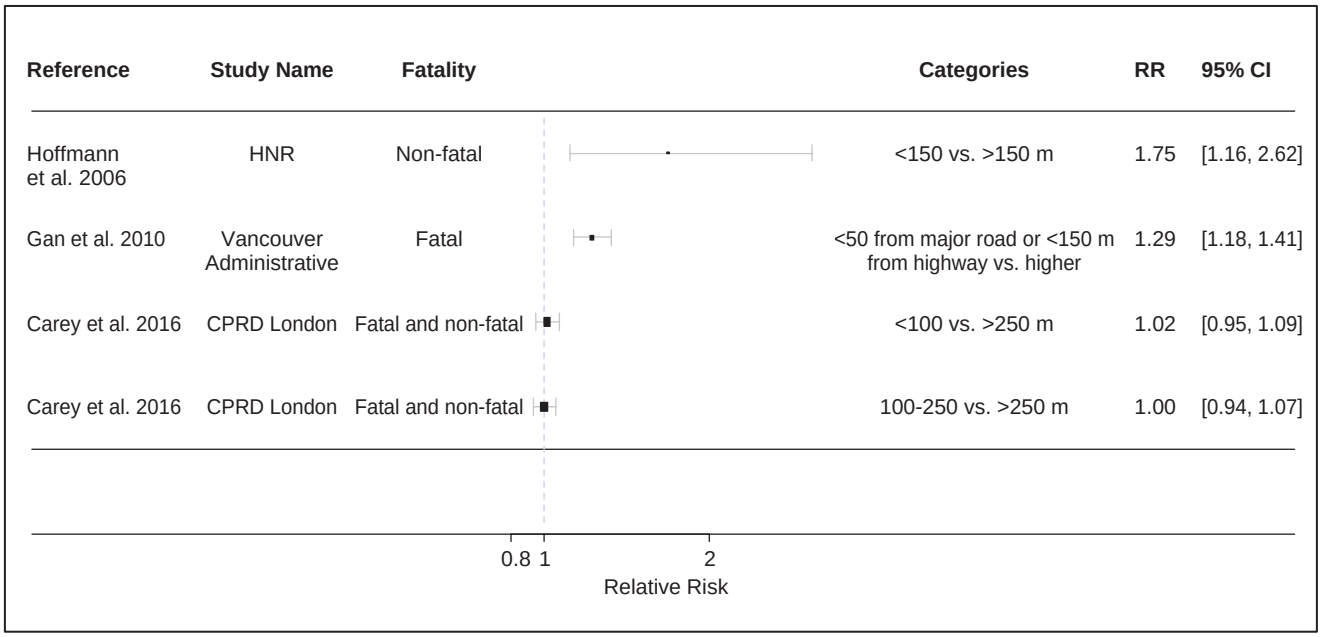

Figure 10.4. Association of distance to major roads with IHD. Hoffmann et al. 2006 is a cross-sectional study.

10.3.4 CO-EXPOSURE WITH NOISE AND OTHER POLLUTANTS

Traffic noise commonly co-occurs with traffic-related air pollution and is also associated with cardiovascular risk (WHO 2018), thus making it a potentially important source of confounding in estimating the association of traffic-related air pollution on IHD risk (Rugel and Brauer 2020; Tétreault et al. 2013). Only three estimates included in the meta-analyses underwent evaluations for sensitivity to adjustment for exposure to noise (Carey et al. 2016; Cesaroni et al. 2014; Gan et al. 2012) (Appendix Table 10A-1). The ESCAPE study reported associations of both PM_{10} and $PM_{2.5}$ with IHD in the subset of participants in nine cohorts for which estimates of noise exposure were available. With adjustment for noise, both associations remained positive, with that for PM_{10} not changing and that for $PM_{2.5}$ attenuating slightly (Cesaroni et al. 2014). In the Vancouver administrative cohort, the positive association of black carbon with fatal IHD was attenuated somewhat with further adjustment for traffic noise (Gan et al. 2012). Similarly, in the CPRD cohort, sensitivity analyses adjusted for daytime and, separately, nighttime noise, reportedly did not change the estimated association of NO_x with IHD (results not shown in Carey et al. 2016). Finally, in the Scania Public Health Cohort study, which did not contribute to the meta-analyses, noise exposure was a covariate in all multivariable-adjusted associations of NO_x with IHD. Nonetheless, unadjusted associations were nearly identical to associations adjusted for noise (Bodin et al. 2016).

No studies reported multipollutant results corrected for general $PM_{2.5}$ or ozone except Hoffmann and colleagues (2006), which corrected the distance measure estimate for general $PM_{2.5}$ and reported similar estimates.

10.3.5 NARRATIVE ASSESSMENT

The studies collectively provide evidence of an association of PM_{10} and suggestive evidence of an association of EC and $PM_{2.5}$ with IHD incidence. This is based on meta-analyses of five and four, respectively, cohort studies each, dominated by the multicohort analysis of 11 European cohorts with more than 100,000 participants, and on positive estimates for fatal IHD from the Vancouver Administrative Cohort of more than 450,000 participants. Four other studies from different areas in Europe and the United States add to this study base, as do a limited number of findings on indirect traffic measures. The presence of an association is further supported by monotonic exposure–response relationships in two well-conducted studies for PM_{10} and $PM_{2.5}$ (Cesaroni et al. 2013; Stockfelt et al. 2017). Additional supporting evidence is provided by associations for metals in PM (Cu, Fe, Zn) and PM_{coarse} in ESCAPE (Cesaroni et al. 2014; Wolf et al. 2015) and by general stability or only slight attenuation of the effect estimates upon adjustment for traffic noise. However, the evidence is weakened by null findings of traffic-specific PM fractions in two studies (Carey et al. 2016; Stockfelt et al. 2017) and by the fact that the traffic specificity for $PM_{2.5}$ and PM_{10} was a priori deemed only moderate.

In contrast to the findings for particulate pollutants, the evidence for gaseous pollutants does not support an association with IHD. For both NO_2 and NO_x the summary estimate is null, based on four to five studies from North America and Europe. The by far most influential study, namely the Vancouver Administrative study (Gan et al. 2011), dominates the analyses with inconsistent results for fatal and nonfatal disease, raising questions regarding the validity of outcome assessment. Similarly, concerns exist in the large CPRD London study (Carey et al. 2016), with inconsistent estimates for IHD and one of its typical clinical consequences, namely congestive heart failure. On the other hand, the evidence for an association is strengthened by consistent associations of NO_2 and NO for fatal disease in the Vancouver study and for combined fatal and nonfatal IHD in the KPNC-Oakland cohort study.

A first challenge in this body of evidence concerns the outcome assessment. IHD is a broad class of outcomes that incorporates diverse pathophysiological mechanisms, not all of which might be equally affected by air pollution. Secondly, misclassification of IHD as congestive heart failure may occur particularly in outpatient settings with less precise diagnostic instruments, since IHD may lead to congestive heart failure and often presents clinically as congestive heart failure (Cowie et al. 1997; Remes et al. 1991; Varas-Lorenzo et al. 2008). Specifically, in the CPRD study (Carey et al. 2016), which is based mainly on outpatient assessments by general practitioners, this potential misclassification of outcome is a concern; it might have contributed to the findings that show consistent positive associations for congestive heart failure but negative or null associations for IHD. A similar mechanism could potentially explain the divergent estimates for combined and for fatal IHD in the Vancouver Administrative Cohort. Moreover, as a correct diagnosis is dependent on access to medical care, differences in access related to SES may lead to bias in analyses of air pollution (Hajat et al. 2015).

Second, although mitigating bias from confounding is an important task in observational studies such as those of the health effects of air pollution, estimated pollutant-IHD associations from three studies were adjusted for variables such as hypertension or diabetes, which plausibly mediate the relation of pollutant exposure to IHD risk (Alexeeff et al. 2018; Gan et al. 2011; Katsoulis et al. 2014). Adjustment for plausible intermediates can attenuate effect estimates and

might have contributed to the negative association of NO_2 with IHD incidence observed in Gan and colleagues (2011), although it is unlikely that this can explain a negative association alone. In addition, adjustment for potential intermediates may also increase the likelihood of inducing a collider bias, resulting in potential upward or downward bias in the three studies (Glymour and Greenland 2008).

Third, age may be an important effect modifier in studies investigating TRAP and IHD. Nearly 40% of KPNC-Oakland participants were younger than 40 years old at baseline, and only about 8% were 65 years or older (Alexeeff et al. 2018). Clinically pronounced IHD is rare in persons under 50, and in cases that do occur, the relationship of risk factors with disease may be different (Rapsomaniki et al. 2014). In this cohort, positive associations of NO_2, NO, and black carbon with IHD were present among participants 65 and older at baseline and absent among younger participants, who dominated the main analysis in this cohort.

In conclusion, the Panel found a moderate level of confidence in the presence of an association between exposure to TRAP and IHD incidence. The moderate assessment was based on four high-quality studies from different regions across Europe, yielding a positive meta-analytic estimate for PM_{10}, two studies with monotonic exposure–response relationships, and on several high-quality studies for EC and $PM_{2.5}$ in different populations from North America and Europe, including the multicohort analysis of 11 cohorts within ESCAPE. Moreover, the consistent associations of NO_2, NO, EC, and $PM_{2.5}$ with fatal IHD, in the by far largest study representative of the general population, lend further support to this assessment. Additional support of an association was supplied by a small number of studies showing consistent associations across several different pollutants, with a reasonable possibility that positive findings are not explained by confounding or chance. Further support is supplied by a small number of studies showing associations with other highly traffic-specific pollutants that were not meta-analysed and from a small number of studies investigating indirect measures of traffic exposure. Nevertheless, the results were not entirely consistent across all exposure indicators. Most notably the Panel observed null findings for NO_2 and NO_x in the meta-analyses. Also, the traffic specificity of the PM_{10} studies—which showed the most robust associations—is only moderate, making the evidence less compelling.

10.3.6. CONFIDENCE ASSESSMENT OF THE BODY OF EVIDENCE

The modified OHAT assessment is conducted only for exposure–outcome pairs for which meta-analyses were conducted. All six studies that contributed results to meta-analyses were cohort studies, thus the initial confidence rating for all exposure–IHD pairs was moderate. Only cohort studies were used, so a combined assessment across study designs was not needed. The factors that reduce or increase confidence are described in the sections that follow. All studies addressed the research question directly, and therefore no downgrade was applied for the downgrading factor indirectness. The Panel decided a priori not to consider the upgrading factor large magnitude of the effect.

10.3.6.1 Factors That Reduce Confidence

Among the factors that reduce confidence, the Panel evaluated the risk of bias as low or moderate in most exposure–outcome pairs and domains (Table 10.4). The risk of bias ratings can be found for the individual studies in Appendix Table 10A-2. The Panel did not downgrade the confidence rating of any of the pollutant-IHD pairs because of risk of bias (Table 10.5). The single study with a high risk of bias rating was set in the Vancouver Administrative Cohort; the rating stemmed from a lack of data on two potentially important confounders: smoking and BMI (Gan et al. 2011). Note that this study does not correct for individual-level SES, although they included an area-level SES variable. In sensitivity meta-analyses excluding the study by Gan and colleagues, estimates were largely unchanged (NO_2) or even increased (EC, $PM_{2.5}$) (Appendix Figure 10A-1). The Panel did not downgrade associations for unexplained inconsistency, as most meta-analyses revealed low or no heterogeneity. Only $PM_{2.5}$ was of moderate heterogeneity, mainly due to magnitude and not due to direction of individual estimates. Heterogeneity for $PM_{2.5}$ was substantially reduced when restricted to specific regions or to studies at lower risk of bias, although this was based on few studies only. With respect to imprecision, the overall sample size of all studies included in a meta-analysis was much larger than the minimum sample size specified in the protocol. Nonetheless, the Panel downgraded evidence for NO_2 and $PM_{2.5}$ for imprecision because the CIs were wide, and the estimates clearly included unity. By contrast, the Panel did not downgrade the evidence on PM_{10} because the estimate was deemed to be in line with an association. The estimate for EC was not downgraded because the CI was precise and in line with an association. The Panel did not downgrade for publication bias, per protocol, because too few studies on each pollutant were available for evaluating this bias.

10.3.6.2 Factors That Increase Confidence

The Panel upgraded the evidence for associations of PM_{10} and $PM_{2.5}$ with IHD following the demonstration of a monotonic exposure–response function in the PPS cohort

Table 10.4. Summary of Risk of Bias Rating for Studies on IHD

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	4	1	1	14	5	3
	Validity of measuring of confounding factors	4	2	0	18	4	0
	Control in analysis	5	1	0	14	8	0
	Overall	1	4	1	2	17	3
2. Selection bias	Selection of participants into the study	6	0	0	22	0	0
3. Exposure assessment	Methods used for exposure assessment	6	0	0	22	0	0
	Exposure measurement methods comparable across the range of exposure	6	0	0	22	0	0
	Change in exposure status	5	1	0	17	5	0
	Overall	5	1	0	17	5	0
4. Outcome measurements	Blinding of outcome measurements	5	1	0	20	2	0
	Validity of outcome measurements	5	1	0	20	2	0
	Outcome measurements	5	1	0	20	2	0
	Overall	4	2	0	18	4	0
5. Missing data	Missing data on outcome measures	6	0	0	22	0	0
	Missing data on exposures	6	0	0	22	0	0
	Overall	6	0	0	22	0	0
6. Selective reporting	Authors reported a priori primary and secondary study aims	6	0	0	22	0	0

(Stockfelt et al. 2017) and the consistent and stable subset analyses censoring participants at higher concentrations in the 11 studies included in the ESCAPE analysis (Cesaroni et al. 2014). Other exposure–response assessments yielded findings that were limited to fatal events (Gan et al. 2011) or that combined all cardiovascular and cerebrovascular events (Alexeeff et al. 2018).

The Panel did not upgrade the evidence on any of the pollutant-IHD associations on the basis of residual confounding or other factors potentially biasing toward the null, despite the above-mentioned concerns in several influential studies regarding possible over adjustment. The Panel decided to refrain from upgrading, because it was considered difficult to determine the direction and magnitude of the resulting bias.

Finally, too few studies were available to evaluate consistency across geographic regions, populations, or study period. Thus, the Panel did not upgrade based on this factor.

10.3.6.3 Evaluation of Confidence for Combined Measures of TRAP

The final ratings for the confidence in the quality of the body of evidence is low for NO_2, moderate for NO_x, EC, and $PM_{2.5}$, and high for PM_{10}, with NO_2 and NO_x indicating no effect. A combined confidence rating for measures of TRAP across different pollutants started with high confidence due to the rating for PM_{10}. The Panel downrated this level of confidence to moderate because of traffic specificity, since all PM_{10} studies had only moderate traffic specificity. In conclusion, based on the modified OHAT assessment, the confidence in the quality of the body of evidence for TRAP and IHD incidence is moderate.

10.3.7 OVERALL CONFIDENCE ASSESSMENT

Based on the narrative assessment (moderate) and the modified OHAT assessment (moderate), the overall confidence in the evidence of an association between TRAP exposure and IHD incidence is moderate.

Table 10.5. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and IHD[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ (N = 5)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	Not sensitive to exclusion of the single study with high RoB.	Low heterogeneity (I^2 = 46%).	Sample size met, but confidence interval wide and includes unity.	No formal evaluation possible.	One study showed positive exposure response for a combined cardiovascular disease category, but relatively little weight (Alexeeff 2018).	Confounding in both directions possible.	Too few studies to evaluate.	
NO_x	Cohort	+++ (N = 4)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	Low or moderate RoB.	Low heterogeneity (I^2 = 0%).	Sample size met and confidence interval includes unity, but precise.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to evaluate.	
EC	Cohort	+++ (N = 5)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	Not sensitive to exclusion of the single study with high RoB.	Low heterogeneity (I^2 = 0%).	Sample size met and estimate consistent with an association.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to evaluate.	

Continues next page

Table 10.5. (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and IHD[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
PM_{10}	Cohort	+++ ($N = 4$)	0	0	0	0	+	0	0	++++ (High)
	Rationale	Cohort design initially rated as moderate.	All studies low or moderate RoB.	Low heterogeneity ($I^2 = 0\%$).	Sample size met and estimate consistent with an association.	No formal evaluation possible.	Monotonic ERF reported in Stockfelt 2017; subset analysis indicating stable effects across range (Cesaroni 2014).	Confounding in both directions possible.	Too few studies to evaluate.	
$PM_{2.5}$	Cohort	+++ ($N = 4$)	0	0	–	0	+	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	One study with high RoB, estimates increased upon exclusion.	Moderate heterogeneity ($I^2 = 63\%$), mainly due to magnitude and not direction of estimates.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	Monotonic ERF reported in Stockfelt 2017; subset analysis indicating stable effects across range (Cesaroni 2014).	Confounding in both directions possible.	Too few studies to evalutate.	

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

10.4 CORONARY EVENTS

10.4.1 STUDY SELECTION AND DESCRIPTION

This section covers studies that investigated a specific subcategory of IHD, namely incidence of acute coronary events, defined as acute myocardial infarction (ICD-10 I21), or cardiac arrest or sudden cardiac death (ICD-10 I46) (Table 10.6 and Table 10.7). Sixteen of these studies were published after the 2010 HEI Traffic Review. Several studies were not included in the TRAP and coronary events review, because the exposure assessment did not fulfill the requirements of the exposure framework, among them, for example, the Women's Health Initiative study (Miller et al. 2007) and the analysis of PM in the Nurses' Health Study (Puett et al. 2009). Also, this section does not include studies investigating endpoints such as the development and progression of atherosclerosis, the most important underlying pathology for coronary events, or studies looking at the influence of long-term traffic-related air pollution on survival after a coronary event has taken place.

Most included studies had starting dates of the relevant exposure period in the 1990s. The study locations were limited to Europe and North America. Of the included studies, 13 studies investigated traffic pollutants, and 8 studies included indirect measures such as distance to traffic or traffic density. NO_2 was the most frequently investigated traffic pollutant. Mean exposures were relatively homogenous across the studies, with annual mean NO_2 ranging from 10 μg/m^3 to 22 μg/m^3 with only one study exhibiting higher mean exposure levels of 37 μg/m^3 (Carey et al. 2013). Annual mean $PM_{2.5}$ ranged from 10 μg/m^3 to 18 μg/m^3. Six studies evaluated the effect of concurrent traffic noise exposure on the estimate for traffic-related air pollutants.

Study designs included two cross-sectional studies, investigating the prevalence of having a history of a coronary event, cohort studies (N = 11) or case-control studies (N = 6), with the Worcester Heart Attack case-control study contributing with three publications to the evidence base. One cohort study investigated a natural experiment by contrasting participants who moved closer to high traffic or further away from high traffic with those who moved without a substantial change in exposure (Hart et al. 2014). Study sizes ranged from two small studies with 905 and 2,225 participants in Eastern Europe (Grazuleviciene et al. 2004; Pindus et al. 2016) to approximately 1.1 million participants in Toronto, Canada (Bai et al. 2018) and 810,000 England-wide (Atkinson et al. 2013). All studies included adult men and women with the exception of the U.S. Nurses' Health Study (Hart et al. 2013, 2014), which included only women, and one small study in Kaunas (Grazuleviciene et al. 2004), which included only men.

Seven studies were based on mostly medium-sized to large prospective population-based cohort studies with strong design features. These studies all had detailed information on lifestyle, individual SES, and comorbidities and usually adjusted for a large number of covariates. Identification of incident coronary events was conducted through active follow-up with one or more of the following: repeated personal contacts, proxy interviews, death certificates, and adjudication using medical records (Hart et al. 2013, 2014; Hoffmann et al. 2015; Kan et al. 2008; Kulick et al. 2018), leading to a high validity and completeness of the outcome assessment, or by linkage with disease registries (Bodin et al. 2016; Roswall et al. 2017).

Four studies were based on large to very large cohort studies that were constructed from the insurance data of a private health maintenance organization (Alexeeff et al. 2018), health administrative databases from the universal provincial insurance in Ontario (Bai et al. 2019), or medical records of general practitioners in England, including patients of the subset of general practitioners in the Greater London area with linked primary care and hospital admissions records for identification of coronary events (Atkinson et al. 2013; Carey et al. 2016). The nationwide analysis of the CPRD cohort was also linked to the national death registry, and this study is included in Chapter 11 Mortality (English National Cohort reported in Carey et al. 2013). The availability and quality of individual-level covariates for lifestyle is limited in those studies, as standardized assessments were not conducted. Validity and completeness of the outcome assessment is limited where these studies rely on secondary data such as reimbursement claims or on ambulatory care medical records, but they have been shown to be highly specific if based on hospital admission data.

The four included case-control studies differed substantially in their design. The Swedish case-control studies (Rosenlund et al. 2006, 2009) identified incident cases through a combined strategy applying standard criteria for acute coronary events to emergency room admission data, hospital discharge data, and death certificates. Through this combined strategy, fatal and nonfatal events could be assessed and were analyzed in comparison to a control population. In the hospital-based case-control studies in the Kaunas Men's Study (Grazuleviciene et al. 2004) and the Worcester Heart Attack Study in Massachusetts, U.S.A. (Madrigano et al. 2013; Tonne et al. 2007, 2009), only patients who reached the hospital were included. Silent or out-of-hospital fatal events could not be identified and included in the study.

The two cross-sectional studies (Chum and O'Campo 2015; Pindus et al. 2016) investigated the history of an acute coronary event in those who had survived this event until the date of participation in the study; they were based on self-reported disease. Only long-term survivors were included in these studies, which may lead to bias (see Sidebar 10.1).

Table 10.6. Key Study Characteristics of Articles Included in the Systematic Review for Coronary Events—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Fatality	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Alexeeff 2018	KPNC Oakland	Cohort	Oakland, California, United States	2010–2015	41,869	Surface monitoring	NO_2	9.9	Fatal and nonfatal	HR	**1.08 (0.93–1.26)**	3.8 ppb
							NO	4.9			1.08 (0.95–1.23)	3.8 ppb
							BC	0.36			1.05 (0.91–1.20)	0.17 µg/m^3
Atkinson 2013	CPRD	Cohort	England	2003–2007	810,686	Dispersion/ CTM	PM_{10} mass	19.7	Fatal and nonfatal	HR	1.01 (0.96–1.07)	3.0 µg/m^3
Bai 2019	ONPHEC	Cohort	Toronto, Canada	1996–2012	1,127,209	LUR	NO_2	21.4	Fatal and nonfatal	HR	**1.01 (0.99–1.03)**	4.0 ppb
							PNC <100 nm	28,453			1.05 (1.02–1.07)	10,029.4 particles/cm^3
Bodin 2016	Scania Public Health Cohort	Cohort	Scania, Sweden	2000–2010	12,843	Dispersion/ CTM	NO_x	13	Fatal and nonfatal	IRR	1.02 (0.86–1.21)	10 µg/m^3
Carey 2016	CPRD London	Cohort	London, United Kingdom	2005–2011	207,042	Dispersion/ CTM	NO_2	37.4	Fatal and nonfatal	HR	**0.88 (0.79–0.97)**	10 µg/m^3
							NO_x	63.0			0.91 (0.84–0.98)	20 µg/m^3
							Traffic $PM_{2.5}$	1.45			0.88 (0.79–0.98)	1 µg/m^3
Grazuleviciene 2004	Kaunas Men's Study	Case-control	Kaunas, Lithuania	1997–2000	2,225[d]	Surface monitoring	NO_2	20.0	Nonfatal	OR	**1.14 (1.00–1.30)**	11.6 µg/m^3

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Table 10.6. (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Coronary Events—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Fatality	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Hoffmann 2015	HNR	Cohort	Ruhr Areas, Germany	2000–2012	4,222	LUR	$PM_{2.5\ abs}$	1.59	Fatal and nonfatal	HR	1.40 (0.87–2.27)	0.98 1×10^{-5}/m
							PM_{10} mass	27.78			1.12 (0.60–2.11)	6.32 µg/m³
							PM_{coarse} mass	9.99			0.88 (0.49–1.5)	5.26 µg/m³
							$PM_{2.5}$ mass	18.41			1.06 (0.55–2.07)	3.51 µg/m³
Madrigano 2013	Worcester Heart Attack	Case-control	Worcester, Massachusetts, United States	1995–2003	13,539	LUR	$PM_{2.5}$ mass	10.50	Fatal and nonfatal	OR	1.05 (1.00–1.11)	1.05 µg/m³
Pindus 2016	RHINE Tartu	Cross-sectional	Tartu, Estonia	2011–2012	905	Dispersion/ CTM	Traffic PM_{10}	3.3	Nonfatal	OR	1.49 (0.81–2.72)	2.2 µg/m³
Rosenlund 2006	SHEEP	Case-control	Stockholm, Sweden	1992–1994	2,938	Dispersion/ CTM	NO_2	14.2	Fatal and nonfatal	OR	**0.99 (0.76–1.30)**	30 µg/m³
									Fatal		1.51 (0.96–2.37)	
									Nonfatal		0.89 (0.67–1.19)	
							CO	66.8	Fatal and nonfatal		1.04 (0.89–1.21)	300 µg/m³
									Fatal		1.22 (0.98–1.52)	
									Nonfatal		0.98 (0.82–1.16)	

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Table 10.6. (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Coronary Events—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Fatality	Effect Measure	Effect Estimate (95% CI)[c]	Increment
							Traffic PM_{10}	2.6	Fatal and nonfatal		1.00 (0.79–1.27)	5 μg/m^3
									Fatal		1.39 (0.94–2.07)	
									Nonfatal		0.92 (0.71–1.19)	
Rosenlund 2009	Stockholm County Case-Control	Case-control	Stockholm, Sweden	1985–1996	301,273	Dispersion/ CTM	NO_2	12.9	Fatal and nonfatal	OR	**1.04 (0.99–1.09)**	31.3 μg/m^3
									Fatal		1.23 (1.15–1.32)	
									Nonfatal		0.94 (0.89–1.00)	
							CO	64.2	Fatal and nonfatal		1.01 (0.97–1.05)	256.0 μg/m^3
									Fatal		1.14 (1.07–1.21)	
									Nonfatal		0.94 (0.89–1.00)	
							Traffic PM_{10}	2.4	Fatal and nonfatal		1.04 (1.00–1.09)	5.7 μg/m^3
									Fatal		1.16 (1.09–1.24)	
									Nonfatal		0.98 (0.93–1.03)	

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Table 10.6. (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Coronary Events—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Fatality	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Roswall 2017	DDCH	Cohort	Copenhagen and Aarhus, Denmark	1993–2011	50,744	Dispersion/ CTM	NO_2	15.7	Fatal	HR	1.17 (1.07–1.28)	7.1 µg/m^3
									Nonfatal		**1.08 (1.03–1.12)**	7 µg/m^3
Tonne 2009	Worcester Heart Attack	Case-control	Worcester, Massachusetts, United States	1995–2003	14,842	LUR	Traffic $PM_{2.5}$	0.35	Fatal and nonfatal	OR	1.10 (1.04–1.16)[e]	0.20 1×10^{-5}/m

HR = hazard ratio; IRR = incidence rate ratio; OR = odds ratio; PNC = particle number concentration.

[a] All studies were in adults (age 18+).

[b] Units are in the increment column.

[c] **Bold** indicates the effect estimate was included in the meta-analysis.

[d] Male population.

[e] Log transformed.

Table 10.7. Key Study Characteristics of Articles Included in the Systematic Review for Coronary Events—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Fatality	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
Carey 2016	CPRD London	Cohort	London, United Kingdom	2005–2011	207,042	Fatal and nonfatal	Density	HR	0.97 (0.86–1.09)	>100,000 heavy vehicle-km/year vs. none
									0.98 (0.90–1.07)	<100,000 heavy vehicle-km/year vs. none
							Distance		0.96 (0.85–1.07)	<100 vs. >250 m
									0.95 (0.87–1.05)	100–250 vs. >250 m
Chum 2015	Toronto Health Survey	Cross-sectional	Toronto, Canada	2009–2011	2,411	Nonfatal	Distance	OR	3.79 (2.25–5.53)[b]	<100 vs. >100 m
Hart 2013	Nurses' Health	Cohort	United States	1988–2008	84,562[b]	Fatal and nonfatal	Distance	HR	1.11 (1.01–1.22)	<50 m to A3 or <100 m to A1/A2 road vs. higher
Hart 2014	Nurses' Health	Cohort	United States	1986–2012	107,130[c]	Fatal	Distance	HR	1.24 (1.03–1.49)	<49 vs. >500 m
									1.07 (0.90–1.27)	50–199 vs. >500 m
									1.06 (0.90–1.25)	200–499 vs. >500 m
						Nonfatal			1.08 (0.96–1.23)	<49 vs. >500 m
									1.09 (0.98–1.22)	50–199 vs. >500 m
									1.03 (0.92–1.14)	200–499 vs. >500 m
Hoffmann 2015	HNR	Cohort	Ruhr Areas, Germany	2000–2012	4,222	Fatal and nonfatal	Density	HR	1.21 (0.91–1.62)	4,302 vehicle-km/day
Kan 2008	ARIC	Cohort	Multiple cities, United States	1987–2002	13,309	Fatal and nonfatal	Density	HR	1.02 (1.01–1.04)[d]	150 vehicles/day
									1.09 (0.94–1.26)	<150 vs. >150 m
Kulick 2018	NOMAS	Cohort	Manhattan, United States	1993–2016	3,287	Fatal and nonfatal	Distance	HR	1.00 (0.69–1.44)	<100 vs. >400 m

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Table 10.7. (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Coronary Events—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Fatality	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
									0.89 (0.63–1.26)	100–200 vs. >400 m
									0.98 (0.72–1.33)	200–400 vs. >400 m
Tonne 2007	Worcester Heart Attack	Case-control	Worcester, Massachusetts, United States	1995–2003	13,538	Fatal and nonfatal	Density	OR	1.05 (1.02–1.08)[c]	903 vehicle-km
									1.04 (1.02–1.06)	<100 vs. >100 m

HR = hazard ratio; OR = odds ratio.

[a] All were studies in adults (age 18+).

[b] Female population.

[c] Log transformed.

10.4.2 META-ANALYSES

Meta-analysis was conducted only for NO_2 (Figure 10.5). Other pollutants were evaluated by fewer than three studies each, and hence no meta-analyses were conducted (Table 10.6). The meta-analytic estimate for NO_2 was positive but imprecise, and the CI contained unity. Three studies showed clearly positive associations, three studies were at or around the null and one study reported a negative association, yielding an overall meta-analytic estimate of 1.03 (95% CI: 0.95–1.11) with moderate heterogeneity of 71% (Figure 10.5). The two studies with the largest weight were the Stockholm County case-control study (Rosenlund et al. 2009) and the ONPHEC administrative cohort study (Bai et al. 2019), both of which showed marginally positive associations. Neither study directly corrected for important confounders such as smoking and BMI. Upon exclusion of these two studies, the meta-analytic estimate of the remaining studies did not change in a relevant way (1.04; 0.91–1.18), although heterogeneity was increased (I^2 = 78%) (Appendix Figure 10B-1). Highest positive point estimates were observed for the Kaunas Men's case-control study (Grazuleviciene et al. 2004), the DDCH cohort (Roswall et al. 2017), and the KPNC Oakland cohort created from a roster of health maintenance organization members (Alexeeff et al. 2018). The cases in the small Kaunas Men's case-control study were restricted to short-term survivors of a myocardial infarction (one week after hospitalization) and therefore might not be representative for the associations in the full population, including individuals who died within the first week of their myocardial infarction. In contrast, the DDCH cohort is a large prospective cohort of the adult general population in Denmark with little selection and a registry follow-up for coronary events, while the KPNC Oakland cohort is a cohort constructed from insurance data with follow-up information from medical records and the death registry. In the analysis of the KPNC and the DDCH cohorts, exposure–response functions revealed no departure from linearity (Alexeeff et al. 2018) or showed a general increase in estimates across tertiles of NO_2 (Roswall et al. 2017).

The CPRD London study is the only study in this group that reported a relatively strong negative association (Carey et al. 2016). This cohort was constructed from medical records of general practitioners and hospital admission data in Greater London, not including out-of-hospital fatal events. The variability of air pollution concentrations was dominated by variability between areas of Greater London (i.e., Inner London versus the rest) rather than by variations within smaller areas (i.e., within areas covered by one general practitioner practice). When the overall estimate was partitioned into between-practice and within-practice effects for two of the investigated pollutants, associations for between-practice exposure differences were similar to the main estimate and negative, while the small-scale within-practice associations for coronary events were positive (Carey et al. 2016).

In stratified analyses, higher effect estimates were observed for fatal events, which was most obvious in those studies that reported estimates for both fatal and nonfatal outcomes separately (Rosenlund et al. 2006, 2009; Roswall

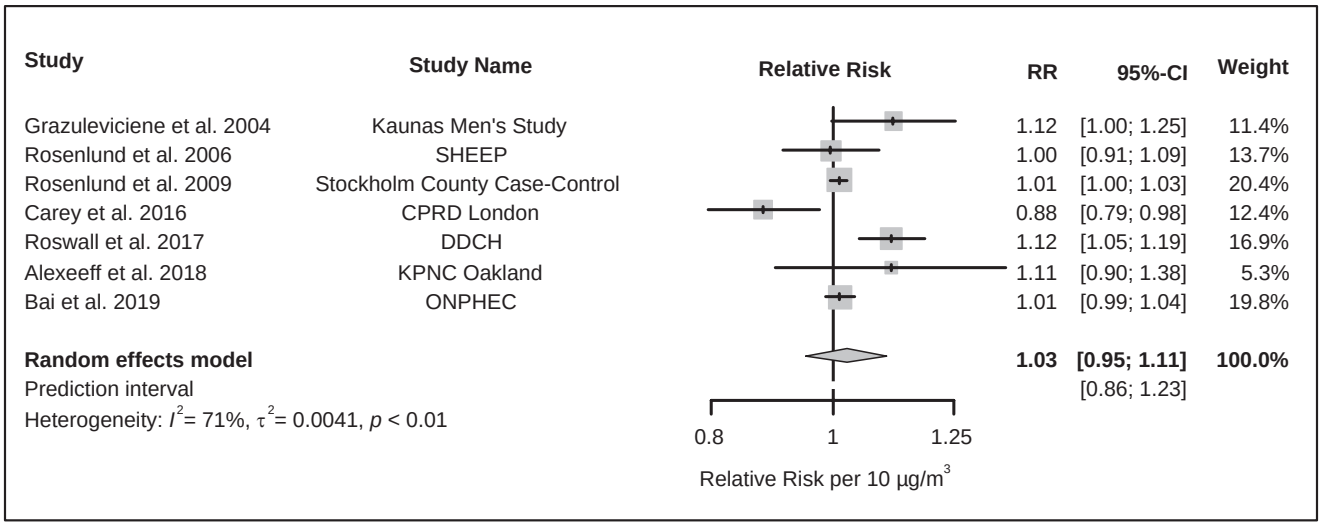

Figure 10.5. Association between NO_2 and incidence of coronary events: meta-analysis. Grazuleviciene et al. 2004 and Roswall et al. 2017 are nonfatal estimates; others combined fatal and nonfatal coronary events.

et al. 2017) (Appendix Figure 10B-2). Exclusion of two studies with only moderate traffic specificity (Alexeeff et al. 2018; Grazuleviciene et al. 2004), attenuated the meta-analytic estimate to the null, contrary to the hypothesized direction (Appendix Figure 10B-3). Differences by region or by publication year could not be evaluated due to insufficient number of studies.

Less information was available for the other pollutants, and no meta-analyses were conducted because there were fewer than three studies. Two medium- to large-sized cohorts in Western Europe reported on NO_x and coronary events incidence (Bodin et al. 2016; Carey et al. 2016). The Swedish Scania study (Bodin et al. 2016) showed positive, though imprecise, point estimates, and the CPRD London cohort (Carey et al. 2016) yielded a negative association of NO_x with incidence of coronary events, similar as for NO_2, for the main analyses and a positive association (1.03; 95% CI: 0.91–1.18) for the within-area exposure difference.

Four studies reported on at least one of the PM pollutant exposures (EC, PM_{coarse}, PM_{10}, or $PM_{2.5}$) and incidence of coronary events (Alexeeff et al. 2018; Atkinson et al. 2013; Hoffmann et al. 2015; Madrigano et al. 2013). For all studies, estimates for the combined outcome fatal and nonfatal events was available. All studies were conducted after the 2010 HEI Traffic Review and reported positive, but mostly imprecise, estimates for the particulate pollutants.

Other investigated pollutants included CO, which was related to fatal, but not to nonfatal coronary events in the two Swedish case-control studies (Rosenlund et al. 2006, 2009), and NO, which was positively associated with combined events in the retrospective KPNC Oakland cohort study (Alexeeff et al. 2018). This association was very similar to the association with NO_2 in the same study. The ONPHEC administrative cohort study in Toronto showed positive associations with UFPs (Bai et al. 2019). Long-term UFP exposure was assessed with an LUR model that was based on a mobile measurement campaign and yielded a robust positive association with first time acute myocardial infarction as well as incident congestive heart failure (Bai et al. 2019). This finding was contrary to the result for NO_2 in this study, which was only related to congestive heart failure, but not to coronary events. Indirect adjustment for individual lifestyle variables (smoking and obesity) as well as adjustment for traffic noise did not change the results for UFPs. Four of the five studies investigating traffic $PM_{2.5}$ or traffic PM_{10} showed positive estimates in the full analysis or in the analysis of fatal coronary events (Pindus et al. 2016; Rosenlund et al. 2006, 2009; Tonne et al. 2009), whereas estimates for combined or nonfatal events were mixed (Pindus et al. 2016; Rosenlund et al. 2006, 2009; Tonne et al. 2009).

10.4.3 ASSOCIATIONS WITH INDIRECT TRAFFIC MEASURES

Additional evidence was provided by eight studies using indirect traffic measures, of which six studies had positive associations of high or increasing traffic exposure with coronary

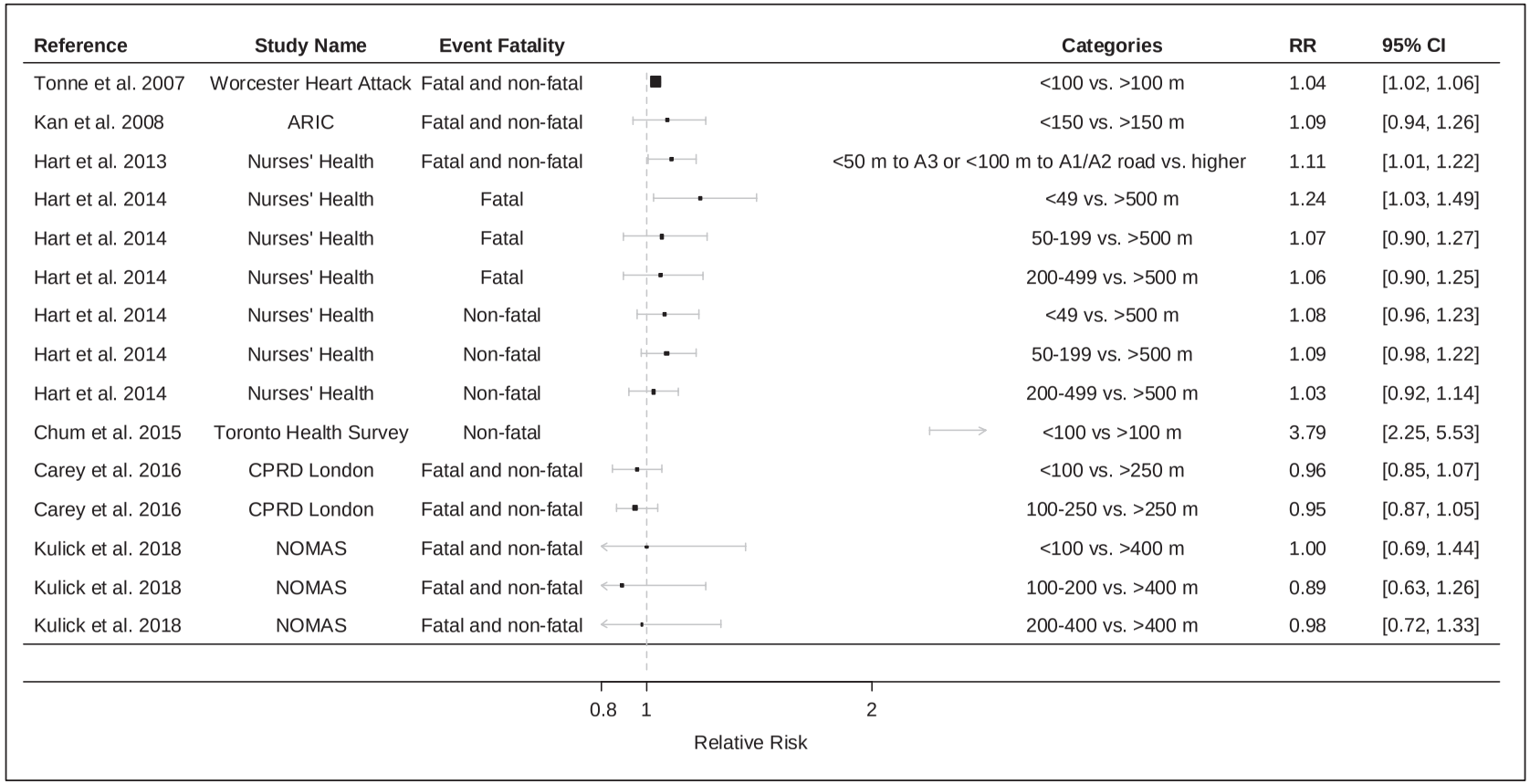

Figure 10.6. Association of distance to major roads with coronary events. Chum and O'Campo 2015 is a cross-sectional study.

events (Table 10.7 and Figure 10.6). Fatal as well as nonfatal coronary events were related to residential proximity with a positive exposure–response relationship (Hart et al. 2014). Monotonic exposure–response relationships were observed in the Worcester Heart Attack case-control study (Tonne et al. 2007) for both distance and density, as well as in the analysis of traffic density in quartiles in the ARIC study (Kan et al. 2008).

10.4.4 CO-EXPOSURE WITH NOISE AND OTHER POLLUTANTS

Because the analysis of traffic-related air pollutants and indirect traffic measures may suffer from confounding by traffic noise, six studies also adjusted for noise exposure (Appendix Table 10B-1). In most studies, effect estimates were reported to be robust to the additional adjustment for either daytime or nighttime noise, while specific estimates were not presented in two studies (Bai et al. 2019; Carey et al. 2016). In the German HNR study, effect estimates for coronary events were slightly attenuated for particulate matter but were stable for EC and traffic density (Hoffmann et al. 2015). In contrast, in the DDCH, the positive NO_2 associations for both fatal and nonfatal coronary events were substantially reduced upon adjustment for the moderately correlated noise indicator (Roswall et al. 2017). In the analysis of the small cross-sectional Toronto Health Survey by Chum and O'Campo (2015), only mutually adjusted results are available, showing very large associations of both traffic density and noise annoyance with coronary events.

Three studies adjusted for general $PM_{2.5}$ and observed stable results for NO_2 and UFP estimates (Bai et al. 2019), indirect traffic measures (Kan et al. 2008), or even slightly enhanced associations for traffic-specific PM_{10} (Pindus et al. 2016). In the only study with adjustment for ambient ozone, results were unaltered (Kan et al. 2008).

10.4.5 NARRATIVE ASSESSMENT

The evidence base provides suggestive evidence of an association of TRAP with incidence of coronary events. This is based on a moderate number of studies on NO_2 with a positive, though imprecise, meta-analytic estimate, including two studies with a monotonic exposure–response relationship (Alexeeff et al. 2018; Roswall et al. 2017), and on results for other pollutants with almost exclusively positive estimates, but too few studies per pollutant to conduct meta-analyses. Additional modest support is provided by associations in some studies investigating indirect traffic measures, partly observing associations in an exposure–response related manner. It is unlikely that residual confounding by traffic noise or other pollutants can explain the associations, as most studies showed stable results or only small changes upon adjustment for co-exposures. Given the overall small numbers of studies per pollutant, there was no clear pattern regarding health effects from pollutants with high versus moderate traffic specificity for pollutants other than NO_2. For NO_2, the meta-analytic estimate was attenuated to the null in the subset of studies with high traffic specificity, contrary to the hypothesized direction, although this is based on a small number of studies only.

The consistently negative association in the main analysis of pollutants with coronary events in the CPRD London study is not fully understood (Carey et al. 2016). As the authors state, the exposure contrast was dominated by differences between areas of London (mostly differences between Inner London and other parts of the city), rather than by small-scale differences from subtle roadside changes. Upon partitioning the total effect into between- and within-area effects, a clear negative association was observed between areas, while the within-area estimate was slightly positive.

Generally, the Panel observed larger estimates for fatal coronary events than for nonfatal coronary events. Although the reasons for this finding remain unclear, potential explanations include a smaller degree of outcome misclassification in more severe cases or pollutant influences on biological processes that determine a more severe course of the disease.

In conclusion, the Panel found a low level of confidence in the presence of an association, due to the small number of high-quality studies per pollutant. Chance, confounding, and other biases cannot be ruled out with appropriate certainty. For NO_2, where the evidence base is larger, it was generally supportive but not entirely consistent with one large study reporting a negative association.

10.4.6 CONFIDENCE ASSESSMENT OF THE BODY OF EVIDENCE

The modified OHAT assessment was conducted only for NO_2. The seven studies included in the meta-analyses were cohort or case-control studies, hence the initial rating for confidence in the quality of the body of evidence was moderate. Only cohort and case-control studies were used, so a combined assessment across study designs was not needed. The factors that reduce or increase confidence are described in the sections that follow. All studies addressed the research question directly, and therefore no downgrade was applied for the downgrading factor indirectness. The Panel decided a priori not to consider the upgrading factor large magnitude of the effect.

10.4.6.1 Factors That Reduce Confidence

Among the factors that reduce confidence, the Panel evaluated the risk of bias as low or moderate in most studies and domains (Table 10.8). The risk of bias ratings can be found for the individual studies in Appendix Table 10B-2. One study, the case-control study from Sweden (Rosenlund et al. 2009), was rated at high risk of bias due to incomplete confounder control for smoking and BMI. One other study was rated high for risk of bias due to selection bias and missing data

Table 10.8. Summary of Risk of Bias Rating for Studies on Coronary Events

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	5	1	1	5	1	1
	Validity of measuring of confounding factors	5	2	0	5	2	0
	Control in analysis	5	2	0	5	2	0
	Overall	1	5	1	1	5	1
2. Selection bias	Selection of participants into the study	6	0	1	6	0	1
3. Exposure assessment	Methods used for exposure assessment	7	0	0	7	0	0
	Exposure measurement methods comparable across the range of exposure	7	0	0	7	0	0
	Change in exposure status	5	2	0	5	2	0
	Overall	5	2	0	5	2	0
4. Outcome measurements	Blinding of outcome measurements	7	0	0	7	0	0
	Validity of outcome measurements	6	1	0	6	1	0
	Outcome measurements	6	1	0	6	1	0
	Overall	6	1	0	6	1	0
5. Missing data	Missing data on outcome measures	6	0	1	6	0	1
	Missing data on exposures	6	1	0	6	1	0
	Overall	5	1	1	5	1	1
6. Selective reporting	Authors reported a priori primary and secondary study aims	7	0	0	7	0	0

(Grazuleviciene et al. 2004). Sensitivity analyses excluding high risk of bias studies revealed stable effect estimates; therefore, no downgrade was applied (Appendix Figure 10B-4). No downgrade was applied for unexplained inconsistency. Heterogeneity was moderate and was primarily apparent in the subgroup of cohort studies where study sizes were partly very large with nonoverlapping CIs. The Panel downgraded for imprecision because the meta-analytic CI was wide and clearly included unity, although the required sample size was sufficient. Given the small number of studies, which makes a formal analysis of publication bias impossible, the Panel did not downgrade due to publication bias as stated in the protocol. See Table 10.9 for the confidence assessment.

10.4.6.2 Factors That Increase Confidence

For NO_2 and incident coronary events, two out of seven studies with a combined weight of 22% showed monotonic exposure–response functions (Alexeeff et al. 2018; Roswall et al. 2017), leading to an upgrade. A few mechanisms of potential bias toward the null were identified in the analysis of NO_2, among them exclusion or underassessment of fatal events in several studies and a potential for overadjustment for spatial variables correlated with exposure in the CPRD study (Carey et al. 2016). Altogether, the evidence for a bias toward the null was considered too low to justify an upgrade, as the degree and direction of bias due to potential overadjustment cannot be predicted with certainty. Too few studies were available to evaluate consistency across geographic regions, populations, or study period.

10.4.6.3 Evaluation of Confidence for Combined Measures of TRAP

For NO_2 and incident coronary events, the rating of confidence in the quality of the body of evidence is moderate. A

Table 10.9. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Coronary Events[a]

	High ++++ Moderate +++ Low ++ Very low +		Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort, Case-control	+++ (N = 7)	0	0	–	0	+	0	0	+++ (Moderate)
	Rationale	Cohort and case-control initially rated as moderate.	Not sensitive to exclusion of two studies with high RoB.	Moderate heterogeneity (I^2 = 71%), primarily due to magnitude not direction.	Sample size met, but confidence interval wide and clearly includes unity.	No formal evaluation possible.	Two studies reported a monotonic ERF (Alexeeff 2018; Roswall 2017).	Confounding in both directions possible.	Too few studies to evaluate.	

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

downgrade was applied due to traffic specificity because exclusion of the two studies with only moderate traffic specificity (Alexeeff et al. 2018; Grazuleviciene et al. 2004) attenuated the meta-analytic estimate to the null. In addition, limited supportive evidence was provided by a small number of studies on other pollutants that were not meta-analyzed and by six studies with positive associations of indirect traffic measures with coronary events. In conclusion, based on the modified OHAT assessment, the confidence in the quality of the body of evidence for TRAP exposure and coronary events is low.

10.4.7 OVERALL CONFIDENCE ASSESSMENT

Based on the narrative assessment (low) and the modified OHAT assessment (low), the overall confidence in the evidence of an association between TRAP exposure and incidence of coronary events is low.

10.5 STROKE

10.5.1 STUDY SELECTION AND DESCRIPTION

Overall, 20 studies were identified that investigated the association of a wide range of traffic-related air pollutants and indirect traffic measures with stroke morbidity (Table 10.10 and Table 10.11). All studies were published after the 2010 HEI Traffic Review deadline, although most studies had starting dates in the 1990s. The study locations were in Europe, North America, China, and Australia. Three studies were exclusively on men or women.

Exposures were assigned based on surface air monitoring data (in two studies), dispersion models or CTM, and LUR models. Most studies had geocoded residence addresses; others had high-resolution postal codes. Most studies considered exposures occurring during periods between 1990 to 2015; one study considered estimated exposure back to 1971 (Andersen et al. 2012a). Exposure assignments ranged from annual average at enrollment or during the one-year prior to the event, to average over all years from enrollment to event. Nineteen studies investigated traffic pollutants, six analyses investigated indirect measures such as distance to traffic or traffic density. NO_x and NO_2 were the most frequently investigated traffic pollutants, followed by EC, PM_{10}, and $PM_{2.5}$. Mean exposures varied considerably across the studies, with annual mean NO_2 ranging from 9 μg/m³ (Lazarevic et al. 2015) to 53 μg/m³ (Katsoulis et al. 2014) and $PM_{2.5}$ from 5 μg/m³ (Dirgawati et al. 2019) to 18 μg/m³ (Hoffmann et al. 2015). The range of mean pollutant exposure was wider across the 11 cohorts in the ESCAPE multicohort analysis, for example, mean $PM_{2.5}$ exposures in individual cohorts up to 31 μg/m³. The majority of the study's exposure assignments for NO_2, NO_x, and EC (which includes $PM_{2.5}$ absorbance) were ranked as high traffic specificity. Four studies evaluated the effect of concurrent noise exposure on the estimate for traffic-related air pollutants.

Most studies investigated stroke incidence with a cohort design, three studies report case-control analyses in the United States (Johnson et al. 2013) or in a Swedish setting (Oudin et al. 2009, 2011) and three studies examined stroke prevalence (history of past stroke) in cross-sectional studies (Lazarevic et al. 2015; Pindus et al. 2016; Qin et al. 2015). The majority of studies defined the outcome as a combination of fatal or nonfatal stroke including hemorrhagic (ICD-9: 431; ICD-10: I60), ischemic (ICD-9: 433, 434; ICD-10: I63), and unspecified stroke (ICD-9: 436; ICD-10: I64). Six studies defined the outcome more broadly (i.e., with less specificity) as cerebrovascular disease (for example ICD-10: I60-I69), included transient ischemic attacks (435, G45) (Dirgawati et al. 2019; Johnson et al. 2013; Katsoulis et al. 2014), or subarachnoid hemorrhage (Gan et al. 2012; Qin et al. 2015). Dirgawati and colleagues (2019) also included retinal infarction (362.3, H34.1). Three studies relying on self-report asked questions regarding any prior diagnosis of stroke nonspecific to type (Lazarevic et al. 2015; Pindus et al. 2016; Qin et al. 2015). A few studies defined the outcome more narrowly as only ischemic stroke (Kulick et al. 2018; Oudin et al. 2009, 2011). A few other studies provided additional estimates specific to outcome type (ischemic, hemorrhagic) (Andersen et al. 2012a; Johnson et al. 2013; Korek et al. 2015), but according to protocol for this review, only the estimate for total strokes (ischemic and hemorrhagic) was used in the meta-analysis if available.

Eleven studies were mostly medium-sized to large prospective population-based cohort studies (N = 2,752 to 99,446). These studies all had detailed information on lifestyle, individual SES, and comorbidities and usually adjusted for a large number of covariates. Two prospective cohort studies included personal contact with participants either by mail, telephone, or in-person study center visits at baseline as well as during follow-up (Hoffmann et al. 2015; Kulick et al. 2018). Identification of incident stroke was conducted through active follow-up with one or more of the following: repeated personal contacts, proxy interviews, death certificates, and adjudication using medical records, leading to a high validity of the outcome assessment, or by linkage with disease registries. Eight prospective cohort studies collected personal information at baseline and then primarily used hospital admissions and disease and death registries to assess nonfatal and fatal stroke incidence (Andersen et al. 2012a; Dirgawati et al. 2019; Katsoulis et al. 2014; Korek et al. 2015; Sørensen et al. 2014; Stafoggia et al. 2014; Stockfelt et al. 2017). Stockfelt and colleagues (2017) reported results for two cohorts (the GOT-MONICA and PPS) in Sweden in a single manuscript. For this report, these are considered as two studies because of large differences in their cohorts. Andersen and colleagues (2012a) and Sørensen and colleagues (2014) are

Table 10.10. Key Study Characteristics of Articles Included in the Systematic Review for Stroke—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Fatality	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Alexeeff 2018	KPNC Oakland	Cohort	Oakland, California, United States	2010–2015	41,869	Surface monitoring	NO_2	9.9	Fatal and nonfatal	HR	**0.97 (0.85–1.11)**	3.8 ppb
									Fatal		1.38 (0.93–2.06)	
							NO	4.9	Fatal and nonfatal		0.98 (0.87–1.11)	3.8 ppb
									Fatal		1.13 (0.86–1.49)	
							BC	0.36	Fatal and nonfatal		**0.96 (0.85–1.08)**	0.17 μg/m^3
									Fatal		0.92 (0.58–1.45)	
Andersen 2012a	DDCH	Cohort	Copenhagen and Aarhus, Denmark	1993–2006	52,215	Dispersion/ CTM	NO_2	15.2	Fatal	HR	1.22 (0.99–1.49)	7.5 μg/m^3
									Nonfatal		1.05 (0.99–1.11)	6.2 μg/m^3
Atkinson 2013	CPRD	Cohort	England	2003–2007	819,370	Dispersion/ CTM	PM_{10} mass	19.7	Fatal and nonfatal	HR	**1.00 (0.93–1.06)**	3.0 μg/m^3
Carey 2016	CPRD London	Cohort	London, United Kingdom	2005–2011	207,047	Dispersion/ CTM	NO_2	37.4	Fatal and nonfatal	HR	**0.88 (0.82–0.95)**	10 μg/m^3
							NO_x	63.0			**0.90 (0.85–0.96)**	20 μg/m^3
							Traffic $PM_{2.5}$	1.45			0.88 (0.81–0.97)	1 μg/m^3
Dirgawati 2019	HIMS	Cohort	Perth, Australia	1996–2012	10,126[d]	LUR	NO_2	13.4	Fatal and nonfatal	HR	**0.96 (0.85–1.08)**	10 μg/m^3
									Fatal		0.93 (0.72–1.19)	

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Table 10.10. (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Stroke—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Fatality	Effect Measure	Effect Estimate (95% CI)[c]	Increment
							NO_x	32.3	Fatal and nonfatal		**1.00 (0.95–1.04)**	10 µg/m^3
									Fatal		0.97 (0.88–1.07)	
							$PM_{2.5\ abs}$	0.9	Fatal and nonfatal		**0.86 (0.71–1.03)**	1 1×10^{-5}/m
									Fatal		0.70 (0.47–1.03)	
							$PM_{2.5}$ mass	5.1	Fatal and nonfatal		**1.01 (0.84–1.21)**	5 µg/m^3
									Fatal		0.71 (0.49–1.02)	
Gan 2012	Vancouver Administrative	Cohort	Vancouver, British Columbia, Canada	1999–2002	445,868	LUR	$PM_{2.5\ abs}$	1.5	Fatal	HR	**1.04 (1.00–1.09)**	0.97 1×10^{-5}/m
Hoffmann 2015	HNR	Cohort	Ruhr Areas, Germany	2000–2012	4,222	LUR	$PM_{2.5\ abs}$	1.59	Fatal and nonfatal	HR	1.57 (0.86–2.86)	0.98 1×10^{-5}/m
							PM_{10} mass	27.78			2.38 (1.06–5.35)	6.32 µg/m^3
							PM_{coarse} mass	9.99			1.79 (0.72–4.46)	5.26 µg/m^3
							$PM_{2.5}$ mass	18.41			2.90 (1.18–7.12)	3.51 µg/m^3
Johnson 2013	Edmonton Stroke	Case-control	Edmonton, Alberta, Canada	2007–2009	42,419	LUR	NO_2	15.4	Fatal and nonfatal	OR	**1.01 (0.94–1.08)**	5 ppb
Katsoulis 2014	EPIC Athens	Cohort	Athens, Greece	1994–2011	2,752	LUR	NO_2	53.1	Fatal and nonfatal	HR	**0.98 (0.71–1.34)**	10 µg/m^3
							PM_{10} mass	39.4			**1.17 (0.60–2.26)**	10 µg/m^3

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Table 10.10. (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Stroke—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Fatality	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Korek 2015	SDPP, SIXTY, SALT, SNAC-K	Cohort	Stockholm, Sweden	1992–2011	20,070	Dispersion/ CTM	NO_x	4.6–17.5	Fatal and nonfatal	HR	**1.20 (0.64–2.29)**	20 μg/m^3
							Traffic PM_{10}	1.7–8			1.20 (0.89–1.63)	10 μg/m^3
Lazarevic 2015	ALSWH	Cross-sectional	Australia	2006–2011	26,991[e]	LUR	NO_2	5	Nonfatal	RR	0.83 (0.58–1.19)	3.3 ppb
Oudin 2009	Scania Stroke	Case-control	Scania, Sweden	2001–2005	556,912	Dispersion/ CTM	NO_x	12.9	Fatal and nonfatal	OR	0.87 (0.73–1.03)	30–60 vs. <10 μg/m^3
											0.95 (0.86–1.06)	20–30 vs. <10 μg/m^3
											0.97 (0.90–1.05)	10–20 vs. <10 μg/m^3
Oudin 2011	Scania Stroke	Case-control[f]	Scania, Sweden	2001–2006	6,302	Dispersion/ CTM	NO_x	About 15	Nonfatal	OR	**0.93 (0.82–1.95)**	10 μg/m^3
Pindus 2016	RHINE Tartu	Cross-sectional	Tartu, Estonia	2011–2012	905	Dispersion/ CTM	Traffic PM_{10}	3.3	Nonfatal	OR	1.21 (0.53–2.77)	2.2 μg/m^3
Sørensen 2014	DDCH	Cohort	Copenhagen and Aarhus, Denmark	1993–2009	51,569	Dispersion/ CTM	NO_2	16.6	Fatal and nonfatal	IRR	**1.08 (1.01–1.16)**	10 μg/m^3
									Fatal		1.47 (1.21–1.80)	
							NO_x	20.8	Fatal and nonfatal		**1.02 (0.98–1.07)**	20 μg/m^3
									Fatal		1.17 (1.05–1.31)	

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Table 10.10. (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Stroke—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Fatality	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Stafoggia 2014	ESCAPE	Cohort	Multiple cities, multiple countries	1992–2010	99,446	LUR	NO_2	8–60	Fatal and nonfatal	HR	**0.99 (0.89–1.11)**	10 µg/m^3
							NO_x	14–107			**0.98 (0.89–1.07)**	20 µg/m^3
							$PM_{2.5\ abs}$	0.5–3.2			**1.08 (0.83–1.41)**	1 1×10^{-5}/m
							PM_{10} mass	14–48			**1.11 (0.90–1.36)**	10 µg/m^3
							PM_{coarse} mass	6–17			1.02 (0.90–1.16)	5 µg/m^3
							$PM_{2.5}$ mass	7–31			**1.19 (0.88–1.62)**	5 µg/m^3
Stockfelt 2017	GOT-MON	Cohort	Gothenburg, Sweden	1990–2011	4,500	Dispersion/ CTM	NO_x	33	Fatal and nonfatal	HR	**1.04 (0.90–1.20)**	20 µg/m^3
							BC	0.8			**1.25 (0.89–1.76)**	1 µg/m^3
							PM_{10} mass	13			**1.48 (0.88–2.49)**	10 µg/m^3
							$PM_{2.5}$ mass	8.5			**1.50 (0.90–2.51)**	5 µg/m^3
							PM_{10} exhaust	0.3			1.07 (0.92–1.23)	0.29 µg/m^3
							Nontail-pipe PM_{10}	1.7			1.10 (0.97–1.24)	1.48 µg/m^3
							Traffic PM_{10}	1.41			1.09 (0.97–1.23)	1.77 µg/m^3
	PPS	Cohort	Gothenburg, Sweden	1990–2011	5,850[d]	Dispersion/ CTM	NO_x	42	Fatal and nonfatal	HR	**1.04 (0.97–1.12)**	20 µg/m^3
							BC	0.9			**1.09 (0.90–1.31)**	1 µg/m^3

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Table 10.10. (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Stroke—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Fatality	Effect Measure	Effect Estimate (95% CI)[c]	Increment
							PM_{10} mass	13			**1.08 (0.80–1.45)**	10 µg/m^3
							$PM_{2.5}$ mass	9.3			**1.06 (0.78–1.44)**	5 µg/m^3
							PM_{10} exhaust	0.4			1.04 (0.97–1.28)	0.29 µg/m^3
							Nontail-pipe PM_{10}	2.0			1.03 (0.96–1.10)	1.41 µg/m^3
							Traffic PM_{10}	2.4			1.03 (0.97–1.10)	1.7 µg/m^3
Qin 2015	33 CCHS	Cross-sectional	Shenyang, Anshan and Jinzhou, China	2009	14,646	Surface monitoring	NO_2	35.28	Nonfatal	OR	1.01 (0.84–1.22) (normal weight)	9 µg/m^3
					1,435						1.15 (0.64–2.07) (obese)	
					8,764						1.22 (0.98–1.51) (overweight)	

HR = hazard ratio; IRR = incidence rate ratio; OR = odds ratio; RR = relative risk.

[a] All studies were in adults (age 18+) except Dirgawati, 2019 (Older Adults 65+). No studies were log transformed.

[b] Units are in the increment column.

[c] **Bold** indicates the effect estimate was included in the meta-analysis.

[d] Male population.

[e] Female population.

[f] Based on prevalent cases.

Table 10.11. Key Study Characteristics of Articles Included in the Systematic Review for Stroke—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Fatality	Traffic Measure	Effect Measure	Effect Estimate (95% CI)	Increment
Andersen 2012a	DDCH	Cohort	Copenhagen and Aarhus, Denmark	1993–2006	52,215	Fatal	Density	HR	0.99 (0.91–1.09)	1,700 vehicle-km/day
						Nonfatal			1.02 (0.99–1.04)	
						Fatal	Distance		1.17 (0.70–1.98)	<50 vs. >50 m
						Nonfatal			1.09 (0.94–1.26)	
Carey 2016	CPRD London	Cohort	London, United Kingdom	2005–2011	207,047	Fatal and nonfatal	Density	HR	1.00 (0.88–1.15)	>100,000 heavy vehicle-km/year vs. none
									1.02 (0.96–1.11)	<100,000 heavy vehicle-km/year vs. none
							Distance		0.98 (0.86–1.12)	<100 vs. >250 m
									1.02 (0.95–1.10)	100–250 vs. >250 m
Hoffmann 2015	HNR	Cohort	Ruhr Areas, Germany	2000–2012	4,222	Fatal and nonfatal	Density	HR	1.06 (0.69–1.64)	4,302 vehicle-km/day
Kulick 2018	NOMAS	Cohort	Manhattan, United States	1993–2016	3,287	Fatal and nonfatal	Distance	HR	1.42 (1.01, 2.02)	<100 vs. >400 m
									1.14 (0.81–1.60)	100–200 vs. >400 m
									1.08 (0.80–1.45)	200–400 vs. >400 m
Lazarevic 2015	ALSWH	Cross-sectional	Australia	2006–2011	26,991[b]	Nonfatal	Distance	RR	1.01 (0.90–1.14)[c]	1 km
Stafoggia 2014	ESCAPE	Cohort	Multiple cities, multiple countries	1992–2010	99,446	Fatal and nonfatal	Density	HR	1.02 (0.95–1.10)	4,000 vehicle-km/day

HR = hazard ratio; RR = relative risk.

[a] All adult studies (age 18+).

[b] Female population.

[c] Log-transformed.

both based on the DDCH study. They are both included in the review, as they provide estimates for different outcome strata for fatality. Stafoggia and colleagues (2014), which reports meta-analyses of data from 11 European cohorts included in the ESCAPE project, is considered and reported as a single study. One study was limited to older men (Dirgawati et al. 2019). It excluded movers (10%), which can potentially lead to concerns about selection bias.

Four studies reported on large (N = 41,869) to very large (N = 819,370) cohort studies that were constructed retrospectively from insurance data of a private health maintenance organization (Alexeeff et al. 2018), health administrative databases from the universal provincial insurance in British Columbia (Gan et al. 2012), or primary care and hospital admissions records of patients of a subset of general practitioners in the greater London area and England-wide (Atkinson et al. 2013; Carey et al. 2016). Although these studies have the advantage of little selection because they are constructed from administrative or routine medical care data bases, the availability and quality of individual-level covariates is often limited. Validity of the outcome assessment is limited in those cases where these studies rely only on secondary data such as reimbursement claims.

Three case-control studies were included, two of which were conducted in a relatively low air pollution area in southern Sweden (Scania) (Oudin et al. 2009, 2011) and one of which was for subjects in Edmonton, Canada (Johnson et al. 2013). The Oudin and colleagues studies used national and local stroke registries to identify first-time ischemic stroke cases. For the later analysis, the investigators obtained personal covariate data from questionnaires sent to the surviving cases (prevalent cases) and to controls (Oudin et al. 2011). Johnson and colleagues (2013) investigated patients who presented to hospital emergency departments with first-time stroke or transient ischemic attack diagnoses and patients who presented to the same emergency departments for minor trauma as controls. This study relied on census tract BMI and smoking data rather than individual-level covariate data. These case-control studies suffer from an incomplete case ascertainment, selecting the study population to immediate (Johnson et al. 2013; Oudin et al. 2009) or long-term survivors (Oudin et al. 2011) of stroke. For the study population of the Scania study (Oudin et al. 2009, 2011), the effect of these restrictions on the evidence base is quantified as follows: fatal strokes outside the hospital equaled only about 1% of overall cases, mild cases were sent home without admission (~9% of overall cases), and patients not surviving until the beginning of the second study were 33% of the overall cases.

Three cross-sectional studies investigated the prevalence of nonfatal stroke in the general population (Lazarevic et al. 2015; Pindus et al. 2016; Qin et al. 2015). These studies primarily rely on questionnaire data and on self-reported disease. Therefore, those studies are more prone to underassessment and misclassification because of selection of cases toward less severe cases who have survived until the time of the study. One study included only women (Lazarevic et al. 2015).

10.5.2 META-ANALYSES

A sufficient number of studies (≥3) were available to perform meta-analyses on NO_2, NO_x, EC, PM_{10}, and $PM_{2.5}$ and stroke incidence (Figure 10.7). The summary effect estimates indicated positive associations for EC, PM_{10}, and PM_{25}, with CIs overlapping unity, and null associations for NO_2 or NO_x.

Figure 10.8 shows the forest plots with individual studies for NO_2 and NO_x. For NO_2, the summary effect estimate is 0.98 (95% CI: 0.92–1.05) for a 10-µg/m³ increment based on seven studies. The direction of the individual associations are variable and the heterogeneity of the studies moderate (I^2 = 64%). Only the Danish DDCH study yielded a statistically significant postive relationship (Sørensen et al. 2014) with an estimate of 1.08 (1.01–1.16), contributing 20% of the weight in the meta-analysis. The estimate of the CPRD London study, also contributing 20% of the weight, stands out because it shows a significantly negative estimate (Carey et al. 2016). The other studies showed effect estimates close to the null with mostly wide CIs overlapping unity. Various subanalyses within these studies yield a more differentiated, yet not entirely consistent

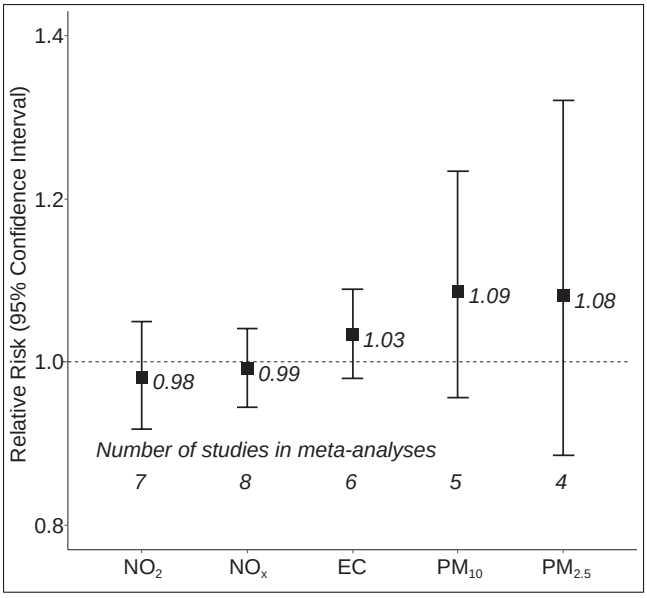

Figure 10.7. Meta-analysis of associations between traffic-related air pollutants and incidence of stroke. The following increments were used: 10 µg/m³ for NO_2, 20 µg/m³ for NO_x, 1 µg/m³ for EC, 10 µg/m³ for PM_{10}, and 5 µg/m³ for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

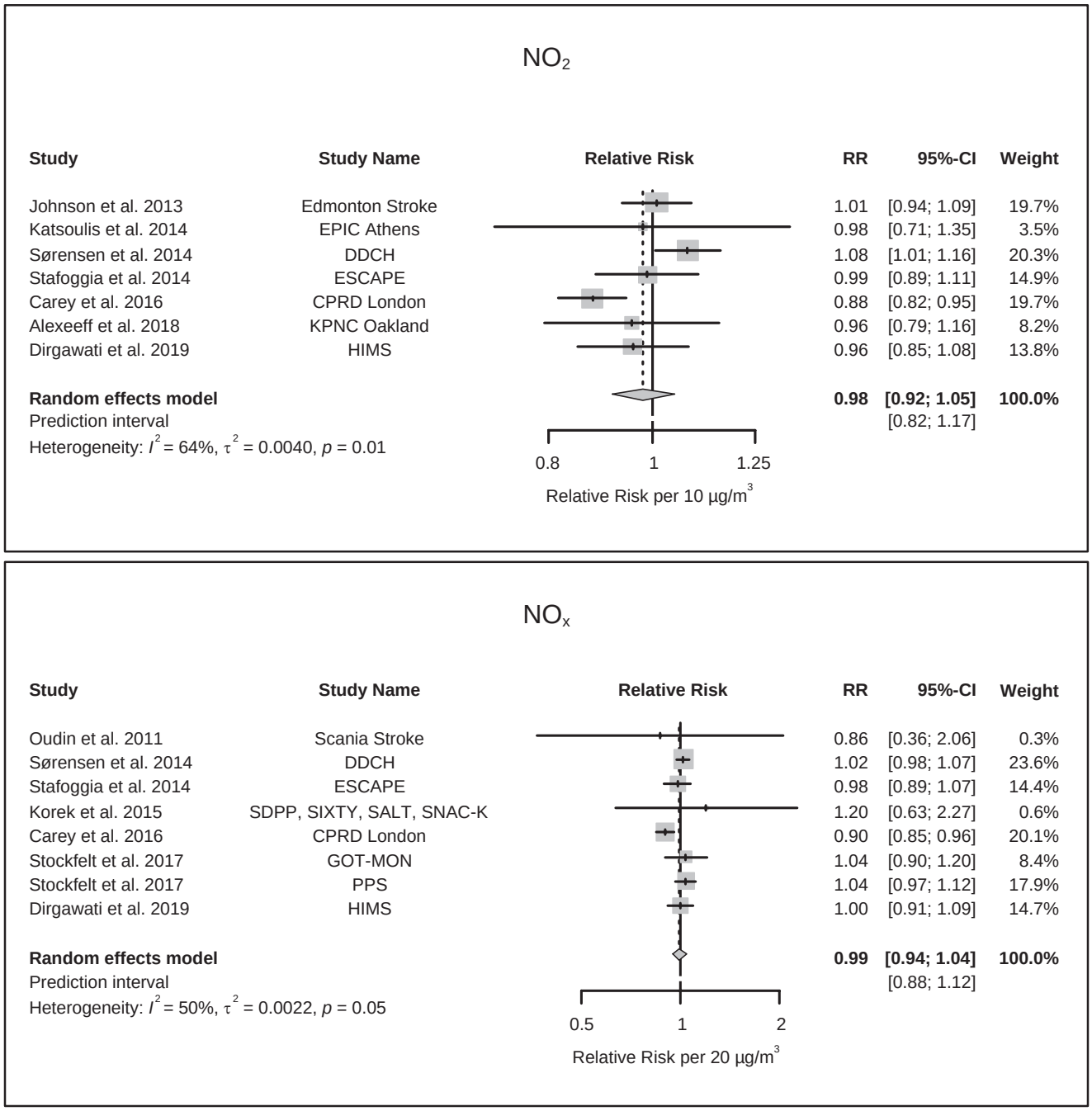

Figure 10.8. Association between NO_2 and NO_x and stroke: meta-analysis. Oudin et al. 2011 are estimates for nonfatal stroke from a case-control study based on prevalent cases; others combined fatal and nonfatal stroke.

picture. In the case-control study of emergency department patients in Edmonton, Canada (Johnson et al. 2013) with 20% of overall weight, analyses stratified by type of outcome displayed elevated effect estimates for acute ischemic, as well as for hemorrhagic stroke, and had a negative estimate for transient ischemic attacks. The small EPIC-Athens cohort study observed very imprecise, though elevated, estimates for women and younger participants, but not in the overall study population (Katsoulis et al. 2014). In contrast, the administrative cohort of predominantly younger participants in Oakland, California, U.S.A., observed higher estimates in older people (age 65+) and among people with diabetes (Alexeeff et al. 2018).

Among the three studies that provided effect estimates by fatality, two showed higher estimates for fatal outcomes than for nonfatal or combined outcomes (Appendix Figure 10C-1), with the Danish DDCH study (Sørensen et al. 2014) and the KPNC Oakland study (Alexeeff et al. 2018) reporting large positive effect estimates (RR = 1.47 to 1.57) for fatal stroke. There was no clear difference according to region of the world, traffic specificity, study design, or level of confounder control (Appendix Figure 10C-2 and Additional Materials). Most studies did not characterize the shape of the exposure–response function. Two analyses from the DDCH with largely overlapping study populations indicated that the exposure–response function was linear and positive for NO_2 (Andersen et al. 2012a; Sørensen et al. 2014), while Dirgawati and colleagues (2019) reported a negative slope in the HIMS cohort. The HIMS cohort study of older men commenced as a randomized controlled trial of screening for vascular disease and had an overall mortality of 54% during follow-up, raising concerns about competing fatal events that might have influenced the stroke estimate. In summary, the NO_2 meta-analytic estimate is consistent with no association.

The analysis of NO_x and stroke incidence included eight individual studies and yielded a meta-analytic estimate of 0.99 (95% CI: 0.94–1.04) for a 20-μg/m^3 increment, indicating no effect. The heterogeneity of the studies was moderate (I^2 = 50%). The CPRD London study (Carey et al. 2016) reports a statistically negative association. In contrast, the other individual NO_x studies report mostly either slightly elevated, but not statistically significant associations, or null results, with mixed evidence regarding a positive, monotonic exposure–response function (e.g., a negative slope in Dirgawati et al. 2019, positive for categories of NO_x in subanalyses in Oudin et al. 2011). No clear picture emerges from the few studies with analyses stratified by fatality (Additional Materials). However, similar to the analysis for NO_2, the association of NO_x with fatal events was stronger than with total events in the DDCH (Sørensen et al. 2014). As only one study was not conducted in Western Europe (Dirgawati et al. 2019), no analysis by region was possible. Only one study was a case-control study reporting prevalent cases (Oudin et al. 2011). One study on NO_x was not included in the meta-analysis, because it was an earlier analysis of the Scania Stroke Study with less individual-level covariate adjustment and exposure only analyzed in categories, of which the highest category was positively associated with ischemic stroke (Oudin et al. 2009). All studies were rated high for traffic specificity.

Six studies were included in the meta analysis of EC and stroke incidence (Figure 10.9). Four of them reported positive, though mostly imprecise, associations. Except for Alexeeff and colleagues (2018), all studies were rated as highly traffic specific. The summary relative risk was 1.03 (95% CI: 0.98–1.09) for a 1-μg/m^3 increment with low heterogeneity, dominated by the Gan and colleagues (2012) study with 84% of the overall weight. This administrative cohort study from Canada analysed fatal strokes in a general population free of cardiovascular disease at baseline, using the provincial health insurance database and linking this with the provincial death registry. Because of limited individual-level information on covariates such as smoking, the comorbidities diabetes, chronic obstructive pulmonary disease, and hypertensive heart disease were used as proxies to control for lifestyle-related risk factors. This might have led to some degree of bias, as these comorbidities potentially act as intermediates on the pathway between exposure and stroke. On the other hand, the magnitude of the residual confounding arising from the lack of adjustment for lifestyle variables is unclear. In sensitivity analyses, excluding this study due to lack of adjustment for lifestyle variables, the summary effect is virtually the same (RR = 1.02), but precision is substantially reduced (95% CI: 0.86–1.20). Although the Panel identified some mechanisms leading to participant selection (exclusion of potential cases) in both the Australian (Dirgawati et al. 2019) and the KPNC Oakland (Alexeeff et al. 2018) studies, these were of no serious concern due to the small weight in the overall analysis. Similar to NO_2 and NO_x, Dirgawati and colleagues (2019) reported a negative slope for incidence of nonfatal strokes over the study's relatively low concentration range of 0.1–1.5 10^5/m for $PM_{2.5\ abs}$. In contrast, Stafoggia and colleagues (2014) reported a positive linear slope of the exposure–response function as a good approximation for most of the included 11 cohorts. The associations were more consistent and stronger among the European studies where EC exposure is generally higher due to a greater proportion of diesel vehicles and closer residential proximity to traffic in dense cities (Eeftens et al. 2012).

Five studies investigating PM_{10} exposure and combined fatal and nonfatal stroke incidence were included in the meta-analysis (Figure 10.9), indicating relative risks greater than 1 for all but one study and a summary estimate of 1.09 (95% CI: 0.96–1.23) with no heterogeneity. The two studies with the largest weight in the meta-analysis are the multicohort analysis of the 11 European cohorts in the ESCAPE study (Stafoggia et al. 2014) with a positive association, and the analysis of the CPRD cohort in England (Atkinson et al. 2013) with a null association. In the latter study, there was some concern because the adjustment revealed a downward influence of adjustment for a very granular neighborhood deprivation index, which was also strongly related to the outcome. Due to this high correlation, there is a chance that the adjustment might have removed the effects of the less spatially resolved air pollution concentrations (Atkinson et al. 2013). The third most influential study was the medium-sized prospective PPS cohort from Sweden with an elevated RR for the more recent exposure of 5 years, but not for current exposure (Stockfelt et al. 2017). This publication also reported a positive association and a linear and monotonically increasing exposure–response function over the 5 to 26 μg/m^3 range in the second analysed cohort, namely the slightly smaller GOT-MONICA cohort (Stockfelt et al. 2017). Stafoggia and colleagues (2014)

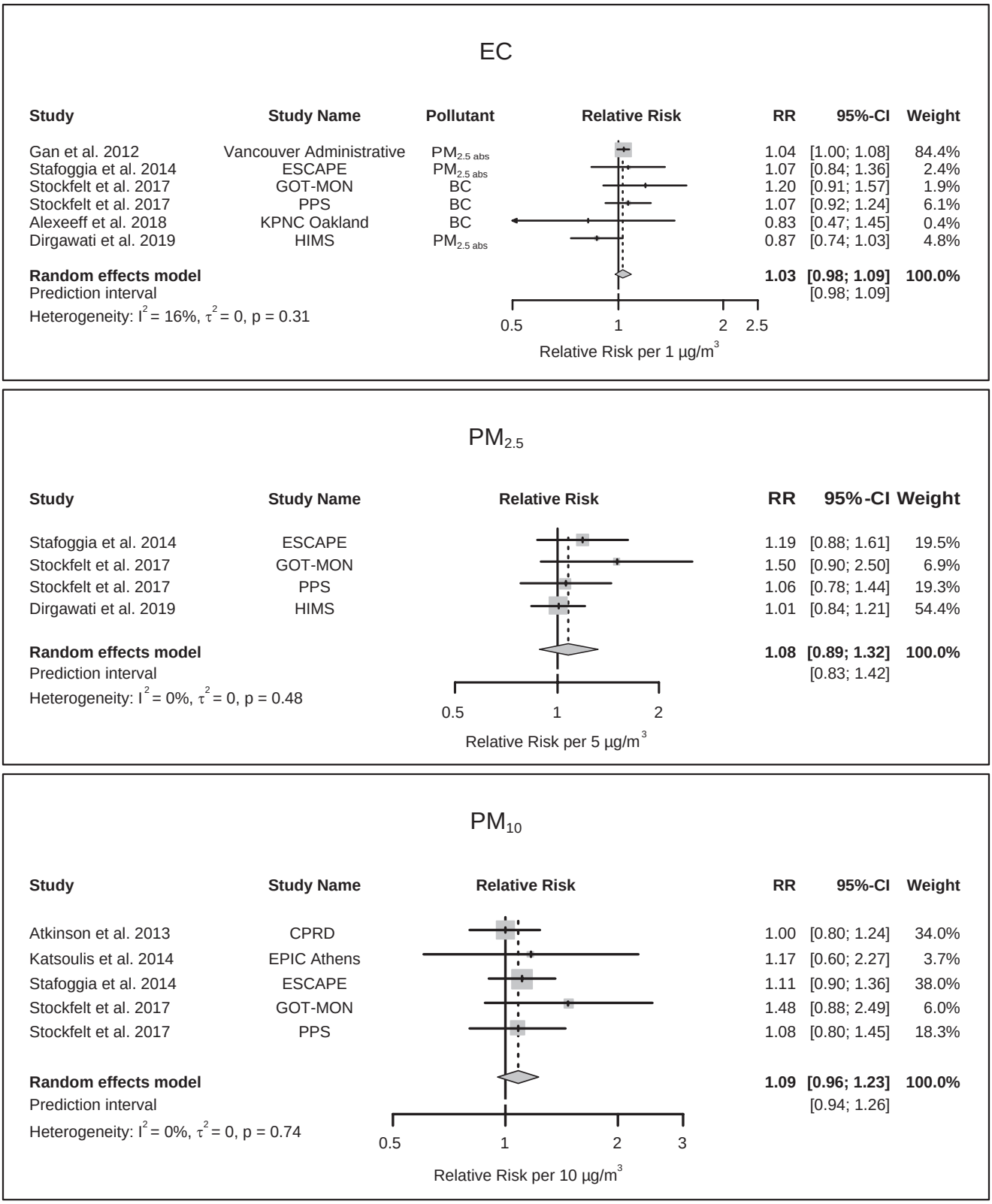

Figure 10.9. Association between EC, PM_{10} and $PM_{2.5}$ and incidence of stroke: meta-analysis. Gan et al. 2012 are estimates for nonfatal stroke; others combined fatal and nonfatal stroke.

reported a linear shape of the exposure–response function for most of the included 11 cohorts. There was no variability according to fatality (all studies reported estimates for combined fatal and nonfatal strokes only), region (all studies came from Western Europe), and traffic specificity (all studies rated moderate).

The effect estimates for the four publications included in the meta-analysis of $PM_{2.5}$ and stroke were all greater than 1 and yielded a summary relative risk of 1.08 (95% CI: 0.89–1.32) for a 5-μg/m^3 increment with no heterogeneity (Figure 10.9). The study contributing about half of the weight in the meta-analysis was the Australian study of older men (Dirgawati et al. 2019), showing a null association. This study also reported a biologically implausible U-shaped exposure–response function. The two other fairly influential studies, contributing 19% each to the overall weight, were the ESCAPE analysis, based on 11 individual cohorts (Stafoggia et al. 2014), and the Swedish PPS cohort (Stockfelt et al. 2017) with positive, but imprecise estimates. Both the European ESCAPE study (Stafoggia et al. 2014) and the Swedish analysis of the GOT-MONICA cohort (Stockfelt et al. 2017) reported a linear and monotonically increasing exposure–response function. Subset analyses in the ESCAPE study also revealed substantially stronger and statistically significant associations when exposures were restricted to levels below 25, 20, and 15 μg/m^3. Upon exclusion of the Australian study (Dirgawati et al. 2019) in analyses by geographic region, the estimate for the remaining Western European studies was substantially higher (1.17; 0.82–1.67). In summary, the $PM_{2.5}$ results show positive but relatively imprecise effect estimates for stroke incidence.

A small number of studies examined other pollutants and their association with stroke; however, numbers were too small to conduct meta-analyses. The multicohort ESCAPE study reported RRs for PM_{coarse} of 1.02 (95% CI: 0.90–1.16) for a 5-μg/m^3 increment (Stafoggia et al. 2014). The HNR study, which was also part of the ESCAPE analysis, also reported an elevated estimate for PM_{coarse}, which was stable upon adjustment for noise (Hoffmann et al. 2015). Overall, four studies investigated indicators of traffic PM_{10}, which were assessed with dispersion models or CTM, all of which were deemed to be highly traffic specific. Stockfelt et al. 2017 reported results for exhaust PM_{10}, nontailpipe PM_{10}, and traffic PM_{10}. The RRs were all larger than 1, with stronger associations for the younger GOT-MONICA cohort than for the older PPS male cohort. Carey and colleagues (2016) examined traffic-specific $PM_{2.5}$ in London and found a negative association (RR = 0.88; 0.81–0.97). Korek and colleagues (2015), reporting on an analysis of four cohorts from Sweden, observed a 1.20 elevated RR (0.89–1.63) for 10-μg/m^3 of traffic-specific PM_{10} estimated with a dispersion model that modeled local road traffic emissions, which were the dominating source of NO_x and PM_{10}. An association was also observed in the very small Estonian cross-sectional study of dispersion-modeled traffic-specific PM_{10} and self-reported stroke (Pindus et al. 2016). NO and stroke incidence was examined in one study, where it was shown to be related to fatal stroke, but not combined fatal and nonfatal stroke (Alexeeff et al. 2018). Two large cross-sectional studies were not included in the meta-analysis of NO_2. The 33 CCHS study in China observed associations between NO_2 from nearby surface monitors and self-reported stroke, specifically in overweight and obese subjects (Qin et al. 2015). In contrast, a study on Australian women showed a negative, though imprecise, estimate for self-reported stroke (Lazarevic et al. 2015). Overall, these studies of other PM sizes or fractions, and specifically the results for the highly traffic-specific PM fractions, were supportive of an association of TRAP with stroke. There were no studies investigating UFPs.

10.5.3 ASSOCIATIONS WITH INDIRECT TRAFFIC MEASURES

Meta-analysis was not conducted for the indirect traffic measures because the varying definitions across the studies precluded such analyses. Altogether, six studies investigated associations with proximity to roads or traffic density (Table 10.11 and Figure 10.10), one of which was the multicohort analysis of 11 European cohorts (Stafoggia et al. 2014). Two studies reported associations with traffic density (Andersen et al. 2012a) or with distance to traffic (Kulick et al. 2018), which also showed a monotonic exposure–response relationship. The other four studies reported inconclusive estimates.

10.5.4 CO-EXPOSURE WITH NOISE AND OTHER POLLUTANTS

The four studies examining the effect of noise adjustment for one or more traffic-related pollutant showed stable or even larger effect estimates (Gan et al. 2012; Hoffmann et al. 2015; Sørensen et al. 2014; Stafoggia et al. 2014) (Appendix Table 10C-1). Adjustment of EC estimates for general $PM_{2.5}$ also yielded stable results in Gan and colleagues (2012). None of the studies tested for the possible role of ozone co-exposure. The single study that corrected for general $PM_{2.5}$ showed stable results (Pindus et al. 2016).

10.5.5 NARRATIVE ASSESSMENT

The study base and the meta-analyses provide evidence for the presence of an association of PM_{10} and suggestive evidence of an association of EC and $PM_{2.5}$ with stroke incidence. This is based on meta-analyses of four to six studies per pollutant. The presence of an association is supported by subset analyses, respectively a monotonic exposure–response relationship in two well-conducted studies for $PM_{2.5}$, including the multicohort ESCAPE analysis and the GOT-MONICA study (Stafoggia et al. 2014; Stockfelt et al. 2017). Additional supporting evidence is provided by positive estimates for highly traffic-specific PM fractions in two studies (Korek et al. 2015; Stockfelt et al. 2017).

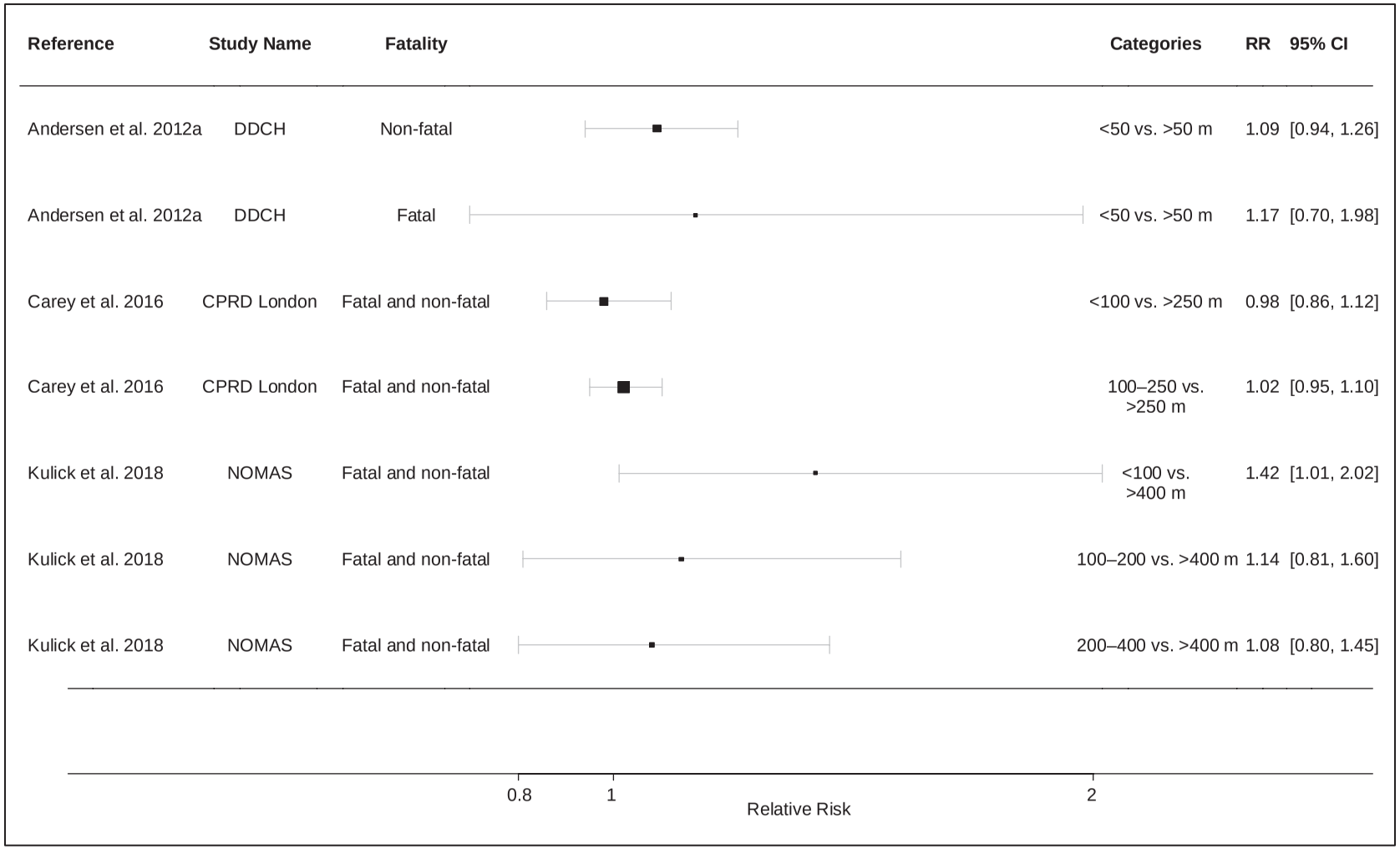

Figure 10.10. Association of distance to major roads with stroke incidence. Lazarevic et al. 2015 is not in the plot because the estimate was log-transformed.

Substantial confounding by traffic noise could be ruled out with reasonable certainty, based on four medium-sized to large studies. Limited, though not entirely consistent, evidence is supplied by studies using indirect traffic measures. Several aspects of the evidence base require discussion.

First, the overall evidence base consisted of 20 studies, of which 19 studies investigated traffic-related pollutants, and 6 studies included indirect measures such as distance to traffic or traffic density. The numbers of studies available for gaseous and particulate pollutants was about equal, but fewer studies could be included in the meta-analysis of particulate air pollutants, as these were more diverse and included specific components such as exhaust PM and nontailpipe PM.

Second, the evidence for particulate air pollutants was stronger than for gaseous pollutants. All meta-analytic estimates for the particulate pollutants (EC, PM_{10}, and $PM_{2.5}$) were positive, showed very little or no heterogeneity, but displayed wide CIs and included unity. Associations of PM_{coarse} and of highly traffic-specific particulate pollutants (i.e., traffic-PM)—for which no meta-analyses were conducted due to small numbers and incomparability of these exposure estimates—also showed mostly positive, but nonsignificant associations. The evidence for the gaseous traffic pollutants was considerably lower. Although a relatively large number of studies investigated NO_2, and NO_x, the overall picture was mixed and the summary estimate was consistent with no association.

The reasons for this difference in evidence between gaseous and particulate pollutants remain unclear. Potential explanations include, but are not limited to, a true lack of an association between gaseous pollutants and stroke incidence, random variation in the available data, better exposure assessment for the more homogeneously distributed particulate air pollutants, or specific biases in the relatively small number of studies that were included in this review.

Third, the accuracy and completeness of the stroke outcome data is a concern in some studies, because patients may not be hospitalized for mild strokes (Oudin et al. 2009), and out-of-hospital fatal strokes may be misdiagnosed, underreported, or not assessed with the applied methods (for example, when using hospital admission data only). Oudin and colleagues (2011) cited estimates indicating 15% of ischemic strokes were not captured in the Swedish hospitalization registry. Most studies did not report on the completeness of the outcome data sources. Most importantly, underassessment of mild stroke cases can potentially be related to exposure via SES by way of access to health care and making use of advanced diagnostic procedures.

Fourth, there was some concern regarding systematic bias in the influential studies based on primary care and hospital admissions records of patients of a subset of general practitioners in the greater London area and England-wide (Atkinson et al. 2013; Carey et al. 2016), which carried 20% to 34% of the weight in the main meta-analyses. Next to problems of accurate diagnosis in a primary care setting, adjustment by small-area SES could have potentially removed the effect of the correlated exposure.

In conclusion, the Panel found a moderate level of confidence in the presence of an association of exposure to TRAP with stroke incidence. The assessment is based on mostly consistent evidence for EC, PM_{10}, and $PM_{2.5}$ associations with stroke from a moderately large number of studies. Several high-quality studies from different regions across Europe and in North America yielded positive meta-analytic estimates for EC, PM_{10}, and $PM_{2.5}$ in different populations, albeit imprecise and with CIs that included unity. The assessment is supported by limited evidence from nonmeta-analysed studies, indirect traffic measures, and relative stability in noise-adjusted models. What makes the evidence less compelling is the absence of evidence for the gaseous pollutants, yielding null findings in the meta-analyses. The Panel refrained from giving a higher rating because the overall number of studies was still rather limited, because the traffic specificity of the PM_{10} and $PM_{2.5}$ exposures was only moderate, and because of the null results in the analyses of the gaseous pollutants NO_2 and NO_x, which are thought to be more traffic specific.

10.5.6 CONFIDENCE ASSESSMENT OF THE BODY OF EVIDENCE

The modified OHAT assessment is only conducted for the studies and exposure–outcome pairs for which a meta-analysis was conducted (N = 12). As the studies included in meta-analyses were cohort or case-control studies, the initial rating for confidence in the quality of the body of evidence was moderate for all pollutant–outcome pairs. Only cohort or case-control studies were used, so a combined assessment across study designs was not needed. The factors that reduce or increase confidence are described in the sections that follow. All studies addressed the research question directly, and therefore no downgrade was applied for the downgrading factor indirectness. The Panel decided a priori not to consider the upgrading factor large magnitude of the effect.

10.5.6.1 Factors That Reduce Confidence

Among the factors that may reduce confidence, the Panel evaluated the risk of bias and ranked it as low or moderate in most exposure–outcome pairs and domains (Table 10.12). The risk of bias ratings for the individual studies can be found in Appendix Table 10C-2. In the two studies that ranked as high risk of bias, this was due to lack of confounder control for smoking and BMI (Gan et al. 2012; Johnson et al. 2013). In addition, Johnson et al. 2013 was also rated high for potential selection bias.

Forest plots with stratification for risk of bias (Appendix Figure 10C-2) show stable and similar overall results when the studies with high risk of bias studies are excluded, and subgroup analyses in Johnson and colleagues (2013) indicate the results are stable with respect to the potential selection

Table 10.12. Summary of Risk of Bias Rating for Studies on Stroke

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	9	1	2	23	5	2
	Validity of measuring of confounding factors	9	3	0	25	5	0
	Control in analysis	11	1	0	22	8	0
	Overall	5	5	2	10	18	2
2. Selection bias	Selection of participants into the study	11	0	1	29	0	1
3. Exposure assessment	Methods used for exposure assessment	12	0	0	30	0	0
	Exposure measurement methods comparable across the range of exposure	12	0	0	30	0	0
	Change in exposure status	10	2	0	21	9	0
	Overall	10	2	0	21	9	0
4. Outcome measurements	Blinding of outcome measurements	11	1	0	28	2	0
	Validity of outcome measurements	11	1	0	28	2	0
	Outcome measurements	11	1	0	28	2	0
	Overall	10	2	0	26	4	0
5. Missing data	Missing data on outcome measures	12	0	0	30	0	0
	Missing data on exposures	12	0	0	30	0	0
	Overall	12	0	0	30	0	0
6. Selective reporting	Authors reported a priori primary and secondary study aims	12	0	0	30	0	0

bias issue. These sensitivity analyses indicated no downgrade was warranted for risk of bias. Heterogeneity was either low (NO_x, EC, PM_{10}, $PM_{2.5}$), or moderate (NO_2). Therefore, no downgrade due to unexplained inconsistency was warranted. The Panel downgraded the level of confidence for all pollutants except NO_x for imprecision because all meta-analyses had sufficient power and met the sample size criterion, but the CIs were wide and clearly included unity. Given the small number of studies in each pollutant–outcome pair, which makes an analysis of publication bias infeasible, the Panel did not downgrade due to publication bias as stated in the protocol. See the confidence assessment in Table 10.13.

10.5.6.2 Factors That Increase Confidence

The Panel upgraded the evidence for associations of PM_{10} and $PM_{2.5}$ with stroke following the demonstration of a monotonic exposure–response function in the GOT-MONICA cohort (Stockfelt et al. 2017) and the consistent and stable subset analyses in the 11 studies included in the ESCAPE multicohort analysis. Moreover, the ESCAPE study also included an investigation of the exposure–response function of individual cohorts, using spline function, suggesting the linear shape was a good approximation (Stafoggia et al. 2014). The Panel identified several mechanisms of potential bias toward the null. Examples of these include mechanisms with a potential for over adjustment and the inclusion of potential intermediates (Alexeeff et al. 2018; Andersen et al. 2012a; Atkinson et al. 2013; Carey et al. 2016). An upgrade was not considered appropriate based on the small number of studies where there are indications that residual confounding or other factors were likely to lead to an underestimation of an apparent association these studies. Similarly, too few studies were available to evaluate consistency across geographic regions, populations, or study period.

Table 10.13. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Stroke[a]

	High ++++ Moderate +++ Low ++ Very low +		Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort, CC	+++ (N = 7)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort and case-control initially rated as moderate.	Not sensitive to exclusion of two studies with high RoB.	Moderate heterogeneity (I^2 = 64%).	Sample size met but confidence interval wide and includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies across different populations.	
NO_x	Cohort, CC	+++ (N = 8)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Cohort and case-control initially rated as moderate.	No studies rated high RoB.	Moderate heterogeneity (I^2 = 50%), at least partly explained by one influential study with concerns.	Sample size met and confidence interval includes unity, but precise.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies across different populations.	
EC	Cohort	+++ (N = 6)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	Not sensitive to exclusion of one study with high RoB.	Low heterogeneity (I^2 = 16%).	Sample size met but confidence interval wide and includes unity.	No formal evaluation possible.	One multicohort study with monotonic ERF (Stafoggia 2014).	Confounding in both directions possible.	Too few studies across different populations.	

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Table 10.13. (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Stroke[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
PM_{10}	Cohort	+++ ($N = 5$)	0	0	–	0	+	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	No studies rated high RoB.	Low heterogeneity ($I^2 = 0\%$).	Sample size met but confidence interval wide and includes unity.	No formal evaluation possible.	Two studies with either monotonic ERF or stable estimates in subset analysis (Stafoggia 2014; Stockfelt 2017).	Confounding in both directions possible.	Too few studies across different populations.	
$PM_{2.5}$	Cohort	+++ ($N = 4$)	0	0	–	0	+	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	No studies rated high RoB.	Low heterogeneity ($I^2 = 0\%$).	Sample size met but confidence interval wide and includes unity.	No formal evaluation possible.	Two studies with either monotonic ERF or stable estimates in subset analysis (Stafoggia 2014; Stockfelt 2017).	Confounding in both directions possible.	Too few studies across different populations.	

CC = case-control; ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

10.5.6.3 Evaluation of Confidence for Combined Measures of TRAP

The final rating of the confidence in the quality of the body of evidence is low for NO_2 and EC, and moderate for NO_x, $PM_{2.5}$, and PM_{10}, with NO_2 and NO_x indicating no effect. The combined confidence rating for measures of TRAP across different pollutants started with moderate confidence. The Panel downgraded to low, because all $PM_{2.5}$ and PM_{10} studies were rated only moderately traffic-specific studies. In conclusion, based on the confidence assessment using OHAT, the confidence in the quality of the body of evidence of TRAP exposure and stroke incidence is low.

10.5.7 OVERALL CONFIDENCE ASSESSMENT

Based on the narrative assessment (moderate) and the modified OHAT assessment (low), the overall confidence in the evidence of an association between TRAP exposure and stroke incidence is low to moderate.

10.6 DIABETES

10.6.1 STUDY SELECTION AND DESCRIPTION

Overall, 21 studies investigated TRAP and diabetes prevalence or incidence (Table 10.14 and Table 10.15), All studies were published after the deadline of the 2010 HEI Traffic Review. Additional studies have been conducted on incidence of gestational diabetes and markers of impaired glucose control, which are, however, not subject of this review.

Eleven studies were conducted in Europe, eight studies in North America, two in China, and one in Australia. Most studies investigated exposure periods in the 2000s, but nine studies had starting dates in the 1990s or earlier. Eleven studies investigated incidence of diabetes, while twelve studies investigated prevalence of diabetes. Out of a total of 21 studies, 16 studies investigated NO_2 or NO_x, 9 studies investigated at least one kind of particulate pollutant, and 7 included distance to traffic or traffic density measures. A few studies or exposures were excluded from the review because the Panel judged that the exposure assessment employed did not sufficiently represent motorized traffic impacts (e.g., the pollutants in the Nurses' Health Study and Health Professionals Follow-Up Study [Puett et al. 2011]). Mean exposures differed five to tenfold depending on pollutant and included studies, with average annual NO_2 as low as 5 $\mu g/m^3$ in Australia and more than 40 $\mu g/m^3$ in Rome. In 14 studies, traffic specificity for at least one pollutant was deemed high.

The evidence base contains analyses from 11 cohort studies and 10 cross-sectional studies. Two cohort studies contributed with two publications to the overall evidence base. Study size ranged from about 500 in Bulgaria, to a few thousand participants in Germany to more than 2 million participants in Canada. Except for four studies investigating only women (Coogan et al. 2012, 2016; Kramer et al. 2010; Lazarevic et al. 2015), all other studies examined adult men and women. Most studies did not formally differentiate between type 1 and type 2 diabetes, but since all studies were conducted in adults, incident type 1 diabetes can be neglected (IDF 2019). We will refer to the disease as diabetes for simplicity in this report. As diabetes in its early stages in adults is painless and has only very unspecific symptoms, it is often undiagnosed. For example in Europe and North America, among all people with diabetes, approximately 40% of cases have not been diagnosed with the disease (IDF 2019). The included studies differ according to whether only known or also heretofore undiagnosed diabetes was assessed. Eight studies conducted clinical examinations and were able to assess known and undiagnosed diabetes, whereas the other studies analyzed self-reported data or registry or insurance claims data, which only assess known diabetes, and therefore will miss a substantial number of cases. Although most studies were based on well-described study populations with in-depth information on potential confounders such as lifestyle and individual SES, the three large Canadian studies (Bai et al. 2018; Clark et al. 2017; Howell et al. 2019) and the large Rome Longitudinal study (Renzi et al. 2018) had no information on individual lifestyle factors. Five studies evaluated concurrent traffic noise exposure. Overall, the identified studies differed substantially in population, methods, and exposure.

Seven studies are traditional population-based studies from Europe, North America, and China (Eze et al. 2014, 2017; Kramer et al. 2010; Park et al. 2015; Weinmayr et al. 2015; Yang et al. 2018, 2019) of medium size (1,775 to 15,477 participants), with clinical examinations and an in-depth assessment of individual-level characteristics at the baseline examination, with a follow-up period of several years and a repeated assessment of disease conducted at a follow-up study center visit. One of these studies was limited to older women, with an average age of 54 and 71 years past baseline and follow-up, respectively (Kramer et al. 2010). In these studies, presence of diabetes at baseline and incidence of diabetes during follow-up was assessed with a multimodal strategy including a questionnaire or personal interview, information on medication, and fasting or nonfasting blood glucose measurements. One study additionally employed the gold standard of oral glucose tolerance testing (Yang et al. 2018, 2019). Exposure assessment was mainly based on LUR or on dispersion or CTM modeling, only the Chinese study employed ground-based monitoring without additional modeling. One study (Weinmayr et al. 2015) specifically modeled traffic PM with a CTM. Three of these five cohort studies also investigated distance measures. None of these studies reported information on the form of the exposure–response function. Only the study by Eze and colleagues (2017), which primarily investigated the association of noise with diabetes

Table 10.14. Key Study Characteristics of Articles Included in the Systematic Review for Diabetes—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Incidence											
Andersen 2012b	DDCH	Cohort	Copenhagen and Aarhus, Denmark	1993–2006	51,818	Dispersion/ CTM	NO_2	14.5	HR	**1.04 (1.00–1.08)**	4.9 µg/m^3
							NO_x	20.9		**1.02 (1.00–1.04)**	11.4 µg/m^3
Bai 2018	ONPHEC	Cohort	Toronto, Canada	1996–2012	1,056,012	LUR	NO_2	21.4	HR	**1.06 (1.05–1.07)**	4.0 ppb
							PNC <0.1 µm	28,383		1.06 (1.05–1.08)	9,948 particles/cm^3
Clark 2017	British Columbia Diabetes Cohort	Cohort	Vancouver, British Columbia, Canada	1994–2002	380,738	LUR	NO_2	32.1	OR	**1.00 (0.98–1.02)**	8.4 µg/m^3
							$PM_{2.5\ abs}$	1.5		**1.03 (1.01–1.04)**	0.9 1×10^{-5}/m
							NO	32.0		1.04 (1.01–1.05)	13.13 µg/m^3
							$PM_{2.5}$ mass	4.1		**1.03 (1.01–1.05)**	1.6 µg/m^3
Coogan 2012	BWHS	Cohort	Los Angeles, California, United States	1995–2005	3,992[d]	LUR	NO_x	43.3	IRR	**1.25 (1.07–1.46)**	12.4 ppb
Coogan 2016	BWHS	Cohort	United States	1995–2013	43,003[d]	LUR	NO_2	18.6	HR	**0.90 (0.82–1.00)**	9.7 ppb
Eze 2017	SAPA-LDIA	Cohort	Multiple cities, Switzerland	2002–2011	2,631	LUR	NO_2	20	RR	**0.92 (0.67–1.26)**	15 µg/m^3
Kramer 2010	SALIA	Cohort	North Rhine-Westphalia, Germany	1985–2006	1,775[d]	LUR	NO_2	34.5	HR	**1.42 (1.16–1.73)**	15 µg/m^3
							$PM_{2.5\ abs}$	0.54		**1.27 (1.09–1.48)**	0.39 1×10^{-5}/m

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Table 10.14. (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Diabetes—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Park 2015	MESA	Cohort	Multiple cities, United States	2000–2012	5,135	LUR	NO_x	49.7–56.5	HR	**1.04 (0.77–1.40)**	47.1 ppb
							$PM_{2.5}$ mass	16.7–17.3		**1.05 (0.87–1.26)**	2.43 μg/m^3
Renzi 2018	Rome Longitudinal	Cohort	Rome, Italy	2008–2013	1,319,193	LUR	NO_2	42.4	HR	**1.00 (1.00–1.01)**	10 μg/m^3
							NO_x	83.9		**1.01 (1.00–1.01)**	20 μg/m^3
							$PM_{2.5\ abs}$	2.7		**1.00 (0.98–1.02)**	1 1×10^{-5}/m
							PM_{10} mass	36.6		1.00 (0.99–1.02)	10 μg/m^3
							PM_{coarse} mass	16.9		0.99 (0.97–1.02)	10 μg/m^3
							$PM_{2.5}$ mass	19.6		**1.00 (0.98–1.02)**	5 μg/m^3
Weinmayr 2015	HNR	Cohort	Ruhr Areas, Germany	2000–2008	3,607	Dispersion/ CTM	PM_{10} mass	20.8–20.9	RR	1.05 (1.00–1.10)	1 μg/m^3
							$PM_{2.5}$ mass	16.7–16.8		**1.03 (0.95–1.12)**	1 μg/m^3
							Traffic $PM_{2.5}$	0.8–0.9		1.36 (0.97–1.89)	1 μg/m^3
Prevalence											
Dijkema 2011	Hoorn Diabetes Screening	Cross-sectional	West Friesland, the Netherlands	1998–2000	8,018	LUR	NO_2	15.2	OR	0.80 (0.63–1.02)	16.5–26 vs. 8.8–14.2 μg/m^3
										1.25 (0.99–1.56)	15.2–16.5 vs. 8.8–14.2 μg/m^3
										1.03 (0.82–1.31)	14.2–15.2 vs. 8.8–14.2 μg/m^3

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Table 10.14. (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Diabetes—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Dzhambov 2016	Plovdiv Diabetes Survey	Cross-sectional	Plovdiv, Bulgaria	2014	513	Dispersion/ CTM	$PM_{2.5}$ mass	20.3–25.0	OR	1.32 (0.28–6.24)	>25 vs. <25 µg/m³
							PAH (BaP)	3.75–6.0		1.76 (0.52–5.98)	>6 vs. <6 ng/m³
Eze 2014	SAPALDIA	Cross-sectional	Multiple cities, Switzerland	2002	6,392	Dispersion/ CTM	NO_2	29.2	OR	**1.21 (1.05–1.39)**	10 µg/m³
							PM_{10} mass	24.4		**1.44 (1.21–1.71)**	10 µg/m³
Howell 2019	CANHEART	Cross-sectional	Ontario, Canada	2008	2,496,458	LUR	NO_2	18	OR	**1.16 (1.14–1.17)**	10 ppb
Lazarevic 2015	ALSWH	Cross-sectional	Australia	2006–2011	26,991[d]	LUR	NO_2	5	RR	**1.04 (0.91–1.20)**	3.7 ppb
Li 2017	CAFEH	Cross-sectional	Boston, Massachusetts, United States	2009–2012	653	Personal exposure	PNC >4 nm	20,000	OR	0.71 (0.46–1.10)[e]	Not reported
O'Donovan 2017	CHAMPIONS	Cross-sectional	Leicestershire, United Kingdom	2004–2011	10,443	Dispersion/ CTM	NO_2	21.4	OR	**1.10 (0.92–1.32)**	10 µg/m³
							PM_{10} mass	16.4		**1.3 (0.5–2.9)**	10 µg/m³
							$PM_{2.5}$ mass	12.0		**1.6 (0.4–4.6)**	10 µg/m³
Park 2015	MESA	Cohort	Multiple cities, United States	2000–2012	5,839	LUR	NO_x	49.7–56.5	OR	1.29 (0.94–1.76)	47.1 ppb
							$PM_{2.5}$ mass	16.7–17.3		**1.16 (0.94–1.42)**	2.43 µg/m³
Renzi 2018	Rome Longitudinal	Cross-sectional	Rome, Italy	2008–2013	1,425,580	LUR	NO_2	42.4	OR	**1.00 (1.00–1.01)**	10 µg/m³
							NO_x	83.9		1.01 (1.00–1.01)	20 µg/m³
							$PM_{2.5\ abs}$	2.7		0.98 (0.96–0.99)	1 1×10^{-5}/m

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Table 10.14. (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Diabetes—Pollutants

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Effect Measure	Effect Estimate (95% CI)[c]	Increment
							PM_{10} mass	36.6		**0.99 (0.98–1.00)**	10 µg/m^3
							PM_{coarse} mass	16.9		0.96 (0.94–0.98)	10 µg/m^3
							$PM_{2.5}$ mass	19.6		**0.98 (0.96–1.00)**	5 µg/m^3
Riant 2018	ELISA-BET	Cross-sectional	Lille and Dunkirk, France	2011–2013	2,797	Dispersion/ CTM	NO_2	21.96	OR	**1.06 (0.90–1.25)**	5 µg/m^3
							PM_{10} mass	26.75		**1.04 (0.86–1.25)**	2 µg/m^3
Yang 2018	33 CCHS	Cross-sectional	Multiple cities, China	2009	15,477	Surface monitoring	NO_2	35.3	OR	1.22 (1.12–1.33)	9 µg/m^3
Yang 2019	33 CCHS	Cross sectional	Multiple cities, China	2009	15477	Surface monitoring	NO_2	35.3	OR	**1.20 (1.08–1.32)**	10 µg/m^3

HR = hazard ratio; IRR = incidence rate ratio; OR = odds ratio; PAH = polycyclic aromatic hydrocarbon; PNC = particle number concentration; RR = relative risk.

[a] All studies were in adults (age 18+).

[b] Units are in the increment column.

[c] **Bold** indicates the effect estimate was included in the meta-analysis.

[d] Female population.

[e] Log transformed.

Table 10.15. Key Study Characteristics of Articles Included in the Systematic Review for Diabetes—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Traffic Measure	Effect Measure	Effect Estimate (95% CI)[b]	Increment
Incidence									
Andersen 2012b	DDCH	Cohort	Copenhagen and Aarhus, Denmark	1993–2006	51,818	Density	HR	1.02 (1.00–1.04)	1,200 vehicle-km/day
								1.07 (0.95–1.21)	<50 vs. >50 m
Kramer 2010	SALIA	Cohort	North Rhine-Westphalia, Germany	1985–2006	1,775[c]	Distance	HR	2.54 (1.31–4.91) (low education)	<100 vs. >100 m
								0.92 (0.58–1.47) (high education)	
Park 2015	MESA	Cohort	Multiple cities, United States	2000–2012	5,135	Distance	HR	0.96 (0.80–1.16)	<100 vs. >100 m
Puett 2011	Nurses' Health Health Professionals Follow-up	Cohort	United States	1989–2002	89,460	Distance	HR	1.11 (1.01–1.23)	0–49 vs. >200 m
								0.96 (0.63–1.48)	50–99 vs. >200 m
								0.96 (0.87–1.06)	100–199 vs. >200 m
Weinmayr 2015	HNR	Cohort	Ruhr Areas, Germany	2000–2008	3,607	Distance	RR	1.37 (1.04–1.81)	<100 vs. 100–200 m
Prevalence									
Dijkema 2011	Hoorn Diabetes Screening	Cross-sectional	West-Friesland, the Netherlands	1998–2000	8,018	Density	OR	1.09 (0.85–1.38)	882–2,007 vs. 63–516 thousand vehicles/day
								1.13 (0.89–1.44)	680–882 vs. 63–516 thousand vehicles/day
								1.25 (0.99–1.59)	516–680 vs. 63–516 thousand vehicles/day
						Distance		0.88 (0.70–1.13)	2–74 vs. 220–1,610 m
								1.17 (0.93–1.48)	74–140 vs. 220–1,610 m
								1.12 (0.88–1.42)	140–220 vs. 220–1,610 m

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Table 10.15. (*Continued*). Key Study Characteristics of Articles Included in the Systematic Review for Diabetes—Indirect Traffic Measures

Reference	Study Name	Study Design	Location	Study Period	Sample Size[a]	Traffic Measure	Effect Measure	Effect Estimate (95% CI)[b]	Increment
Lazarevic 2015	ALSWH	Cross-sectional	Australia	2006–2011	26,991[c]	Distance	RR	0.99 (0.95–1.04)[d]	1 km
Park 2015	MESA	Cohort	Multiple cities, United States	2000–2012	5,839	Distance	OR	1.10 (0.91–1.34)	<100 vs. >100 m

HR = hazard ratio; OR = odds ratio; RR = relative risk.

[a] All studies were in adults (age 18+).

[b] **Bold** indicates the effect estimate was included in the meta-analysis.

[c] Female population.

[d] Log transformed.

incidence, provided NO_2 estimates with and without adjustment for noise.

Three medium to large (2,797 to 10,443 participants) cross-sectional studies with in-depth outcome assessment based on clinical examinations were conducted in Europe (Dijkema et al. 2011; O'Donovan et al. 2017; Riant et al. 2018), two of which were conducted in the framework of diabetes screening programs. These two screening studies at least partially included high-risk populations for diabetes (Dijkema et al. 2011; O'Donovan et al. 2017). The outcome was assessed with multimodal strategies, also including HbA1c (Riant et al. 2018) or oral glucose tolerance tests (O'Donovan et al. 2017). While Riant and colleagues (2018) and O'Donovan and colleagues (2017) used a dispersion model or CTM, Dijkema and colleagues (2011) investigated NO_2 by LUR in quartiles and indirect traffic measures.

Four medium to very large studies (3,992 to 89,460 participants) from the United States, Denmark, and Australia relied on self-reported or register-based outcome assessment (Andersen et al. 2012b; Coogan et al. 2012, 2016; Puett et al. 2011). The studies by Coogan and Lazarevic were restricted to women, while the study by Puett consisted of one female and one male substudy. Only one study conducted a prevalence analysis (Lazarevic et al. 2015), while the others investigated incidence of diabetes. The studies investigated NO_2 or NO_x modeled by LUR or by dispersion models or CTM, with the exception of the analysis of the Nurses' Health Study and the Health Professionals Follow-up Study, of which only an estimate for distance measurements was included (Puett et al. 2011). One study investigated the exposure–response relationship (Andersen et al. 2012b). None of these studies included an evaluation of the effect of noise adjustment.

Four very large Canadian and European studies (Bai et al. 2018; Clark et al. 2017; Howell et al. 2019; Renzi et al. 2018) with up to 2.5 million participants were based on administrative data, using population or health insurance registries for inception of the cohort and vital statistics as well as health insurance claims data and hospital admission data for outcome assessment. Although these studies have the advantage of a high degree of representativeness for the general population, outcome assessment is less certain, as it includes only diagnosed diabetes. In addition, administrative studies usually lack information on personal lifestyle and sometimes also information on individual-level SES status. Instead, these studies use one or several area-level SES variables such as mean income or unemployment rate for adjustment.

Three additional cross-sectional studies add to the evidence base. One study conducted a very elaborate exposure assessment for UFPs in Boston, including daily activity questionnaires (Li et al. 2017), and one study analyzed BaP from a dispersion model in a small convenience sample in Bulgaria (Dzhambov and Dimitrova 2016). Both studies relied on self-reported diabetes. Lazarevic and colleagues (2015) is a large study in Australian women, based on health insurance and questionnaire data.

10.6.2 META-ANALYSES

Figure 10.11 shows the results of the meta-analyses by pollutant, based on up to seven individual studies per analysis. Most studies were conducted on NO_2. Individual study results for NO, PM_{coarse}, UFPs, traffic-specific PM, and components were not included in the meta-analyses due to low numbers of studies; they are presented in Table 10.14. All pollutants yielded positive meta-analytic point estimates above unity for prevalence and incidence of diabetes. The estimate for NO_2 and diabetes prevalence was significantly elevated. Point estimates for EC and PM_{10} were relatively high, but imprecise, partly due to the lower number of included studies.

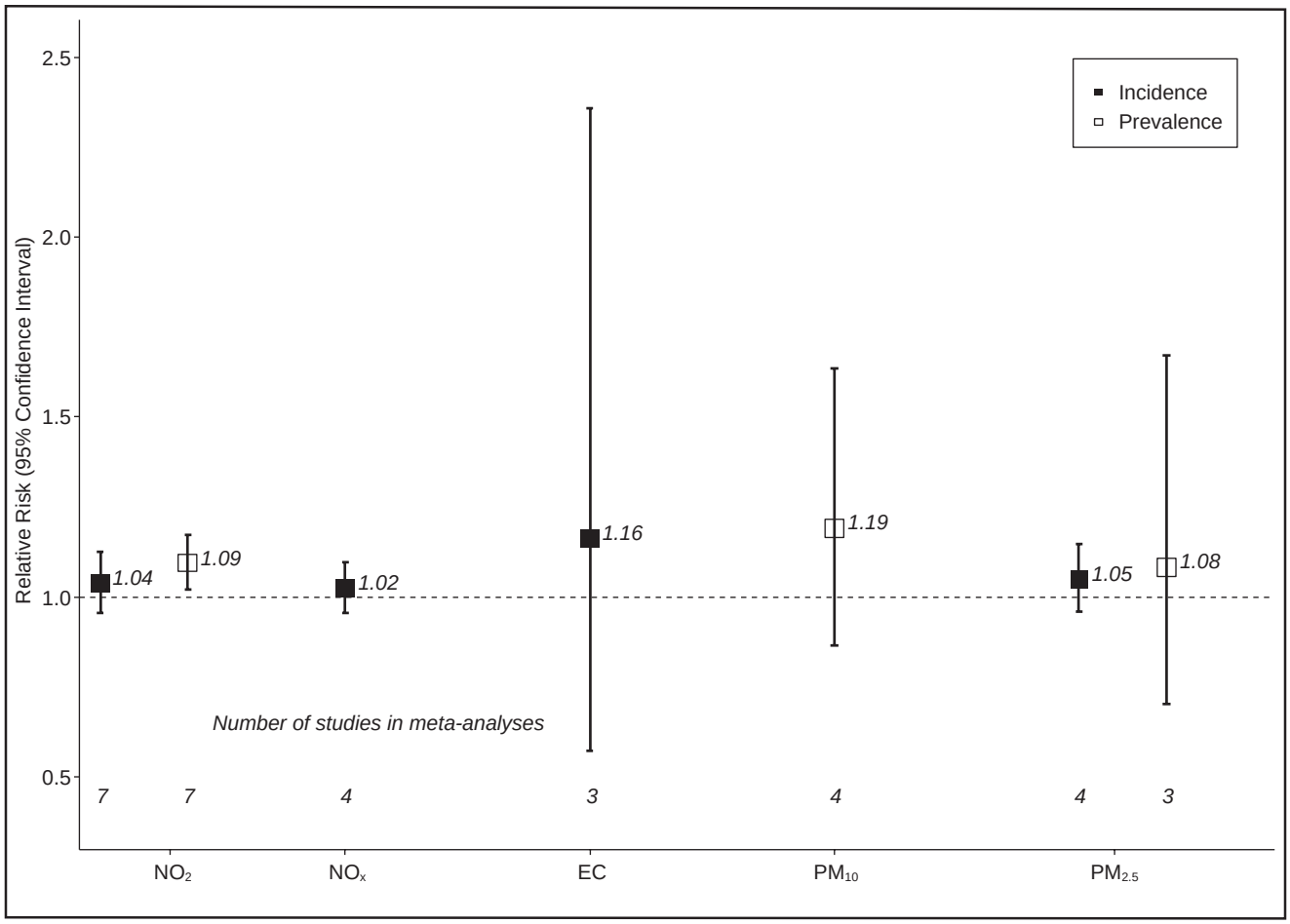

Figure 10.11. Meta-analysis of associations between traffic-related air pollutants and diabetes prevalence and incidence. The following increments were used: 10 µg/m³ for NO_2, 20 µg/m³ for NO_x, 1 µg/m³ for EC, 10 µg/m³ for PM_{10}, and 5 µg/m³ for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

Figure 10.12 shows the forest plots with individual studies for NO_2 and NO_x. Seven studies each were included in the meta-analysis of NO_2 and diabetes prevalence and incidence. Results were mixed in the incidence analysis with three positive, two negative, and two essentially null estimates, resulting in high heterogeneity between studies (I^2 = 95%) and a meta-analytic estimate of 1.04 (95% CI: 0.96–1.13). The studies were conducted in Western Europe and North America, both regions displaying mixed results (Appendix Figure 10D-1). The most influential studies were three studies based on administrative data, with each of them contributing about 18% to the overall weight. Two of these studies yielded estimates close to the null, and one study of about 1 million Canadians showed a positive association (Bai et al. 2018). This study also showed a monotonic exposure–response relationship (Bai et al. 2018). The large DDCH study in Denmark also observed a positive association and a positive monotonic exposure–response function for NO_2 (Andersen et al. 2012b). The two studies with clinical examinations for outcome assessment including the assessment of undiagnosed diabetes were the smallest studies with least weight, yielding one significantly positive and one null estimate (Eze et al. 2017; Kramer et al. 2010). The high estimate for the German SALIA study can at least partly be explained by a decline in exposures during the early phase of follow-up before the exposure assessment was conducted (Kramer et al. 2010). The general decline in exposure lead to a smaller exposure contrast within the study area, while the health effects were presumably the result of a larger exposure contrast before a reduction of exposure. There was no clear difference between studies with more in-depth confounder control compared with studies based on administrative data with a lack of personal lifestyle information, or by region. With the exception of one study, traffic specificity was high and results stable upon exclusion of the single study with only moderate traffic specificity (Appendix Figure 10D-2).

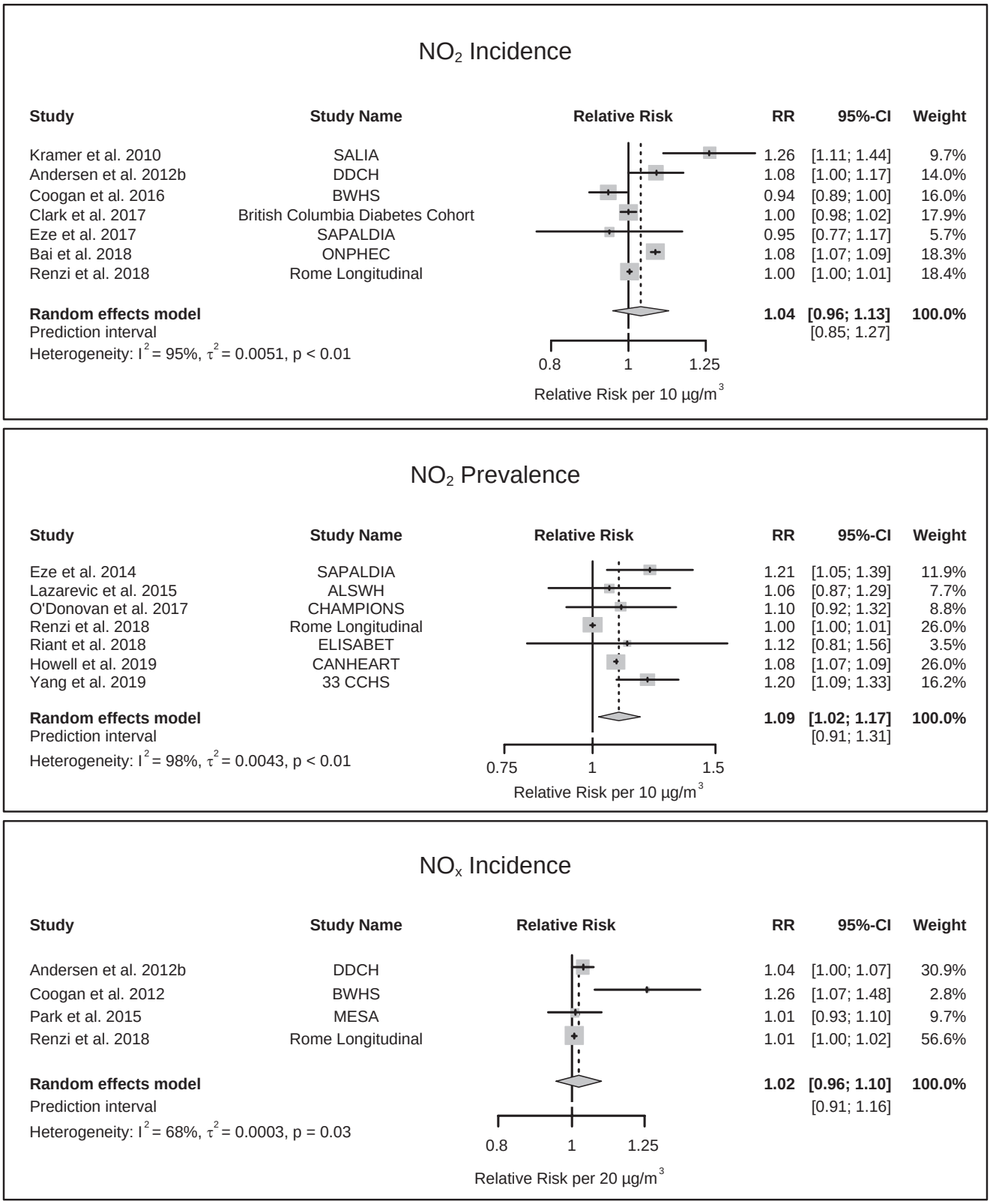

Figure 10.12. Association between NO_2 and NO_x and diabetes incidence and prevalence: meta-analysis.

All but one prevalence study yielded positive point estimates, resulting in a significantly elevated meta-analytic estimate of 1.09 (95% CI; 1.02–1.17) with high heterogeneity (I^2 = 98%). The two most influential studies were the CANHEART study from Canada showing a significantly elevated estimate, and the Rome Longitudinal study, with an estimate of 1.00 (Howell et al. 2019; Renzi et al. 2018). There was insufficient evidence to assess differences in estimates across regions of the world (Appendix Figure 10D-3). After exclusion of one study with only moderate traffic specificity, the meta-analytic estimate was stable (Appendix Figure 10D-4). A stronger positive meta-analytic estimate of 1.17 (1.09–1.25) with no heterogeneity (I^2 = 0%) was observed for those studies that corrected for smoking (Appendix Figure 10D-5). In addition to more extensive control for confounding, in this subset of studies all had clinical examinations for a more complete outcome assessment. One study not included in the meta-analysis is the cross-sectional screening study by Dijkema and colleagues (2011), which was conducted in a low traffic exposure environment in the Netherlands and did not yield an association of NO_2 in categories with diabetes.

No clear association (1.02; 95% CI: 0.96–1.10) with a moderate heterogeneity (I^2 = 68%) was observed for the four studies included in the meta-analysis of NO_x with incidence of diabetes (Figure 10.12). All studies yielded positive point estimates. The overall result was dominated by the effect estimate of 1.01 (1.00–1.02) of the large administrative Rome Longitudinal Study (Renzi et al. 2018) with 57% of the weight. The other highly influential study was the DDCH cohort from Denmark, yielding a positive association that was strengthened when limiting the cases to those with confirmed diabetes (Andersen et al. 2012b). Upon exclusion of the Rome Longitudinal Study with incomplete confounder control, the meta-analytic estimate increased to 1.07 (0.82–1.40) (Additional Materials).

Altogether eight studies investigated EC, PM_{10}, or $PM_{2.5}$ in relation to diabetes; of those, three studies investigated EC and incidence of diabetes, four studies investigated PM_{10} and prevalence of diabetes, four studies investigated the association of $PM_{2.5}$ with incidence and three with prevalence of diabetes (Figure 10.13). Six studies were conducted in Europe and two in North America. Traffic specificity was rated high a priori for the three studies examining EC and was moderate for all PM studies. All meta-analyses yielded positive associations with high (EC and diabetes incidence, PM_{10} and diabetes prevalence), moderate ($PM_{2.5}$ and incidence of diabetes), or low ($PM_{2.5}$ and prevalence of diabetes) heterogeneity. Except for the administrative Rome Longitudinal Study, which was by far the largest of these studies with 1.4 million participants and which dominated most of the analyses, all studies displayed positive point estimates. In all analyses, the studies with more extensive individual-level information on lifestyle and an outcome assessment based on clinical examinations (Eze et al. 2014; Kramer et al. 2010; O'Donovan et al. 2017; Park et al. 2015; Riant et al. 2018; Weinmayr et al. 2015) showed higher estimates, albeit with mostly large CIs due to relatively low numbers of participants. Exclusion of the Rome Longitudinal Study in sensitivity analyses according to level of confounder control yielded significantly elevated estimates for PM_{10} (1.43; 95% CI: 1.28–1.59) and reduced heterogeneity to zero (Appendix Figure 10D-7).

Studies not included in the meta-analysis added limited evidence: Dzhambov and Dimitrova 2016 observed an elevated RR for high versus low exposure to $PM_{2.5}$, which is, however, uninformative due to a wide CI. One study compared the general $PM_{2.5}$ estimate with the estimate for $PM_{2.5}$ from traffic only, using a CTM (Weinmayr et al. 2015). This analysis, for which traffic specificity was also rated high, yielded a substantially larger association for the traffic source-specific $PM_{2.5}$ compared with the general $PM_{2.5}$ or PM_{10} mass estimate. The two large Canadian administrative cohorts investigated NO (Clark et al. 2017) and UFPs (Bai et al. 2018), both studies observed clear positive associations with diabetes incidence. PM_{coarse} with moderate traffic specificity was investigated in a cross-sectional and a longitudinal analysis in the Rome cohort, showing a null or significantly negative association for incidence and prevalence, respectively (Renzi et al. 2018).

10.6.3 ASSOCIATIONS WITH INDIRECT TRAFFIC MEASURES

Seven studies investigated various distance or traffic-density measures, four of them from Western Europe (Andersen et al. 2012b; Dijkema et al. 2011; Kramer et al. 2010; Weinmayr et al. 2015), two from the United States (Park et al. 2015; Puett et al. 2011) and one from Australia (Lazarevic et al. 2015) (Table 10.15). All studies except one (the incidence effect estimate in Park et al. 2015) show positive, though mostly imprecise, estimates for highly traffic-exposed subgroups compared with the reference groups (Figure 10.14).

10.6.4 CO-EXPOSURE WITH NOISE AND OTHER POLLUTANTS

The most frequently investigated co-exposure was traffic noise, which was included in five studies with multiple exposures (Appendix Table 10D-1). In the Rome Longitudinal Study, most estimates were unchanged or changed only slightly upward or downward upon inclusion of noise (Renzi et al. 2018). In contrast, in the large British Columbia Cohort, the elevated estimates for the highly traffic-specific pollutants NO and EC were slightly reduced while the estimate for $PM_{2.5}$ was stable (Clark et al. 2017), and no substantial change was observed in SAPALDIA or the Plovdiv Diabetes Survey for NO_2, PM_{10}, or polycyclic aromatic hydrocarbons (Dzhambov and Dimitrova 2016; Eze et al. 2014, 2017). Adjustment of the NO_x estimate for ozone in the large Rome Longitudinal Study did not influence the estimate (Renzi et al. 2018).

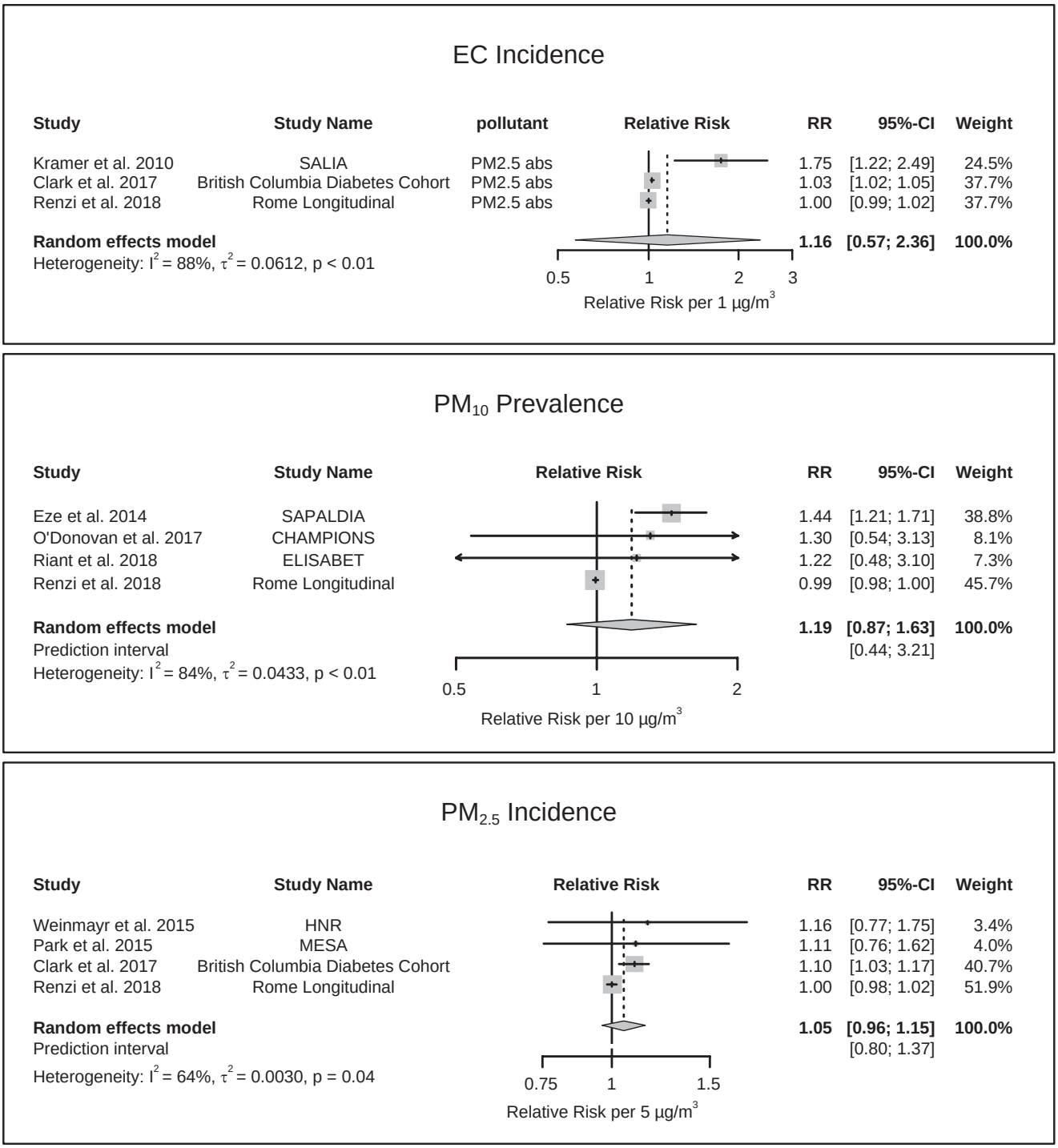

Figure 10.13. Association between EC, PM_{10}, $PM_{2.5}$, and diabetes prevalence and incidence: meta-analysis. *Figure continues next page.*

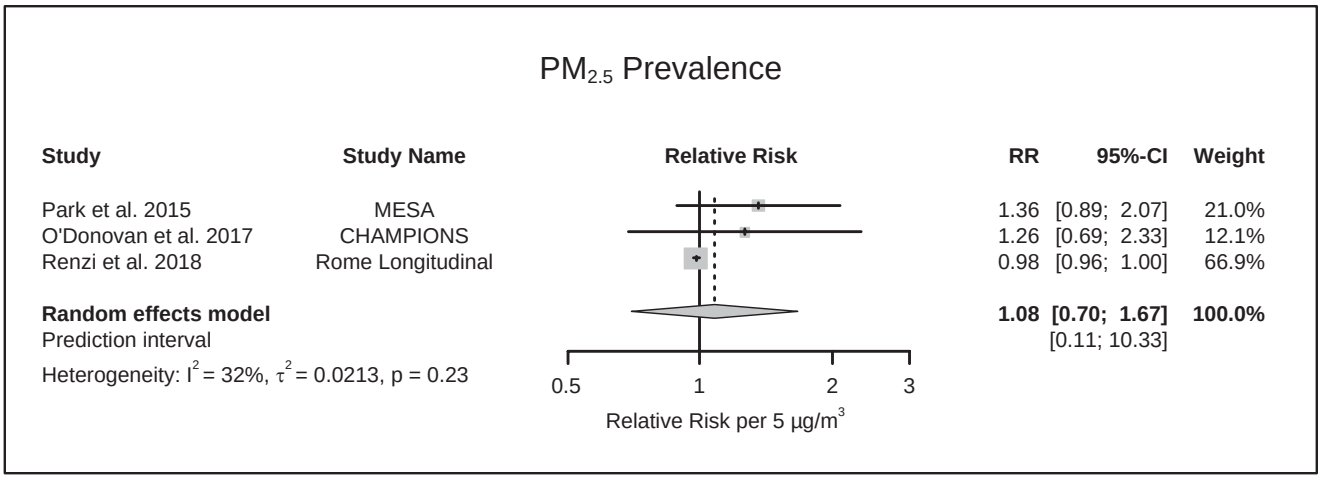

Figure 10.13. *(Continued).*

10.6.5 NARRATIVE ASSESSMENT

The study base and the meta-analyses provide evidence for the presence of an association of NO_2 with prevalence of diabetes in adults. There is somewhat less evidence for an association of NO_2, NO_x, EC, PM_{10}, and $PM_{2.5}$ with incidence or prevalence of diabetes. The evidence is based on a moderate number of studies examining NO_2 and fewer studies on traffic-related particles.

The evidence is strengthened by two large studies showing a positive and monotonic exposure–response relationship and seven studies showing positive associations with indirect traffic measures for either incidence or prevalence of disease. In four of the five studies that adjusted for noise, there was no indication of major confounding by traffic noise.

Important aspects in this body of evidence were the quality of the outcome assessment, with studies using a more elaborate outcome assessment generally showing stronger associations. Potential explanations include a higher degree of outcome misclassification with underassessment of the outcome in lower SES groups, as diagnosis is at least partly dependent on access to and making use of health care. Another aspect is incomplete confounder control. Upon exclusion of studies without individual lifestyle variables, the associations were stable or increased markedly in sensitivity analyses.

For NO_2, the findings for prevalence were more consistent than for incidence. Several possible explanations exist. Most studies on incidence were conducted in middle-aged to older adults, whose population at risk at the beginning of follow up was already selected toward a healthier subgroup of those free of diabetes. Potentially, this group is less susceptible. Moreover, follow-up time in most studies was relatively short, yielding limited power to detect associations during follow-up, while prevalence estimates are based on life-time exposure.

In conclusion, the positive meta-analytic summary estimate for NO_2 and diabetes prevalence in adults in a moderately large number of studies conducted in different populations provides evidence for an association. This finding is supported by the fact that all studies but one provided positive estimates for traffic-related PM and either incidence or prevalence of diabetes. Further supporting evidence is provided by studies that had a more valid outcome assessment and more detailed confounder control; they also had higher effect estimates. In addition, all of the seven studies that analyzed indirect traffic measures found associations with at least one indirect traffic measure. It is unlikely that potential biases have affected all estimates of association in the same direction in diverse populations from different regions or that the observed associations can be explained by concurrent traffic noise exposure. In conclusion, the Panel rates the confidence in the presence of an association between TRAP and diabetes as moderate.

10.6.6 CONFIDENCE ASSESSMENT OF THE BODY OF EVIDENCE

The modified OHAT assessment is conducted only for exposure–outcome pairs for which a meta-analysis was conducted. As the 16 studies included in meta-analyses were cross-sectional and cohort studies, the initial ratings for confidence in the body of evidence were low or moderate for the respective pollutant–outcome pairs. The factors that reduce or increase confidence are described in the sections that follow. All studies addressed the research question directly, and therefore no downgrade was applied for the downgrading factor indirectness. The Panel decided a priori not to consider the upgrading factor large magnitude of the effect.

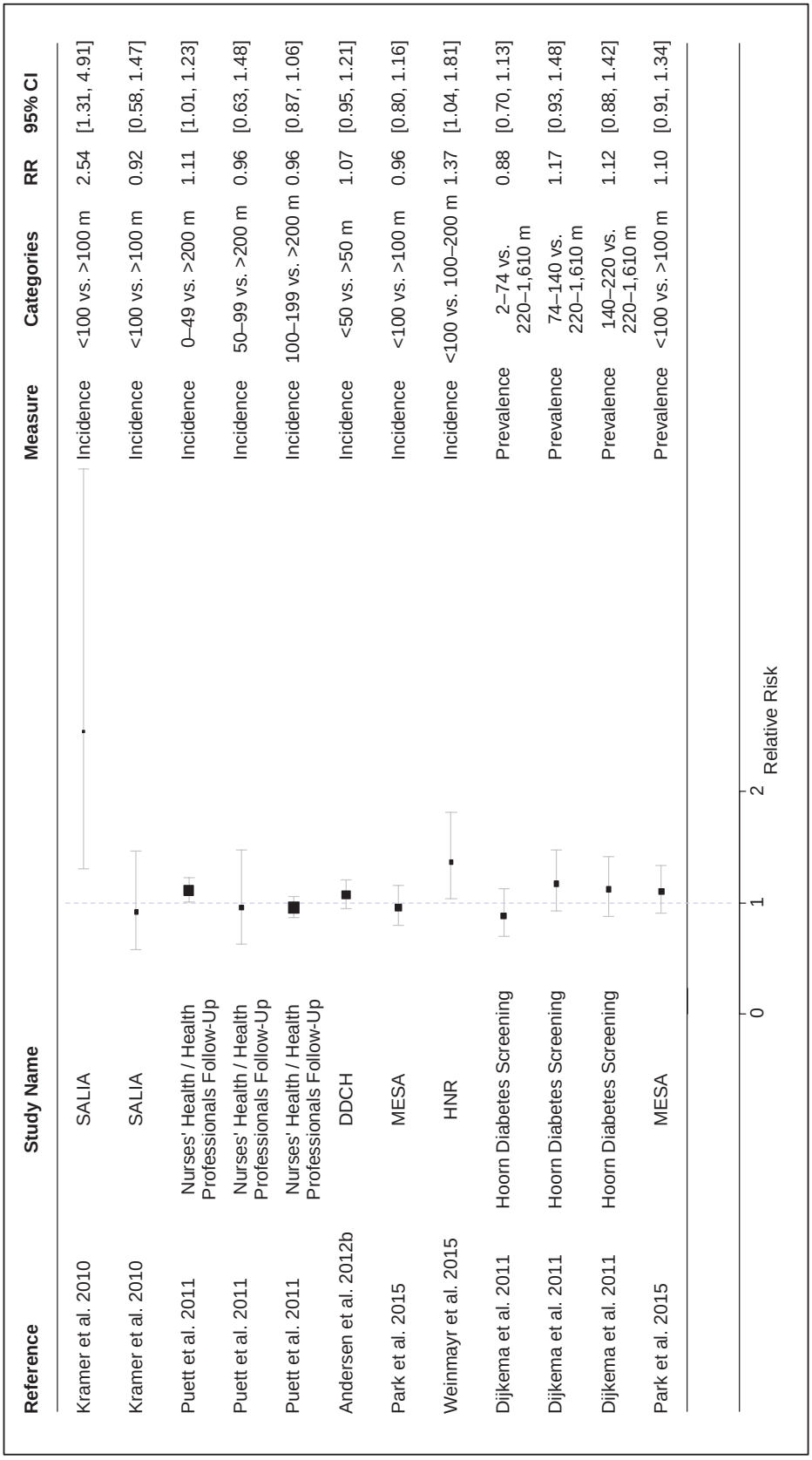

Figure 10.14. Association of distance to major roads with diabetes prevalence and incidence. SALIA estimates correspond to low and high education correspondingly.

10.6.6.1 Factors That Reduce Confidence

Among the factors that reduce confidence, the Panel evaluated the risk of bias as low or moderate in most exposure–outcome pairs and domains (Table 10.16). The risk of bias ratings can be found for the individual studies in Appendix Table 10D-2. The small number of studies rated at high risk of bias was due primarily to incomplete confounder control in the very large studies based on administrative data (25% of meta-analyzed studies and 38% of analyzed exposure–outcome pairs) (Bai et al. 2018; Clark et al. 2017; Howell et al. 2019; Renzi et al. 2018). In these studies, individual lifestyle characteristics such as smoking or BMI were missing. Moreover, some of those studies (Bai et al. 2018; Clark et al. 2017) lacked individual-level SES; although they corrected for area-level SES. Sensitivity analyses excluding high risk of bias studies revealed stable or substantially increased effect estimates (Figure 10.15); therefore, no downgrade was applied. The increase in meta-analytic estimates after exclusion of high risk of bias studies due to confounding suggests a bias toward the null from confounding in those studies. However, the small number of studies in the stratified meta-analyses does not allow any strong conclusions. Only two studies were additionally rated high risk of bias in other domains (Eze et al. 2017; Yang et al. 2019). High risk of selection bias resulted from a potential for healthy survivor bias due to long survival in a cohort before inclusion into the respective analysis (Eze et al. 2017). High risk of bias for missing outcome data resulted from exclusion of more than 60% of the original study population in the analysis (Yang et al. 2019). Exclusion of these studies in sensitivity analyses did not substantially change the meta-analytic estimate (Appendix Figure 10D-8); and no downgrade was applied.

The Panel downgraded the association of NO_2 with incidence of diabetes due to unexplained inconsistency. This was due to a high heterogeneity of 95%, which could not be clearly explained by study design, population, or applied methods.

Table 10.16. Summary of Risk of Bias Rating for Studies on Diabetes

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	12	0	4	20	0	12
	Validity of measuring of confounding factors	16	0	0	32	0	0
	Control in analysis	14	2	0	29	3	0
	Overall	10	2	4	17	3	12
2. Selection bias	Selection of participants into the study	12	3	1	25	6	1
3. Exposure assessment	Methods used for exposure assessment	16	0	0	32	0	0
	Exposure measurement methods comparable across the range of exposure	16	0	0	32	0	0
	Change in exposure status	12	4	0	24	8	0
	Overall	12	4	0	24	8	0
4. Outcome measurements	Blinding of outcome measurements	13	3	0	29	3	0
	Validity of outcome measurements	16	0	0	32	0	0
	Outcome measurements	16	0	0	32	0	0
	Overall	13	3	0	29	3	0
5. Missing data	Missing data on outcome measures	13	2	1	28	3	1
	Missing data on exposures	16	0	0	32	0	0
	Overall	13	2	1	28	3	1
6. Selective reporting	Authors reported a priori primary and secondary study aims	16	0	0	32	0	0

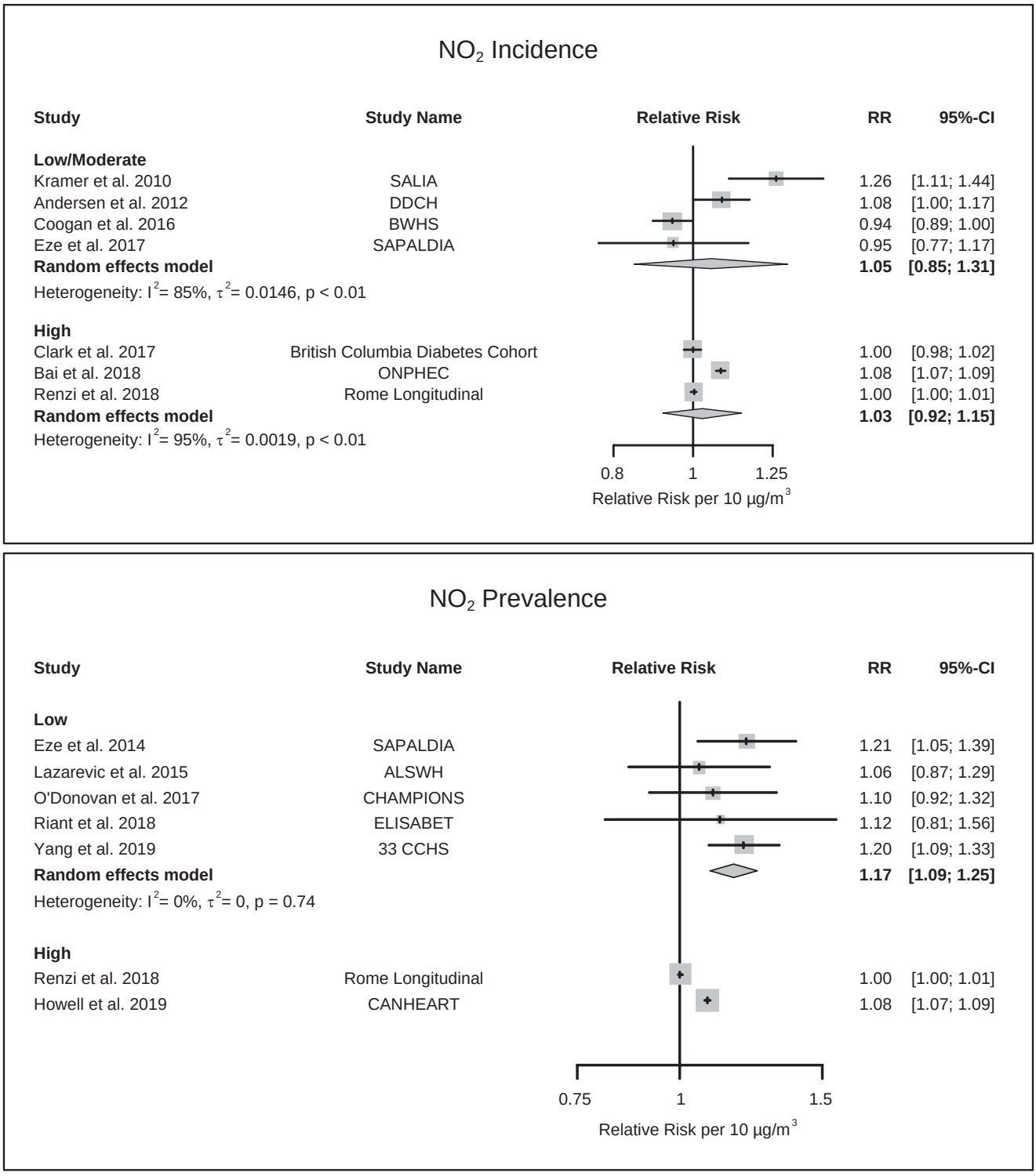

Figure 10.15. Association between NO_2 and incidence or prevalence of diabetes and between PM_{10} and prevalence of diabetes: meta-analysis by risk of bias confounding. *Figure continues next page.*

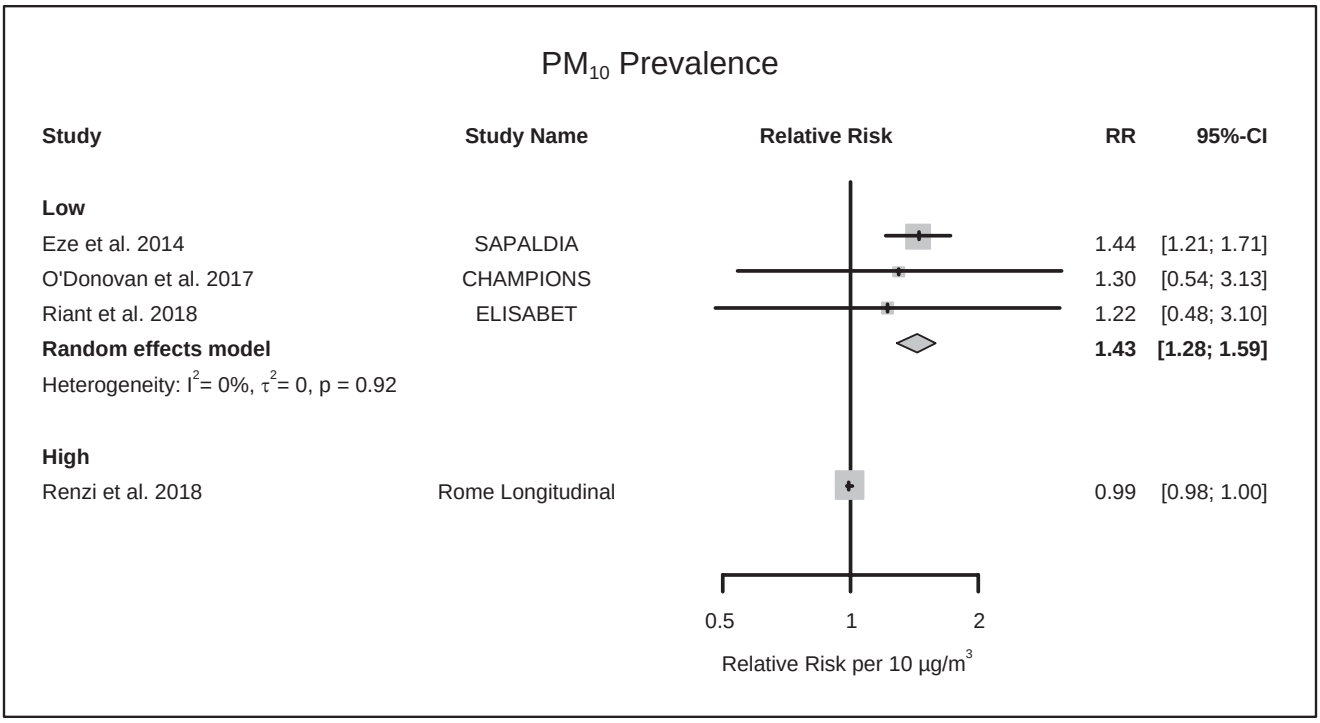

Figure 10.15. *(Continued).*

Although a high or moderate degree of heterogeneity of effect estimates was observed across studies for most of the other pollutants, no downgrade was applied because heterogeneity could at least in part be explained by differences between very large administrative cohort studies and the studies with extensive adjustment and clinical outcome assessment, leading to nonoverlapping CIs. For imprecision, the Panel downgraded the confidence for all exposure–outcome pairs except for NO_2 with prevalence of diabetes because the CI was wide despite the fact that all meta-analysis had sufficient power and the minimum sample size was met. Note that all these estimates clearly included unity. Given the small number of studies in each pollutant–outcome pair, which makes an analysis of publication bias infeasible, the Panel did not downgrade due to publication bias as stated in the protocol (Table 10.17).

10.6.6.2 Factors That Increase Confidence

Few studies evaluated the exposure–response function in each pollutant–outcome pair. For NO_2 and incident diabetes, the large DDCH study presented a monotonic exposure–response function, as well as the very large Canadian study (Bai et al. 2018), contributing in total 32% of the weight in the meta-analysis. Hence, the level of confidence was upgraded for NO_2 and incident diabetes. No other upgrades for evidence of a monotonic exposure–response function were conducted. The Panel noted that the underassessment of the true prevalence or incidence of the outcome will lead to substantial outcome misclassification, which may be differential or nondifferential. In most cases of nondifferential outcome misclassification, this will lead to a bias toward the null, and in differential outcome misclassification, the bias could be in either direction. Since the studies with incomplete outcome assessment systematically show lower effect estimates, the Panel concludes that bias toward the null due to outcome misclassification is likely. Evidence for this is supplied in the analysis of NO_2, PM_{10}, and diabetes prevalence. Upon exclusion of the studies with outcome misclassification, the summary estimate for both pollutant–outcome pairs increased substantially, and heterogeneity was reduced to zero (Figure 10.15). The Panel upgraded the confidence for NO_2, and diabetes prevalence based on the five remaining studies. Because numbers of studies were too small for PM_{10} and diabetes prevalence, no upgrade was applied here. Because numbers of studies were too low in the stratified analyses according to region or time period, no upgrade for consistency was applied.

10.6.6.3 Combined Confidence for All Study Designs and Multiple Outcomes

For NO_2 and diabetes, the combined rating of the quality of the evidence base is moderate, based on a score of moderate for NO_2 and diabetes prevalence and low for NO_2 and incidence. Both study designs show evidence of a positive

Table 10.17. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Diabetes[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)				
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating	Rating Across Study Designs
NO_2	Cohort	+++ ($N = 7$)	0	–	–	0	+	0	0	+ + (Low)	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	Four studies with high RoB but results not sensitive to exclusions of those studies.	High heterogeneity ($I^2 = 95\%$), due to both magnitude and direction.	Sample size met, but confidence interval wide and includes unity.	No formal evaluation possible.	Two influential studies show monotonic ERF (Andersen 2012b; Bai 2018).	Confounding in both directions possible.	Too few studies to evaluate.		The combined rating is based on the higher confidence rating. Both study designs show evidence of a positive association, therefore no reason for a downgrade.
	Cross-sectional	++ ($N = 7$)	0	0	0	0	0	+	0	+++ (Moderate)	
	Rationale	Cross-sectional design initially rated as low.	Three studies with high RoB, increased or stable effect estimates after excluding high RoB studies.	High heterogeneity ($I^2 = 98\%$) due to magnitude not direction.	Sample size met, and confidence interval does not include unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Larger estimates in studies with better confounder control suggests residual confounding toward the null.	Across different populations robust association, but too few studies.		
NO_x	Cohort	+++ ($N = 4$)	0	0	–	0	0	0	0	++ (Low)	NA
	Rationale	Cohort design initially rated as moderate.	One study high RoB, but increased estimate after exclusion.	Moderate heterogeneity ($I^2 = 68\%$) mostly due to magnitude not direction.	Sample size met, but confidence interval wide and includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess robustness across populations.		

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Table 10.17. (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Diabetes[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)				
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating	Rating Across Study Designs
EC	Cohort	+++ (N = 3)	0	0	–	0	0	0	0	++ (Low)	NA
	Rationale	Cohort design initially rated as moderate.	Elevated estimate based on one study with moderate RoB. Two studies with high RoB show effect closer to the null.	High heterogeneity (I^2 = 88%) due to magnitude not direction.	Sample size met, but confidence interval wide and includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Insufficient evidence for robustness across populations.		
PM_{10}	Cross-sectional	++ (N = 4)	0	0	–	0	0	0	0	+ (Very low)	NA
	Rationale	Cross-sectional design initially rated as low.	One of 4 studies high RoB but increased estimate upon exclusion of the high RoB study.	High heterogeneity (I^2 = 84%) due to magnitude not direction.	Sample size met, but confidence interval wide and includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Larger estimates in studies with better confounder control, but number of studies considered too small for upgrade.	All studies European, no consistency check possible.		

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Table 10.17. (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Diabetes[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)				
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating	Rating Across Study Designs
$PM_{2.5}$	Cohort	+++ (N = 4)	0	0	–	0	0	0	0	++ (Low)	++ (Low)
	Rationale	Cohort design initially rated as moderate.	Two studies high RoB, but increased estimate upon exclusion of high RoB studies.	Moderate heterogeneity (I^2 = 64%) due to magnitude not direction.	Sample size met, but confidence interval wide and includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Larger estimates in studies with better confounder control, but number of studies considered too small for upgrade.	Insufficient evidence for robustness across populations.		Both study designs show estimates in the same direction.
	Cross-sectional	++ (N = 3)	0	0	–	0	0	0	0	+ (Very low)	
	Rationale	Cross-sectional design initially rated as low.	One study high RoB, no sensitivity analysis due to low numbers.	Low heterogeneity (I^2 = 32%).	Sample size met, but confidence interval wide and includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Larger estimates in studies with better confounder control, but number of studies too small.	Insufficient evidence for robustness across populations.		

ERF = exposure–response function; RoB = Risk of Bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

association; therefore no reason for a downgrade was present. The combined rating of confidence for $PM_{2.5}$ was low because the individual ratings according to study design were low and very low, respectively. Both study designs show evidence of a positive association; therefore no reason for a downgrade was present. For the other pollutant–outcome pairs, only one study design was available for meta-analysis; therefore no up- or downgrade was feasible.

10.6.6.4 Evaluation of Confidence for Combined Measures of TRAP

A combined confidence rating for measures of TRAP across different pollutants started with moderate confidence due to the rating for NO_2. No change in the confidence grading was applied due to consistency of the direction of effect in the body of evidence. No change was also applied due to traffic specificity, since studies with high traffic specificity did not show consistently higher estimates than those with moderate traffic specificity and because there is insufficient variability of traffic specificity in several pollutant–outcome groups. In conclusion, based on the modified OHAT assessment, the confidence in the quality of the body of evidence between TRAP exposure and diabetes is moderate.

10.6.7 OVERALL CONFIDENCE ASSESSMENT

Based on the narrative assessment (moderate) and the confidence assessment (moderate), the overall confidence in the evidence of an association between TRAP exposure and diabetes is moderate.

10.7 OVERALL DISCUSSION

10.7.1 SUMMARY OF MAIN FINDINGS

Based on 57 studies altogether, the Panel found moderate confidence in the evidence for an association between long-term exposure to TRAP and IHD and between TRAP and diabetes, low-to-moderate confidence in the evidence for an association of TRAP with stroke, and low for an association of TRAP with coronary events. This was based on a combination of a narrative assessment and a modified OHAT assessment.

For diabetes and IHD, the meta-analytic estimates were consistent with a positive association of NO_2 with diabetes and of EC and PM_{10} with IHD. The evidence was strengthened by studies showing monotonic exposure–response functions, several studies showing associations to other highly traffic-specific pollutants that were not meta-analysed, and from a small number of studies investigating indirect measures of traffic exposure. Specifically in the case of TRAP and diabetes, extensive sensitivity analyses and meta-analyses revealed stronger associations for studies with better confounder control and more elaborate and complete outcome assessment. The evidence for TRAP and IHD was generally weakened by null associations for the gaseous pollutants NO_2 and NO_x in the main meta-analyses. For stroke, the meta-analytic estimates of EC, PM_{10}, and $PM_{2.5}$ were positive, though imprecise, and the CIs included unity. The evidence was strengthened by several high-quality studies with a positive exposure–response function or a subset analysis indicating stable effects across levels of exposure. In addition, several individual studies investigating pollutants highly likely indicative of traffic, such as UFP or traffic-specific PM fractions, provided support for an association. However, the evidence for TRAP and stroke was generally weakened by null associations for the gaseous pollutants NO_2 and NO_x in the main meta-analyses. For coronary events, the meta-analytic estimate for NO_2 was positive but imprecise and the CI contained unity. Furthermore, the evidence base for other pollutants was too limited to rule out chance or bias with appropriate certainty. Because all investigated cardiometabolic outcomes are likely influenced by traffic noise, some studies investigated possible confounding or effect modification by noise with mostly similar results after adjustment for co-exposure to noise.

Compared with the 2010 HEI Traffic Review, which included only three studies on IHD and coronary events and no studies on stroke and diabetes, the body of evidence has increased substantially. However, despite the relatively large number of studies overall, the available evidence per health outcome was substantially smaller, with about 20 studies per endpoint. Among these health outcomes, the type of exposures were quite diverse, which resulted in a generally small number of individual studies to be evaluated per exposure–outcome pair.

The evidence found for TRAP and morbidity of cardiovascular disease (IHD, coronary events, stroke) is partly consistent with the results for cause-specific mortality (Chapter 11). The evidence was rated high for circulatory and IHD mortality, based on a relatively large number of studies with significantly elevated meta-analytic estimates for NO_2, EC, and $PM_{2.5}$. In line with this finding, the pollutants EC and $PM_{2.5}$ were also the pollutants with the strongest evidence for an association with IHD morbidity, although the relatively low number of studies in the morbidity analyses and the imprecise estimates for $PM_{2.5}$ and PM_{10} prevented stronger conclusions. Of note, in the morbidity analyses, the few studies with separate estimates for fatal and nonfatal disease showed substantially stronger estimates for fatal disease than for nonfatal disease, supporting the mortality findings. This observation includes the estimate for NO_2 and IHD morbidity, which was null in the primary meta-analysis. In contrast to the generally consistent findings for IHD morbidity and cause-specific mortality, the low rating for coronary events, a subcategory of IHD, diverged from the high rating for cause-specific mortality. This is primarily due to the small number of studies in the coronary events morbidity analysis, which did not allow for thorough sensitivity analyses to investigate

risk of bias and exclude chance findings. Nevertheless, almost all included studies consistently revealed positive estimates, with higher estimates for fatal events, and these were supported by results from a small number of studies investigating indirect measures of traffic exposure.

The evidence for stroke was consistently rated low to moderate for both morbidity and cause-specific mortality, based on a limited number of studies in both analyses and reduced confidence due to imprecision of estimates. Note that diabetes mortality was not included in the set of outcomes. Diabetes mortality is prone to substantial outcome misclassification because diabetes is infrequently indicated as a primary cause of death on death certificates, but rather as a contributing condition. IHD or stroke are frequently coded as causes of death in patients with diabetes.

10.7.2 FINDINGS IN COMPARISON WITH OTHER STUDIES

Evidence from other reviews and studies not included in this review provide support for the Panel's conclusions; however, direct comparisons are difficult due to selection of studies and estimates that were deemed to best reflect traffic-related exposure differences.

For the association of general NO_2 with cardiovascular disease, including the outcomes IHD and coronary events, the U.S. Environmental Protection Agency (U.S. EPA) concludes, based on largely overlapping studies with those reported in this review, that the "evidence from epidemiological studies (is) generally supportive but not entirely consistent (U.S. EPA 2016). For cerebrovascular disease, the evidence available for NO_2 was considered inconsistent. Uncertainty regarding the degree to which potential confounding by traffic-related copollutants and noise was a concern, as well as limited coherence with evidence showing effects on cardiovascular risk factors. Specifically, a paucity of toxicological studies with not entirely consistent findings regarding the mode of action of NO_2 was described.

The U.S. EPA rates the association of total ambient $PM_{2.5}$ with cardiovascular effects as causal, mainly based on the findings for cardiovascular mortality, and evaluates the epidemiological evidence for cardiovascular and cerebrovascular morbidity as inconsistent (U.S. EPA 2019). Of note, this rating pertains to total ambient $PM_{2.5}$, which sets the U.S. EPA review apart from the current HEI review, which only considered studies where the $PM_{2.5}$ exposure estimate informs about traffic-related differences in exposure. Key evidence in the U.S. EPA review comes from the Women's Health Initiative study with associations for cardiovascular morbidity (Miller et al. 2007), the California Teachers cohort with an association for stroke but not cardiac disease (Lipsett et al. 2011), and the Nurses' Health and the Health Professionals Study showing no associations for cardiovascular morbidity (Hart et al. 2015). None of these $PM_{2.5}$ estimates were included in the $PM_{2.5}$ analysis of this review because they were not considered sufficiently traffic specific. According to the U.S. EPA, biological plausibility was provided by a few, but not all studies investigating the underlying pathology of atherosclerosis, by consistent evidence from animal toxicological studies at relevant $PM_{2.5}$ concentrations, and by human studies on cardiovascular risk factors. Again, these toxicological studies were also not limited to traffic-specific PM exposures.

For diabetes, the evidence for NO_2 is considered "generally consistent and supportive," and for $PM_{2.5}$ and PM_{coarse} it is considered "suggestive, but not sufficient to infer a causal relationship" (U.S. EPA 2016, 2019). Similar as for the cardiovascular and cerebrovascular events, the U.S. EPA noted uncertainty regarding potential confounding by traffic-related co-exposures and regarding the limited toxicological evidence for NO_2. For total ambient $PM_{2.5}$, evidence for diabetes was considered inconsistent. In contrast, consistent effects on glucose and insulin homeostasis were observed in several epidemiological studies, and coherent evidence was provided by toxicological studies. Nevertheless, there was uncertainty regarding independent effects in copollutant models and some concerns with exposure measurement error.

Scheers and colleagues (2015) conducted a review and meta-analysis of 20 epidemiological studies and reviews on long-term ambient PM exposure and stroke. For stroke incidence, they found statistically significant associations with $PM_{2.5}$ and PM_{10}. The pooled hazard ratios (HR) for general air pollution were slightly lower. They also reported unexplained geographical variability in this review because studies of PM_{10} exposures in Asia were null, while studies of PM_{10} exposures in North America and Europe were positive.

In contrast to these findings for stroke, in a recent review on cardiovascular morbidity by Rugel and Brauer (2020), who analyzed the effects of correlated environmental exposures in urban populations, the authors concluded that "when TRAP and noise were considered jointly, evidence was sufficient for increased cardiovascular morbidity with higher noise exposures; sufficient for no effect of TRAP on cardiovascular disease morbidity; sufficient for increased mortality with higher TRAP exposures." This review was limited to studies of at least two environmental exposures, and therefore the number of studies was smaller than in the current review. Moreover, outcomes were grouped more broadly, preventing a direct comparison of results. Nevertheless, the conclusion is contrary to the findings in this HEI review, which generally showed mostly stable or only slightly attenuated results of TRAP when adjusting for noise.

After completion of the systematic search for this review, the Panel identified a few additional studies that provide evidence on TRAP and cardiometabolic outcomes. For example, in a follow-up analysis of the German Heinz Nixdorf Recall cohort, including a longer observation time and

using a dispersion and chemistry transport model for highly traffic-specific pollutant estimations, NO_2, $PM_{2.5}$, PM_{10}, and accumulation mode particles were related to incident stroke with clearly stronger associations for traffic-specific pollutants than for total or industry-related pollutants (Rodins et al. 2020). No associations were observed for EC. In a follow-up analysis of this cohort for diabetes incidence, traffic-source-specific NO_2, $PM_{2.5}$, PM_{10}, and accumulation mode particles were all significantly associated with diabetes, as were total PM_{10} and total accumulation mode particles (Lucht et al. 2020).

The recently published European ELAPSE project (Effects of Low-Level Air Pollution: A Study in Europe) provides substantial additional information (Brunekreef et al. 2021). This project consists of a pooled cohort from up to 14 European (sub)cohorts and an analysis of 7 European administrative cohorts. The exposure estimates in ELAPSE were based on a European-wide hybrid exposure model with a resolution of 100 × 100 meters, which would fulfill the requirements of the exposure framework of this review. The analysis of the pooled cohort with more than 130,000 participants provided consistent evidence for an association of NO_2, EC, and $PM_{2.5}$ with stroke incidence, and of NO_2 and (borderline) EC with IHD. The estimate for $PM_{2.5}$ and IHD was also positive but included unity. For stroke, the exposure–response functions were monotonic with steeper slopes at lower exposures. Based on 14 (sub)cohorts with altogether more than 380,000 participants, the associations for cause-specific mortality for cardiovascular disease, IHD, cerebrovascular disease, diabetes, and a combined category of cardiometabolic disease were significantly elevated for NO_2, EC, and $PM_{2.5}$ with exposure–response functions generally indicating steeper slopes at lower exposure levels. Adjustment for noise in a subset of cohorts mostly yielded slightly lower effect estimates. In the analysis of the seven administrative cohorts, consistent associations were observed of NO_2, EC, and $PM_{2.5}$ with cardiovascular and stroke mortality. Point estimates for cause-specific mortality were substantially lower for the administrative cohorts compared with the results for the pooled traditional cohorts with detailed confounder information and control. This is similar to the findings in the current HEI review for cardiometabolic morbidity outcomes, also generally observing higher estimates in those studies with better confounder control. Subset analyses and splines showed mostly monotonic exposure–response functions.

10.7.3 STRENGTHS AND LIMITATIONS

Major strengths of this review, which apply to all outcomes, include the systematic approach to study selection and evaluation using an a priori specified framework for exposure assessment and for a systematic evaluation of the epidemiological evidence. The use of several indicators of TRAP allowed the evaluation of consistency across pollutants and enabled the Panel to base its conclusions on a larger number of studies with diverse exposure metrics, in contrast to focusing only on a few meta-analyzed pollutants. The outcomes were grouped into relatively specific subgroups of cardiovascular disease to allow a more detailed evaluation of cardiovascular and metabolic disease. The application of two complementary schemes for evaluation of the epidemiological evidence, namely the narrative assessment and the modified OHAT assessment, enhances the informative value of the final conclusions. The identified studies were located in diverse areas of the world with different populations (general population, general patient populations, different age ranges) and different study designs (various types of cohort studies, case-control and cross-sectional studies). Several studies with in-depth characterization of the study population and an excellent outcome assessment were available. Many studies presented different model specifications, allowing the Panel to evaluate the effect of various adjustment strategies. The more recent studies also were more likely to include an evaluation of traffic noise or other co-exposures.

Next to the general limitations of this review which apply to all health outcomes (e.g., difficulties judging which studies can be interpreted as studies in which the contrast in exposure is primarily related to traffic, difficulties in applying the formal risk of bias and modified OHAT assessment), the relatively low number of studies per pollutant–outcome pair was a limitation. This prevented the Panel from conducting more in-depth stratified analyses by region, traffic specificity, and study design, and from evaluating publication bias. In many cases, this resulted in inconclusive stratified and sensitivity analyses.

A second specific limitation of this body of evidence was related to the outcome assessment. Since it is difficult to correctly diagnose the diseases under question in an epidemiological study, several different approaches were applied, which all have their specific strengths and weaknesses. Most importantly, they will lead to different degrees of underassessment and misclassification of cardiometabolic disease subtypes, depending on study design, age of the study population, and data source, as described in more detail at the beginning of the chapter (Sidebar 10.1). In the case of nondifferential outcome misclassification (that is, the misclassification is not related to the exposure), a bias toward the null is most likely. In the case of differential outcome misclassification (i.e., dependent on the exposure status, such as through correlation with individual SES), it can create bias toward or away from the null in unpredictable ways.

Another observation is the effect estimate in very large studies that are constructed from administrative data with little individual-level information, is often smaller and very precise when compared with smaller traditional cohort studies with clinical examinations and an in-depth assessment of individual-level characteristics. For example, this was

observed for the associations of: (1) NO_2, EC, and $PM_{2.5}$ with IHD; (2) NO_2 and coronary events; (3) NO_2, NO_x, PM_{10}, and $PM_{2.5}$ and diabetes; but not for (4) stroke analyses. These lower estimates in studies with less in-depth personal information could result from residual confounding in cases of negative confounding. Moreover, potential nondifferential outcome misclassification of less severe clinical disease, which is more likely to occur in data from administrative or health insurance data collected in an outpatient care setting, could result in bias toward the null. On the other hand, differential outcome misclassification, for example due to SES-related access to and making use of health care, could lead to bias in either direction. In meta-analyses, these very large administrative studies dominate with their larger sample size and study weight, deemphasizing the potentially less biased estimates from smaller studies.

Other issues identified in this set of studies regard the potential for selection bias or collider bias, for example when the analysis is restricted to survivors of an event. Other mechanisms of selection depend on the recruitment methods for an epidemiological study. For example, a study with a dedicated in-person examination at a study center will lead to a more selected group of participants than studies based on administrative data or only questionnaire-based assessments. These selection mechanisms may potentially introduce collider bias. Another challenge in this set of studies is that many studies used time-to-event data to analyze associations of exposure with cardiovascular or cerebrovascular events. Due to the increasing use of preventive interventions or interventions that lead to the abortion of pending coronary events, the time to event analysis is becoming more problematic and might not yield a valid estimate of the disease risk (Singh and Holmes 2011).

A limitation of this review is its focus on clinically manifest disease and the exclusion of nonfatal precursor conditions from the systematic review and meta-analysis. Nonfatal precursor conditions include increases in blood pressure, systemic inflammatory responses, effects on the autonomic nervous system and on glucose homeostasis, and atherosclerosis. A high-level succinct review on the mechanistic evidence of health effects of exposure to TRAP is included in Chapter 3 to inform on the biological plausibility of TRAP effects on the cardiometabolic system. The exclusion of these outcomes potentially downplays the strength of the overall evidence for TRAP and cardiometabolic outcomes. Several large meta-analyses have also reported consistent short-term associations between TRAP and hospital admissions for cardiovascular disease subgroups (IHD, myocardial infarction, stroke), particularly for NO_2 and CO (Chapter 4). Although these studies utilize administrative databases and cannot distinguish the first event, they provide additional support for the negative health effects of high pollution exposure on the selected cardiovascular outcomes. This abundant epidemiological, as well as toxicological literature, underlines the associations reported in this review, although most evidence is available for nontraffic-specific exposures.

10.7.4 UNANSWERED QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

In cities, where the majority of the world's population resides, traffic remains the most important source of air pollution. The available studies provide overall moderate evidence for the selected cardiometabolic diseases, but for most of the investigated pollutant–outcome pairs, specifically for coronary events, additional studies are needed to draw more definitive conclusions. Attention needs to be dedicated to outcome assessment, as cardiometabolic outcomes are difficult to assess with adequate precision in epidemiological studies (Sidebar 10.1). Future studies should also include a detailed assessment of TRAP and other factors associated with traffic, most notably traffic noise, but also greenspace and area-level SES. Future studies should include a detailed examination of the characterization of the exposure–response function.

Although the role of TRAP has been shown with reasonable certainty to be at least partly responsible for the demonstrated effects of residency close to high traffic, the role of other traffic-related exposures needs more attention. There is clear evidence that noise and area-level SES, and to a lesser degree lack of greenspace, which are all related to traffic as well, have adverse health effects on cardiometabolic health and quality of life (Diez Roux et al. 2016; Schultz et al. 2018; WHO 2018; Yuan et al. 2020). The interplay of these exposures in terms of confounding and potential synergism needs to be better understood for effective prevention and urban planning. One traffic-related pollutant, the long-term exposure to UFPs, is still understudied in relation to effects on the cardiometabolic system, but also in relation to other outcomes including clinical and preclinical conditions. For this, further developments—primarily in exposure assessment—are needed.

Although there is a large toxicological and epidemiological evidence base for the biological actions of particles on vascular dysfunction, acceleration of atherosclerosis, increased propensity for thrombosis, and imbalance of the autonomic nervous system, fewer studies have investigated mechanisms underlying potential cardiovascular effects following NO_2 exposures. Recent evidence from repeated exposures in rodents and in vitro work have reported an increased presence of markers for oxidative stress and inflammation, evidence of endothelial dysfunction, and atherogenic effects (Chapter 3). Nevertheless, a better understanding of the molecular and cellular actions of NO_x on the cardiometabolic system is still necessary to provide more mechanistic evidence for the observed adverse health effects. For this, medium- to long-term studies on animal models at close to ambient concentrations are needed. Moreover, the role of multiple concurrent exposures needs to be investigated to

understand potential synergistic, or even antagonistic, effects of various components of air pollution.

One further challenge is identifying the most critical time period for the development of disease and the elicitation of adverse acute effects on the cardiometabolic system. All of the investigated diseases in this chapter have long preclinical phases of disease development, going as far back as pregnancy, childhood, and possibly even beyond. Studies targeting early precursor conditions in children and young adults should be conducted to investigate the development of cardiometabolic disease and potential intervention effects on reversibility of the disease process after reductions of exposure.

In the epidemiological analyses of cardiometabolic disease, more attention should be paid to the etiology and risk factors of the investigated disease outcome to prevent over adjustment by including in the statistical analysis conditions that lie on the mechanistic pathway from exposure to disease. Furthermore, the role of short-term traffic exposures, which was not covered in the systematic review, requires further attention. It is still unclear how repeated high short-term exposures contribute to disease development, while their role in triggering acute events has been demonstrated in many studies (Mills et al. 2015).

With cities starting to rethink urban planning and changing toward car-free cities, active transport, and increased green space (for example Paris, Barcelona, Copenhagen), the effects of these changes on cardiometabolic health should be evaluated. Comprehensive accountability studies that include an assessment of changes in exposure, lifestyle, and quality of life are recommended to provide evidence for the usefulness of various interventions.

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MATERIALS AVAILABLE ON THE HEI WEBSITE

Appendices 10A to 10E and Additional Materials 10.1 to 10.5 contain supplemental material not included in the main report. They are available on the HEI website at *www.healtheffects.org/publications.*

Appendices

10A Ischemic Heart Disease

10B Coronary Events

10C Stroke

10D Diabetes

10E References for Studies Included in the Systematic Review of Cardiometabolic Outcomes

Additional Materials

10.1 Ischemic Heart Disease

10.2 Coronary Events

10.3 Stroke

10.4 Diabetes

10.5 Risk of Bias Rationales for Studies Included in Meta-analyses

ABBREVIATIONS

BMI	body mass index
CI	confidence interval
CTM	chemical transport model
EC	elemental carbon
HR	hazard ratio
ICD	International Classification of Diseases
IDF	International Diabetes Federation
IHD	ischemic heart disease
IRR	incidence rate ratio
LUR	land use regression
NO	nitric oxide
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
OHAT	Office of Health Assessment and Translation
OR	odds ratio
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
$PM_{2.5\ abs}$	$PM_{2.5}$ absorbance
PM_{10}	particulate matter ≤10 μm in aerodynamic diameter
PM_{coarse}	particulate matter between 2.5 and 10 μm in aerodynamic diameter
PNC	particle number concentration
RR	relative risk
SES	socioeconomic status
TRAP	traffic-related air pollution
UFPs	ultrafine particles
U.S. EPA	U.S. Environmental Protection Agency
WHO	World Health Organization

PART C: FINDINGS FROM SYSTEMATIC LITERATURE REVIEWS OF EPIDEMIOLOGICAL STUDIES

Chapter 11

Traffic-Related Air Pollution and Mortality

CONTENTS

CHAPTER 11

Traffic-Related Air Pollution and Mortality

11.1 SUMMARY

Using the exposure framework, we identified a large number of studies (N = 48) that reported associations between traffic-related air pollution (TRAP*) and all-cause and cause-specific mortality. Most studies were conducted in North America and Europe and included several large studies with very precise effect estimates. The evidence base has increased substantially since the publication of the 2010 HEI Traffic Review. All studies used the cohort design. Across the outcomes, almost one million participants were included in the studies with detailed information on individual lifestyle factors such as smoking and body mass index (BMI). Very large population-based administrative cohorts provided information on several million individuals but lacked data on individual lifestyle factors. The administrative cohorts typically included data on individual- and area-level socioeconomic status (SES). Across all studies, exposure assessment was based on land use regression (LUR) or on chemical transport models (CTMs). Follow-up periods differed across studies, but many had follow-up extending until 2010–2015. The assessment was primarily based on studies of general population samples of adults. Nitrogen dioxide (NO_2), elemental carbon (EC), and particulate matter ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$) were the most studied pollutants. Table 11.1 summarizes the evidence for associations between TRAP and mortality, including meta-analysis, narrative assessment, and the confidence assessment of the Panel.

The meta-analytic summary estimates for all pollutants documented higher all-cause mortality risks associated with higher exposures. The meta-analytic summary estimates for NO_2, EC, and $PM_{2.5}$ and all-cause mortality were statistically significantly larger than unity. The large majority of studies reported positive associations with all-cause mortality. The summary estimate was not heavily influenced by any individual study. For the other pollutants, the summary estimates were larger than unity, but with wider confidence intervals (CIs). Heterogeneity in magnitude of relative risks (RRs) from individual studies was moderate to high and partly explained by a priori defined factors such as study region, risk of bias due to confounding or selection, adjustment for smoking, and the inclusion of (administrative) cohorts with precise effect estimates.

Studies have accounted for a large number of covariates, including smoking, body mass index, individual- and area-level SES, and traffic noise, although not all studies accounted for all factors. Studies addressed other potential biases, including those related to residential history and missing data through imputation. The finding of associations between TRAP and all-cause mortality in substantially different populations—including different geographical regions—lent further support to the confidence in the presence of the observed associations. It is less likely that potential biases have affected air pollution effect estimates in the

Highlights

- A large number of studies were available to assess associations between traffic-related air pollution and all-cause and cause-specific mortality (N = 48 studies). The evidence base has increased substantially compared with the 2010 HEI Traffic Review.
- All studies on mortality were cohort studies, with outcome during follow-up determined by linkage to mortality registries. Most studies were conducted in North America and Europe, with some in Asia and Australia. NO_2, $PM_{2.5}$, and elemental carbon were the most studied pollutants. The studies accounted for a large number of individual- and area-level covariates.
- Summary estimates by meta-analysis showed that NO_2, EC, and $PM_{2.5}$ were associated with all-cause, circulatory, ischemic heart disease, respiratory, and lung cancer mortality. Associations of those pollutants with stroke and chronic obstructive pulmonary disease (COPD) mortality were less certain related to the smaller number of studies.
- The overall confidence in the evidence for an association between traffic-related air pollution exposure and mortality was high for all-cause, circulatory, and ischemic heart disease mortality. The Panel's overall confidence was moderate to high for lung cancer, moderate for respiratory, low to moderate for stroke, and low for COPD mortality.

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* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

same direction in different populations. Studies have been conducted by multiple research groups. The large majority of studies for NO_2 and EC were rated by the Panel as being highly specific to TRAP. Summary estimates were elevated for both the high and moderate traffic specificity studies, with somewhat higher estimates for the high traffic specificity studies. Other additional subgroup analyses (e.g., on whether adjustment for smoking was performed) supported the robustness of the findings. The 11 studies considering indirect traffic measures (distance to major roads and traffic density) provided further support for an association of TRAP with all-cause mortality. Considering the summary estimates of the meta-analysis, robustness of the findings, the number of well-designed studies accounting for important biases, and the consistency of findings across geographical areas, the Panel had high confidence in the presence of an association between TRAP and all-cause mortality.

In a formal assessment of risk of bias across most domains, most studies were rated as low to moderate risk of bias. The exception was the confounding domain where about 25% of studies were rated as high risk of bias, due to incomplete adjustment for confounders deemed by the Panel a priori to be important to this assessment. The strict application of the risk of bias tool resulted in a high risk of bias assessment for most administrative cohort studies, despite the indirect support of a limited impact of missing lifestyle factors on the reported associations in these studies. Application of the modified Office of Health Assessment and Translation (OHAT) method resulted in three assessments of high confidence (NO_2, EC, and $PM_{2.5}$), two moderate (nitrogen oxides [NO_x] and PM_{10}) and two low confidence (Cu and Fe). The Panel's overall assessment of the confidence in the quality of the body of evidence between all-cause mortality and TRAP was high because the highest rating was high across pollutants; furthermore, there was support from other pollutants and indirect traffic measures. The pollutants with the largest number of studies (NO_2, EC, and $PM_{2.5}$) had high confidence ratings. The low confidence assessment was for pollutants with only three studies apiece. The meta-analytic summary estimates of these pollutants were also above unity, although with less precision. In conclusion, the overall confidence in the evidence for an association between TRAP exposure and all-cause mortality, based on the narrative and modified OHAT assessment, was high.

Many of the above studies additionally considered the association between TRAP and cause-specific mortality, predominantly circulatory mortality (Table 11.1). Fewer studies were selected that considered other causes of death. In meta-analyses, consistently positive associations were found between multiple pollutants and mortality from circulatory and ischemic heart diseases (IHD). Associations with respiratory and lung cancer mortality were also positive but tended to be less precise. Associations between TRAP and stroke and chronic obstructive pulmonary disease (COPD) mortality were mostly inconsistent, related partly to the small number of available studies. The narrative assessment resulted in a judgement of a high confidence for circulatory and IHD mortality, moderate confidence for respiratory and lung cancer mortality, and low confidence for stroke and COPD mortality. The differences among these judgments were primarily due to the evidence from the meta-analysis and the level of consistency observed across pollutants and indirect traffic measures. The modified OHAT assessment resulted in high confidence in the quality of the body of evidence between TRAP and mortality for circulatory, IHD, and lung cancer; moderate confidence for mortality for respiratory and stroke and low confidence for COPD.

In conclusion, the overall confidence in the association between TRAP exposure and cause-specific mortality based on a narrative and a modified OHAT assessment was high for circulatory and IHD, moderate to high for lung cancer, moderate for respiratory, low to moderate for stroke mortality, and low for COPD mortality.

11.2 ALL-CAUSE MORTALITY

Section 11.2 provides the assessment for all-cause mortality and Section 11.3 for cause-specific mortality. Section 11.4 provides an overall discussion and the Panel's evaluation of confidence in an association between TRAP and mortality given the available literature included in this report.

This section starts with a characterization of the available literature reporting on associations between all-cause mortality and exposure to TRAP (Section 11.2.1). Results of the primary meta-analyses of associations with individual pollutants are discussed in the second section (11.2.2). The third section (11.2.3) presents additional meta-analyses stratified according to a priori set criteria, including geographic region. Section 11.2.4 summarizes associations between all-cause mortality and indirect measures of traffic (distance from major roads and traffic density). Section 11.2.5 provides the broad narrative evaluation of the confidence in an association with TRAP, based on the evidence documented in the previous sections. Section 11.2.6 summarizes the risk of bias assessment on this body of evidence, feeding into the formal assessment of confidence in associations between exposure to TRAP and all-cause mortality (Section 11.2.7). Section 11.2.8 provides the overall confidence assessment, combining the narrative and modified OHAT assessment.

11.2.1 STUDY SELECTION AND DESCRIPTION

The all-cause and cause-specific mortality outcomes selected were similar to those used in the 2015 Global Burden of Disease study of ambient air pollution (Cohen et al. 2017). The included causes of death were the broad categories of circulatory and respiratory disease and the more specific causes of IHD, stroke, COPD, acute lower respiratory infection (ALRI),

Table 11.1. Summary of the Confidence in the Evidence for an Association Between Traffic-Related Air Pollution (TRAP) and All-Cause and Cause-Specific Mortality[a]

Pollutant	All-Cause	Circulatory	Respiratory	Lung Cancer	IHD	Stroke	COPD
Meta-analytic Summary Estimate and Narrative Assessment to Assess Confidence in the Presence of an Association with TRAP							
NO_2	1.04 (1.01–1.06) *N* = 11	1.04 (1.00; 1.09) *N* = 10	1.05 (1.00; 1.09) *N* = 8	1.04 (1.01; 1.07) *N* = 5	1.05 (1.03; 1.08) *N* = 6	1.01 (0.98; 1.04) *N* = 6	1.03 (1.00; 1.05) *N* = 3
EC	1.02 (1.00; 1.04) *N* = 11	1.02 (1.00; 1.04) *N* = 9	1.01 (0.98; 1.05) *N* = 8	1.02 (0.88; 1.19) *N* = 3	1.05 (0.99; 1.11) *N* = 6	Fewer than three studies	Fewer than three studies
$PM_{2.5}$	1.03 (1.01; 1.05) *N* = 12	1.04 (1.01; 1.08) *N* = 11	1.03 (0.97; 1.10) *N* = 7	1.06 (0.99; 1.13) *N* = 6	1.07 (1.04; 1.10) *N* = 7	1.04 (1.01; 1.07) *N* = 3	Fewer than three studies
Narrative assessment	Sizable number of well-designed large cohort studies in a variety of locations, supporting associations for multiple pollutants and indirect traffic measures.	Sizable number of well-designed large cohort studies in a variety of locations, supporting associations for multiple pollutants and indirect traffic measures.	Sizable number of well-designed large cohort studies in a variety of locations, with associations found only for some pollutants and indirect traffic measures.	Modest number of well-designed large cohort studies mostly in Europe, associations for some pollutants and indirect traffic measures.	Modest number of well-designed large cohort studies) mostly in Europe, supporting associations for multiple pollutants and indirect traffic measures.	Small number of well-designed large cohort studies, inconsistent associations across pollutants and indirect traffic measures.	Small number of well-designed large cohort studies, inconsistent associations across pollutants and indirect traffic measures.
	High	**High**	**Moderate**	**Moderate**	**High**	**Low**	**Low**
Modified OHAT Assessment to Assess Confidence in the Quality of the Body of Evidence							
NO_2	High	High	High	High	High	Moderate	Low
EC	High	High	Moderate	Low	Moderate	Fewer than three studies[b]	Fewer than three studies
$PM_{2.5}$	High	High	Low	High	Moderate	Moderate	Fewer than three studies[b]
TRAP	**High**	**High**	**Moderate**	**High**	**High**	**Moderate**	**Low**
Overall Assessment Combining the Narrative Assessment and Modified OHAT Assessment							
TRAP	**High**	**High**	**Moderate**	**Moderate to high**	**High**	**Low to moderate**	**Low**

COPD = chronic obstructive pulmonary disease; IHD = ischemic heart disease; OHAT = Office of Health Assessment and Translation.

[a] The table presents only the three pollutants most widely used. The individual pollutants are considered as indicators of the TRAP mixture. Relative risks (RR) and 95% confidence intervals are expressed per 10, 1, and 5 μg/m^3 increments for NO_2, EC, and $PM_{2.5}$, respectively. *N* = number of studies.

[b] The studies provided some support for an association.

and lung cancer. Diabetes mortality was not included in the set of outcomes, because diabetes mortality is prone to substantial outcome misclassification. Diabetes is infrequently indicated as a primary cause of death on death-certificates; the comorbidities IHD or stroke are often given instead. Further details regarding the outcome definitions are given in Chapter 5.

A total of 48 studies were selected that reported associations between traffic-related air pollutants or indirect traffic measures and all-cause and cause-specific mortality. Table 11.2 shows the 31 studies identified as including effect estimates for all-cause mortality. Most studies were conducted in North America and Europe, and a few were based in Asia and Australia. Compared with the 2010 HEI Traffic Review, the evidence base has increased substantially, mostly related to the publication of studies conducted after the completion of the 2010 review. The selection of studies in the current review was also more inclusive because the Panel included both studies from the near road and broader neighborhood environment, indicative of exposure to TRAP as described in Chapters 5 and 6. We excluded from this review a sizable number of air pollution cohort studies, especially those considering exposures to $PM_{2.5}$. The Panel judged that these studies did not sufficiently represent exposures from motorized vehicle traffic, as described in Chapter 6. Studies not meeting the criteria of the exposure framework included the original Harvard Six Cities Study, the ACS-CPS II, the U.S.-wide Medicare cohort, and CanCHEC (Crouse et al. 2012; Di et al. 2017; Dockery et al. 1993; Jerrett, 2013; Pope et al. 1995, 2002; Turner 2016). The main factors from the exposure framework contributing to the exclusion of studies were exposure assessed by monitoring of $PM_{2.5}$; insufficient spatial resolution of the exposure surface or subject address; and a large (national) study area without an adjustment for between-community exposure variation.

All selected studies used the cohort study design. The studies differed substantially in sample size, ranging from several thousands to several million participants in the cohorts based on administrative data. Most cohorts had extensive information available on individual lifestyle factors, such as smoking and BMI. Studies based on large administrative cohorts lacked data on individual lifestyle factors. However, these studies typically included detailed data on individual- and area-level socioeconomic factors, likely reducing the opportunity for residual confounding by unmeasured lifestyle factors. Exposure assessment was based on LUR or dispersion/CTM. No studies were selected based on (interpolation of) monitoring data alone. Follow-up periods differed across studies, but many studies had follow-up extending until 2010–2015. Most studies were performed in general population samples of adults. A few studies were conducted only with older adults or in populations of patients suffering from specific conditions, such as IHD. A small number of studies were conducted only in men or in women. Mean TRAP exposures were mostly moderate (e.g., annual average $PM_{2.5}$ exposure <30 $\mu g/m^3$ and NO_2 <40 $\mu g/m^3$) but differed widely across studies. In summary, the identified studies differed substantially in type and size of population, age of the population, follow-up period, included covariates, exposure-assessment methods and distribution of exposure.

Following the design of the early U.S. cohort studies on long-term exposure to $PM_{2.5}$ (Dockery et al. 1993; Pope et al. 1995, 2002), a fairly large number of cohort studies with detailed individual lifestyle information assessed traffic-related air pollutants and were included in the evidence base. This group of studies in general population samples includes the Danish Diet and Cancer study in Copenhagen and Aarhus, Denmark (Hvidtfeldt et al. 2019; Raaschou-Nielsen et al. 2012); female teachers across California of the California Teachers study (Ostro et al. 2015); participants from ACS-CPS II in New York and Los Angeles with $PM_{2.5}$ estimated by city-specific LUR (Krewski 2009) and from the nationwide ACS-CPS II using a novel LUR (Jerrett et al. 2017); participants 65 years and older in Hong Kong, China (Yang et al. 2018) and in the Shizuoaka region in Japan (Yorifuji et al. 2010, 2013); and two Australian adult cohorts at low pollution levels in Perth and Sydney (Dirgawati et al. 2019; Hanigan et al. 2019). Several cohorts followed populations of more than 100,000 participants (Beelen et al. 2008, 2014; Ostro et al. 2015), including the ESCAPE study, a multicenter study of 19 individual cohorts across Europe with a total of 320 thousand participants (Beelen et al. 2014).

Several studies were designed as follow-up of selected patient populations, including studies of stroke and myocardial infarction survivors in England (Tonne and Wilkinson 2013); London, UK (Desikan et al. 2016; Maheswaran et al. 2010; Tonne et al. 2016); Boston and Worcester, MA (von Klot et al. 2009; Wilker et al. 2013); and in patients with respiratory disease (Finkelstein et al. 2005; Jerrett et al. 2009). The rationale for inclusion of these studies is that these conditions are common in the general population and that these patients may be particularly sensitive to TRAP. The cohort studies in patient populations were typically smaller than the general population studies (Table 11.2), with the exception of the myocardial infarction survivor study in England and Wales (Tonne and Wilkinson 2013).

The Panel also included several cohort studies that followed cohorts exclusively based on administrative databases, including studies following: all residents of the metropolitan area of Rome (Badaloni et al. 2017; Cesaroni et al. 2013); all residents of the city of Barcelona (Nieuwenhuijsen et al. 2018); 800 thousand adults selected from a General Practitioners network from multiple cities across England (Carey et al. 2013); and a 1% random sample of the 1971 English census (Hansell et al. 2016). From the North American administrative cohort studies on general air pollution exposures, only the NO_2 estimate from a subset of the Canadian 1991 CanCHEC cohort based on the Canadian census was considered to sufficiently reflect a traffic impact (Crouse et al. 2015).

Table 11.2. Key Study Characteristics of Cohort Studies Included in the Systematic Review for All-Cause Mortality—Pollutants

Reference	Study Name	Location	Study Period	Sample Size	Age (years)	Sex	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Effect Estimate (95% CI)[b]	Increment
Badaloni 2017	Rome Longitudinal	Rome, Italy	2001–2010	1,249,108	Adults (18+)	Both	LUR	$PM_{2.5\ abs}$	3	**1.05 (1.03–1.06)**	1.5 1×10^{-5}/m
								PM_{10} mass	37	**1.03 (1.01–1.04)**	17.2 µg/m^3
								$PM_{2.5}$ mass	20	**1.03 (1.01–1.05)**	6.6 µg/m^3
								$PM_{2.5}$ Cu	15	**1.06 (1.04–1.08)**	15.4 ng/m^3
								$PM_{2.5}$ Fe	260	**1.05 (1.03–1.07)**	275.5 ng/m^3
								$PM_{2.5}$ Zn	24	1.06 (1.04–1.08)	16.3 ng/m^3
Bauleo 2019	Civitavecchia Study	Civitavecchia, Italy	1996–2013	71,362	Adults (18+)	Both	Dispersion/ CTM	NO_x	5.8	**0.98 (0.91–1.05)**	12.8 µg/m^3
Beelen 2008	NLCS-AIR	The Netherlands	1987–1996	117,528	Adults (18+)	Both	LUR	NO_2	36.9	**1.08 (1.00–1.16)**	30 µg/m^3
								BC	16.5	**1.05 (1.00–1.11)**	10 µg/m^3
								$PM_{2.5}$ mass	28.3	**1.06 (0.97–1.16)**	10 µg/m^3
Beelen 2014	ESCAPE	Multiple cities, multiple countries	1985–2008	315,615	Adults (18+)	Both	LUR	NO_2	5.2–59.8	**1.01 (0.99–1.03)**	10 µg/m^3
								NO_x	8.7–107.3	**1.02 (1.00–1.04)**	20 µg/m^3
								$PM_{2.5\ abs}$	0.5–3.2	**1.02 (0.97–1.07)**	1 1×10^{-5}/m
								PM_{10} mass	13.5–48.1	**1.04 (1.00–1.09)**	10 µg/m^3
								PM_{coarse} mass	4.0–20.7	1.04 (0.98–1.1)	5 µg/m^3
								$PM_{2.5}$ mass	6.6–31.0	**1.07 (1.02–1.13)**	5 µg/m^3

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Table 11.2 (*Continued*). Key Study Characteristics of Cohort Studies Included in the Systematic Review for All-Cause Mortality—Pollutants

Reference	Study Name	Location	Study Period	Sample Size	Age (years)	Sex	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Effect Estimate (95% CI)[b]	Increment
Beelen 2015	ESCAPE	Multiple cities, multiple countries	1985–2008	291,816	Adults (18+)	Both	LUR	$PM_{2.5}$ Cu	1–12	**0.98 (0.92–1.04)**	5 ng/m^3
								$PM_{2.5}$ Fe	40–320	**1.03 (0.98–1.09)**	100 ng/m^3
								$PM_{2.5}$ Zn	16–41	1.03 (0.99–1.08)	20 ng/m^3
Carey 2013	English National Cohort	England	2003–2007	830,842	Adults (18+)	Both	Dispersion/CTM	NO_2	22.5	**1.02 (1.00–1.04)**	10.7 µg/m^3
								PM_{10} mass	19.7	**1.00 (0.98–1.02)**	3.0 µg/m^3
								$PM_{2.5}$ mass	12.9	**1.00 (0.98–1.02)**	1.9 µg/m^3
Cesaroni 2013	Rome Longitudinal	Rome, Italy	2001–2010	1,265,058	Adults (18+)	Both	LUR	NO_2	43.6	**1.03 (1.02–1.03)**	10 µg/m^3
							Dispersion/CTM	$PM_{2.5}$ mass	23.0	1.04 (1.03–1.05)	10 µg/m^3
Cohen 2019	Israel Coronary Intervention[c]	Petah Tikva, Israel	2004–2017	10,627	Adults (18–64)	Both	LUR	NO_x	24.5	1.07 (0.98–1.18)	<25 vs. >25 ppb
Crouse 2015	1991 CanCHEC	Multiple cities, Canada	1991–2006	735,590	Adults (18+)	Both	LUR	NO_2	25.2	**1.05 (1.04–1.07)**	5 ppb
Desikan 2016	South London Stroke Register[c]	London, United Kingdom	2005–2012	1,800	Adults (18+)	Both	Dispersion/CTM	NO_2	44.59	0.97 (0.87–1.08)	5.0 µg/m^3
								NO	34.39	0.96 (0.85–1.08)	8.86 µg/m^3
								NO_x	78.98	0.96 (0.85–1.08)	14.0 µg/m^3

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Table 11.2 (*Continued*). Key Study Characteristics of Cohort Studies Included in the Systematic Review for All-Cause Mortality—Pollutants

Reference	Study Name	Location	Study Period	Sample Size	Age (years)	Sex	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Effect Estimate (95% CI)[b]	Increment
								PM_{10} mass	28.84	1.12 (0.98–1.29)	2.2 μg/m^3
								$PM_{2.5}$ mass	15.35	1.28 (1.08–1.53)	1.9 μg/m^3
								$PM_{2.5}$ exhaust	0.8	0.98 (0.84–1.14)	0.3 μg/m^3
								Nontail-pipe $PM_{2.5}$	0.92	0.94 (0.85–1.03)	0.2 μg/m^3
Dirgawati 2019	HIMS	Perth, Australia	1996–2012	11,627	Older Adults (65+)	Male	LUR	NO_2	13.4	**1.06 (1.00–1.13)**	10 μg/m^3
								NO_x	32.3	**1.02 (1.00–1.04)**	10 μg/m^3
								$PM_{2.5\ abs}$	0.9	**1.12 (1.02–1.22)**	1 1×10^{-5}/m
								$PM_{2.5}$ mass	5.1	**1.07 (0.98–1.16)**	5 μg/m^3
Hanigan 2019	45 and Up Study	Sydney, Australia	2006–2015	75,148	Adults (18+)	Both	LUR	NO_2	17.75	**1.03 (0.98–1.07)**	5 μg/m^3
								$PM_{2.5}$ mass	4.49	**1.05 (0.98–1.12)**	1 μg/m^3
Hansell 2016	ONS-Longi-tudinal	England and Wales, United Kingdom	1971–2009	367,658	Adults (18–64)	Both	LUR	BS	42.7	**1.02 (1.01–1.04)**[d]	10 μg/m^3
								PM_{10} mass	20.7	**1.24 (1.16–1.34)**[d]	10 μg/m^3
Hvidtfeldt 2019	DDCH	Copenhagen and Aarhus, Denmark	1993–2015	49,564	Adults (18–64)	Both	Dispersion/ CTM	NO_2	25.0	**1.07 (1.04–1.10)**	10 μg/m^3
								BC	0.92	**1.09 (1.04–1.15)**	1 μg/m^3
								PM_{10} mass	25.1	**1.12 (1.03–1.22)**	10 μg/m^3

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Table 11.2 (*Continued*). Key Study Characteristics of Cohort Studies Included in the Systematic Review for All-Cause Mortality—Pollutants

Reference	Study Name	Location	Study Period	Sample Size	Age (years)	Sex	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Effect Estimate (95% CI)[b]	Increment
								$PM_{2.5}$ mass	18.0	**1.13 (1.05–1.21)**	5 μg/m^3
Jerrett 2009	Toronto Respiratory Cohort[c]	Toronto, Canada	1992–2002	2,360	Adults (18+)	Both	LUR	NO_2	22.9	1.17 (1.00–1.36)	4 ppb
Krewski 2009	ACS-CPS II LA	Los Angeles, California, United States	1982–2000	22,905	Adults (18+)	Both	LUR	$PM_{2.5}$ mass	20	**1.14 (1.03–1.27)**	10 μg/m^3
	ACS-CPS II NYC	New York City, New York, United States	1982–2000	44,056	Adults (18+)	Both	LUR	$PM_{2.5}$ mass	14.3	**0.98 (0.95–1.02)**	1.5 μg/m^3
Maheswaran 2010	South London Stroke Register[c]	London, United Kingdom	1995–2006	3,320	Adults (18+)	Both	Dispersion/ CTM	NO_2	41	1.28 (1.11–1.48)	10 μg/m^3
								PM_{10} mass	25	1.52 (1.06–2.18)	10 μg/m^3
Nafstad 2004	Oslo men's cohort	Oslo, Norway	1972–1998	16,209	Adults (18–64)	Male	Dispersion/ CTM	NO_x	10.7	**1.08 (1.06–1.11)**	10 μg/m^3
Nieuwenhuijsen 2018	Barcelona Mega Cohort	Barcelona, Spain	2010–2014	792,649	Adults (18–64)	Both	LUR	NO_2	53.42	**1.01 (1.00–1.02)**	5 μg/m^3
								$PM_{2.5\ abs}$	2.64	**1.02 (1.00–1.05)**	1 1×10^{-5}/m
								PM_{10} mass	38.29	**1.00 (0.97–1.03)**	10 μg/m^3
								$PM_{2.5}$ mass	16.08	**1.03 (0.99–1.06)**	5 μg/m^3
Ostro 2015	California Teachers Study	California, United States	1995–2007	101,884	Adults (18+)	Female	Dispersion/ CTM	EC	1.1	**1.00 (0.97–1.04)**	0.8 μg/m^3
								$PM_{2.5}$ mass	17.9	**1.01 (0.98–1.05)**	9.6 μg/m^3
								$PM_{2.5}$ Cu	0.5	**1.00 (0.98–1.03)**	0.4 ng/m^3

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Table 11.2 (*Continued*). Key Study Characteristics of Cohort Studies Included in the Systematic Review for All-Cause Mortality—Pollutants

Reference	Study Name	Location	Study Period	Sample Size	Age (years)	Sex	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Effect Estimate (95% CI)[b]	Increment
								$PM_{2.5}$ Fe	0.4	**1.00 (0.97–1.04)**	0.2 μg/m^3
								On-road diesel	0.4	1.00 (0.97–1.04)	0.4 μg/m^3
								On-road gasoline	0.3	0.99 (0.95–1.02)	0.3 μg/m^3
								$PM_{0.1–0.01}$	1,293	1.01 (0.98–1.05)	969 ng/m^3
Raaschou-Nielsen 2012	DDCH	Copenhagen and Aarhus, Denmark	1993–2009	52,061	Adults (18–64)	Both	Dispersion/ CTM	NO_2	16.9	1.08 (0.98–1.18)[e]	1 μg/m^3
Stockfelt 2015	PPS	Gothenburg, Sweden	1970–2007	6,557	Adults (18–64)	Male	Dispersion/ CTM	NO_x	42	**1.02 (1.01–1.04)**	10 μg/m^3
Tonne 2013	MINAP[c]	England and Wales, United Kingdom	2004–2010	154,204	Adults (18+)	Both	Dispersion/ CTM	NO_2	18.8	1.01 (0.98–1.04)	10 μg/m^3
								NO_x	28.3	1.00 (0.99–1.02)	10 μg/m^3
								PM_{10} mass	17	1.01 (0.92–1.10)	10 μg/m^3
								$PM_{2.5}$ mass	11	1.20 (1.04–1.38)	10 μg/m^3
Tonne 2016	London MI Cohort[c]	London, United Kingdom	2003–2010	18,138	Adults (18+)	Both	Dispersion/ CTM	NO_2	37.1	1.04 (0.99–1.10)	8 μg/m^3
								NO_x	61.8	1.03 (0.98–1.08)	19.2 μg/m^3
								Nontail-pipe $PM_{2.5}$	0.7	1.04 (1.00–1.09)	0.3 μg/m^3
								Traffic $PM_{2.5}$	0.6	1.02 (0.98–1.07)	0.3 μg/m^3
Villeneuve 2013	Ontario Tax Cohort	Toronto, Canada	1982–2004	58,760	Adults (18+)	Both	LUR	Benzene	0.64	1.05 (1.03–1.08)	0.1 μg/m^3

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Table 11.2 (*Continued*). Key Study Characteristics of Cohort Studies Included in the Systematic Review for All-Cause Mortality—Pollutants

Reference	Study Name	Location	Study Period	Sample Size	Age (years)	Sex	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Effect Estimate (95% CI)[b]	Increment
von Klot 2009	Worcester Heart Attack[c]	Worcester, Massachusetts, United States	1995–2005	3,895	Adults (18+)	Both	LUR	EC	0.45	1.15 (1.03–1.29) (after 2nd year of survival)	0.2 μg/m^3
										1.02 (0.93–1.11) (in first 2 years of survival)	0.2 μg/m^3
Yang 2018	Hong Kong Elderly	Hong Kong, China	1998–2011	61,386	Older Adults (65+)	Both	LUR	NO_2	104	**1.00 (0.97–1.03)**	25.6 μg/m^3
								NO	147	0.99 (0.97–1.02)	167 μg/m^3
								BC	12.1	**1.03 (1.00–1.05)**	9.6 μg/m^3
								$PM_{2.5}$ mass	42.2	**1.03 (1.01–1.06)**	5.5 μg/m^3
Yap 2012	Renfrew/ Paisley	Glasgow, Scotland	1972–1998	15,188	Adults (18+)	Both	LUR	BS	19.3	**1.08 (1.02–1.15)**	10 μg/m^3
	Collaborative Cohorts			6,255					23.2	**1.01 (0.95–1.06)**	
Yorifuji 2010	Shizuoka Elderly	Shizuoka, Japan	1999–2006	12,029	Older Adults (65+)	Both	LUR	NO_2	25	1.02 (0.96–1.08)	10 μg/m^3
Yorifuji 2013	Shizuoka Elderly	Shizuoka, Japan	1999–2009	13,412	Older Adults (65+)	Both	LUR	NO_2	22	**1.12 (1.07–1.18)**	10 μg/m^3

BC = black carbon; BS = black smoke.

[a] Units are in the increment column.

[b] Effect estimates are expressed as relative risk or hazard ratio. **Bold** indicates the effect estimate was included in the meta-analysis.

[c] Indicates a patient population.

[d] Odds ratio.

[e] Log transformed.

11.2.2 PRIMARY META-ANALYSIS

Figure 11.1 shows the meta-analytical summary effect estimates for all pollutants and all-cause mortality based on meta-analyses of the general population studies. No meta-analyses were conducted for distance and traffic density measures, nor for pollutants for which there were fewer than three studies. The number of studies included in Figure 11.1 (N = 20) is fewer than the total number of selected studies (N = 31) (Table 11.2), especially due to exclusion of studies in patient populations (Cohen et al. 2019; Desikan et al. 2016; Jerrett et al. 2009; Maheswaran et al. 2010; Tonne et al. 2016; Tonne and Wilkinson 2013; von Klot et al. 2009), studies that used log-transformed exposures (e.g., Raaschou-Nielsen et al. 2012), and exclusion of studies in the same population for which a more informative study has been published (e.g., Yorifuji et al. 2013 instead of Yorifuji et al. 2010). The general exclusion criteria for meta-analyses are described in Chapter 5. NO_2, EC, and $PM_{2.5}$ were the most studied pollutants (more than 10 studies for each pollutant). Studies summarized here as EC studies used a variety of indicators, including EC, black smoke (BS), black carbon (BC), and $PM_{2.5}$ absorbance ($PM_{2.5\ abs}$), which were combined in the analysis after harmonization. Three or more studies were also available for NO_x, PM_{10}, Cu, and Fe. The Panel did not identify a sufficient number of studies to perform a meta-analysis for nitric oxide (NO), carbon monoxide, PM with aerodynamic diameter between 10 µm and 2.5 µm (PM_{coarse}), ultrafine particles (UFPs; particles 100 nm or less in diameter), polycyclic aromatic hydrocarbons, and benzene.

The meta-analytic summary estimates for all pollutants documented positive associations with all-cause mortality.

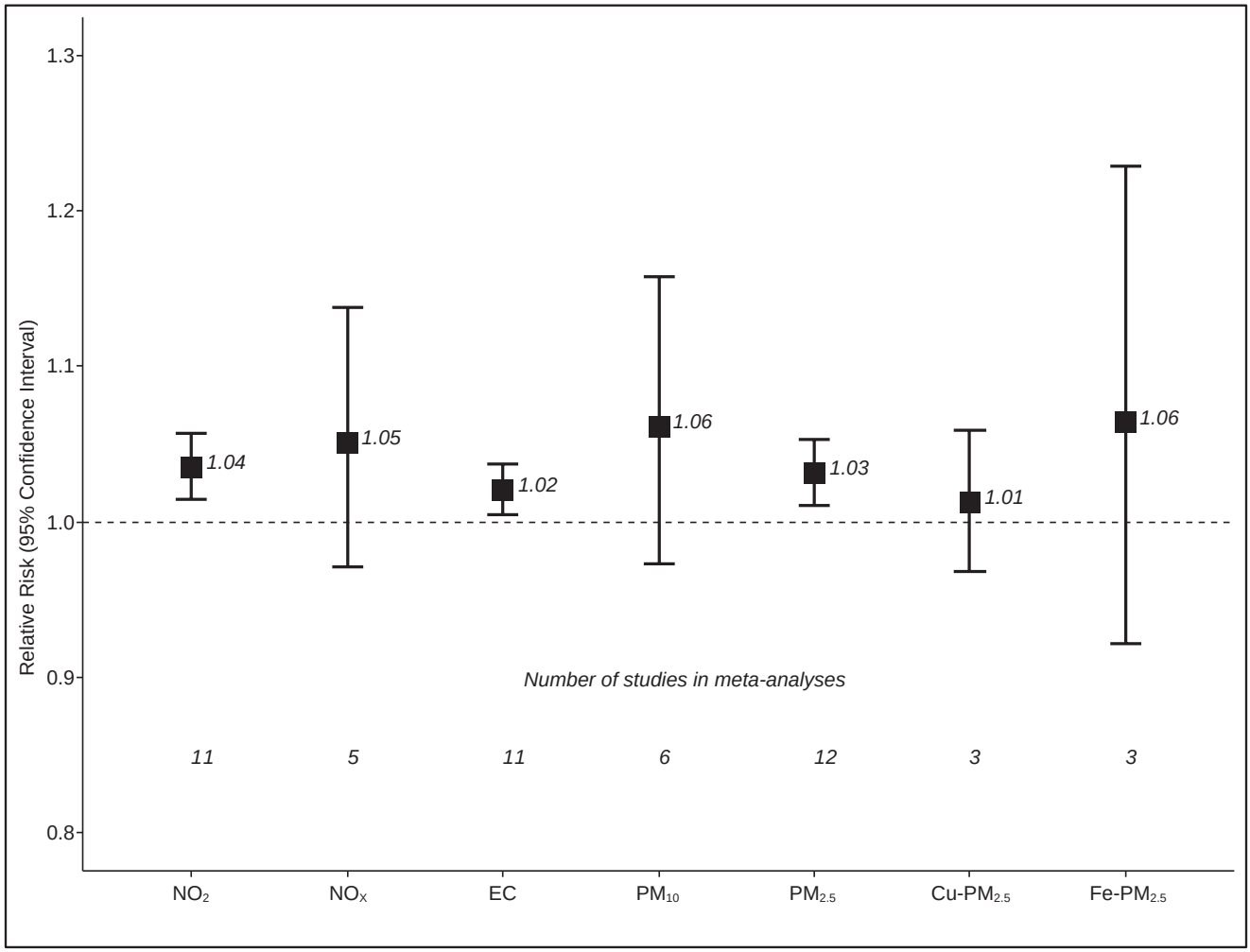

Figure 11.1. Meta-analysis of associations between traffic-related air pollutants and all-cause mortality. The following increments were used: 10 µg/m³ for NO_2, 20 µg/m³ for NO_x, 1 µg/m³ for EC, 10 µg/m³ for PM_{10}, 5 µg/m³ for $PM_{2.5}$, 5 ng/m³ for Cu, and 500 ng/m³ for Fe. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

The summary estimates for NO_2, EC, and $PM_{2.5}$—pollutants with more than 10 studies—supported statistically significant associations. We use the term RR to describe effect estimates, as it is easier to communicate than the technically more correct hazard ratio. For the other pollutants, the effect estimates were above unity but with wider CIs. Most studies contribute information on multiple pollutants (Table 11.2); therefore, results for the different pollutants were not completely independent.

Figure 11.2 and Appendix Figure 11A-1 (available on the HEI website) show the forest plots with individual studies. The forest plots for NO_2, EC, and $PM_{2.5}$ are shown in the main text as most studies have used these pollutants as an indicator of TRAP. For all three pollutants, the large majority of studies reported positive associations with mortality, although not all were statistically significant in the individual studies. The combined estimate was not influenced heavily by an individual study, as indicated by the weights in the forest plots. The meta-analytical summary effect estimate for the eleven studies of NO_2 was 1.04 (95% CI: 1.01–1.06) per 10-μg/m³; for the eleven studies of EC was 1.02 (1.00–1.04) per 1-μg/m³; and

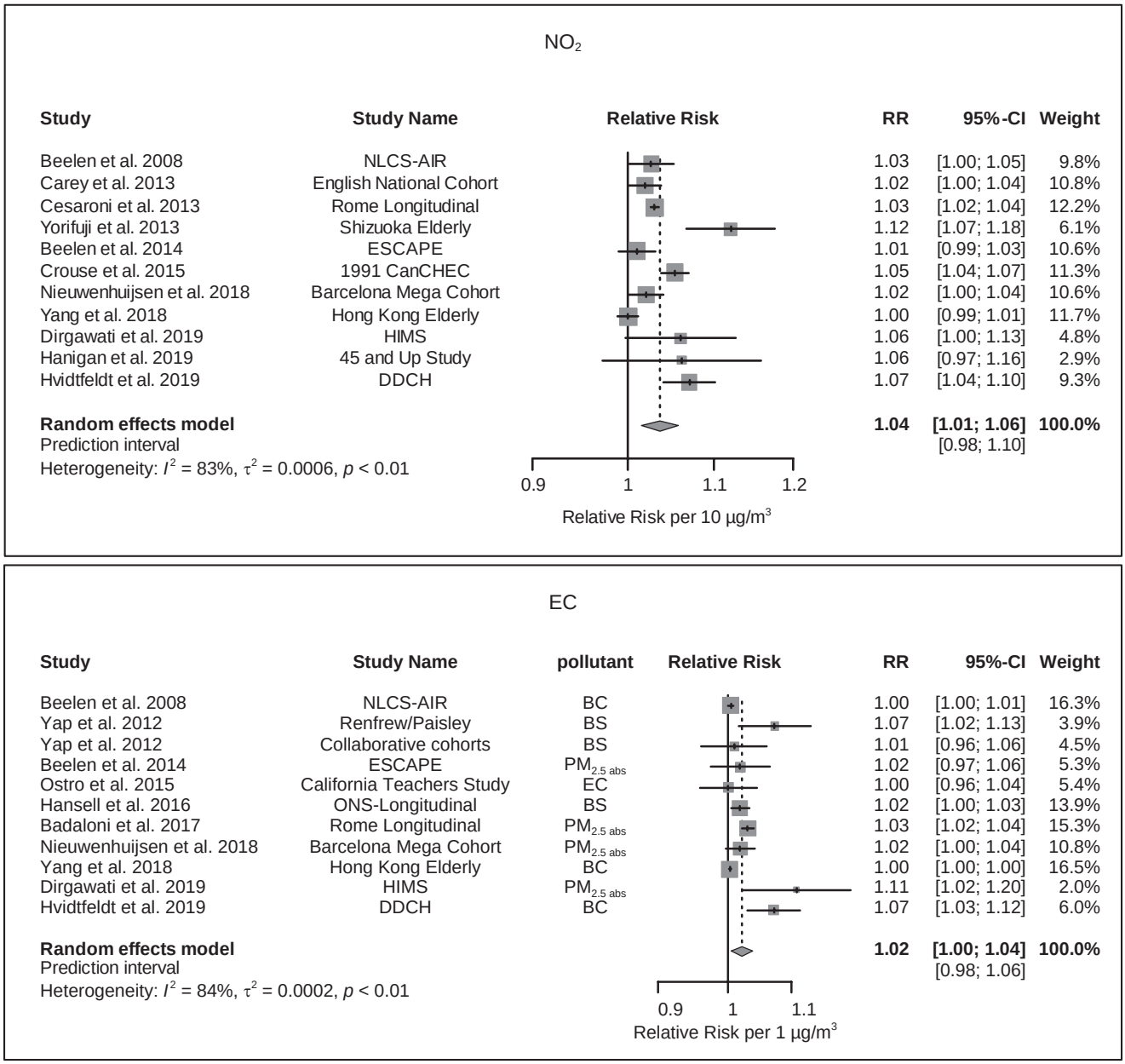

Figure 11.2. Association between NO_2, EC, and $PM_{2.5}$ and all-cause mortality: meta-analysis. *Figure continues next page.*

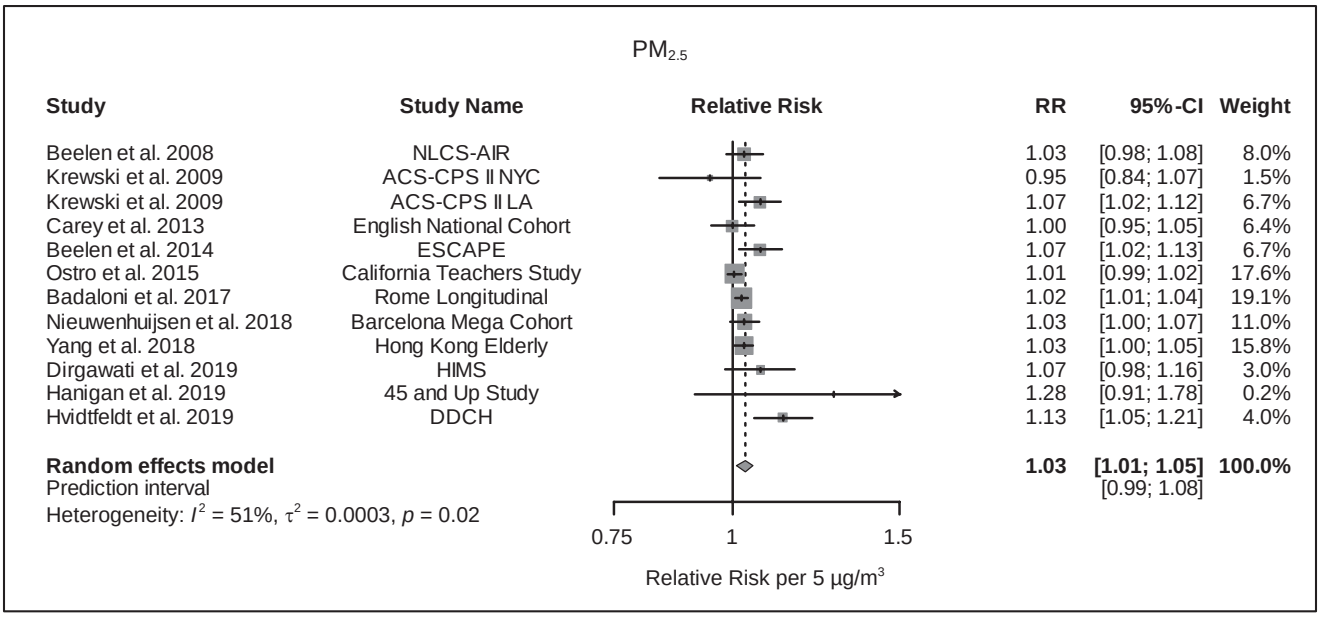

Figure 11.2. *(Continued).*

for the 12 studies of $PM_{2.5}$ was 1.03 (1.01–1.05) per 5-µg/m³. Heterogeneity of effect estimates judged by the I^2 was moderate for $PM_{2.5}$ and high for NO_2 and EC. The Panel notes that RRs can all be considered as small, (e.g., for NO_2 all RRs were between 1.00 and 1.12). The I^2 statistic is expressed on a relative scale. Such heterogeneity was mainly due to the magnitude of the individual effect estimates, not due to a mix of effect estimates below and above unity.

The meta-analytical summary effect estimate for the five studies of NO_x and all-cause mortality was 1.05 (95% CI: 0.97–1.14) per 20-µg/m³ (Appendix Figure 11A.1), with all but one study (Bauleo et al. 2019) showing associations. Overall heterogeneity for studies of NO_x was high. The meta-analytical summary effect estimate for the six studies of PM_{10} mortality was 1.06 (0.97–1.16) per 10-µg/m³, with four studies showing RRs above unity and two studies where the RR equaled unity (Carey et al. 2013; Nieuwenhuijsen et al. 2018). The overall heterogeneity was high. For both Cu and Fe in $PM_{2.5}$ three studies were available, of which the Rome Longitudinal study showed an association and had high weight in the meta-analysis (Badaloni et al. 2017), the California Teachers study a null finding (Ostro et al. 2015) and the ESCAPE study a positive association for Fe and a negative association for Cu, both with wide CIs (Beelen et al. 2015).

For NO, PM_{coarse}, UFPs, and benzene only one or two studies were available. The two NO studies showed no associations, with RRs below unity. The single studies on PM_{coarse}, UFPs, and benzene showed associations with mortality. Overall, these pollutants added very little information for the overall confidence assessment.

The finding of associations between TRAP and all-cause mortality in substantially different populations lent further support to the confidence in the presence of an association. It is unlikely that potential biases have affected air pollution effect estimates in the same direction in different populations (e.g., because most covariates can be positively or negatively correlated with air pollution exposures). This argumentation applies less to the potential confounder traffic noise, as it derives from the same source, and thus will be positively correlated with air pollution in all populations, although with different magnitude (Sections 11.2.3 and 11.2.5). Populations differed in many aspects, including the geographical region, age distribution, and type of population. The evidence base included several large to very large studies resulting in precise effect estimates. In total, almost one million participants were included in the studies with detailed individual lifestyle information, such as smoking and BMI and a range of other potential confounders.

Additional evidence of an association was provided by several very large studies (several million participants in total) based on linking exposure to administrative databases. These studies provide very large statistical power but have less information to adjust for individual lifestyle factors, such as smoking. Despite this limitation, these studies are informative, as they typically adjust rigorously for various measures of individual- and area-level SES. As individual and neighborhood SES are strong predictors of health behaviors and risk factors such as smoking and obesity, it is not clear that there is much residual confounding by individual smoking and BMI after accounting for individual and neighborhood SES. Because the analyses are performed in secure environments,

administrative cohorts may have access to individual income data (e.g., through linkage with tax records). Rigorous adjustment for SES is important because for smoking or other lifestyle factors to be a confounder, there needs to be a correlation with TRAP exposure (Shin et al. 2014; Strak et al. 2017). This correlation is plausible through SES (Strak et al. 2017; Vodonos et al. 2018). Furthermore, the direction of the association between air pollution exposure and confounders likely differs in different populations, and therefore residual confounding does not necessarily bias the effect estimates upward (Brunekreef et al. 2021; Chen and Hoek 2020; Vodonos et al. 2018). Finally, the administrative studies have used a range of methods to assess potential confounding by missing lifestyle factors, including indirect adjustment approaches, assessment of an association between exposure and smoking in a subgroup (e.g., Badaloni et al. 2017), and adjustment for pre-existing disease as proxies of smoking and BMI (e.g., Cesaroni et al. 2013), and area-level rates of lung cancer as a proxy for smoking (e.g., Hansell et al. 2016). These adjustments have increased the confidence in the presence of an association in these studies. The administrative database studies cover very large and representative populations, often the full population, and there is less potential selection bias compared with the traditional (smaller) cohort studies. A strength of most studies (traditional and administrative cohorts) is the inclusion of both individual- and area-level SES covariates, following the strategy developed in ACS-CPS II (Pope et al. 2002). Individual and neighborhood SES have been found to be risk factors for mortality (Meijer et al. 2012; van Kamp et al. 2004), and thus both may confound associations between air pollution and mortality. The association between individual SES and mortality has been well documented in different countries (Chetty et al. 2016; Gallo et al. 2012).

In the selection of studies, the Panel carefully evaluated the exposure-assessment strategy employed in each study using the newly developed exposure framework explained in Chapter 6. The included mortality studies, therefore, all used state-of-the-art exposure-assessment methodologies, either LUR or dispersion/CTM models. There was no mortality study included that used monitoring only. The studies differed in their exposure-assessment methodology, which may have contributed to the observed heterogeneity, but that can also be viewed as a strength, as the potential for confounding may differ between those that used LUR models (based on predictors such as local traffic intensity and population density) and those that used dispersion models (based on emission estimates from inventories) (Klompmaker et al. 2021).

11.2.3 ADDITIONAL META-ANALYSES AND CO-EXPOSURE WITH NOISE

Figure 11.3 shows that the majority of studies for NO_2 and EC were rated as having high traffic specificity. Only two studies were rated as having moderate traffic specificity for both pollutants. A priori all $PM_{2.5}$ studies included in this review were rated as moderate traffic specificity (see Chapter 6). The meta-analytic summary estimates were above unity for the high traffic specificity studies, with somewhat higher estimates for the high traffic specificity studies compared with the two moderate traffic specificity studies.

Appendix Figure 11A-2 illustrates that the cohort studies conducted in patient populations, which were excluded in the primary meta-analysis, also showed predominantly positive associations between NO_2, EC, and $PM_{2.5}$ and all-cause mortality. There were five, one, and two studies available for NO_2, EC, and $PM_{2.5}$, respectively. Patient cohorts tended to be small, providing less precise, more variable effect estimates than the general population studies. For NO_2, the meta-analytical summary estimate of the five studies in patients was 1.09 (95% CI: 0.93–1.26), larger but more imprecise than the summary estimate for the general population studies.

Appendix Figure 11A-3 illustrates that associations between NO_2, EC, and $PM_{2.5}$ and all-cause mortality were found in different geographic regions of the world. Most studies included in the review were from Europe; however, associations were also found in other regions of the world.

Appendix Figure 11A-4 illustrates that associations between NO_2, EC, and $PM_{2.5}$ and all-cause mortality were also found in the studies that adjusted for individual smoking habits. The majority of studies adjusted for smoking. For NO_2 and $PM_{2.5}$, RRs tended to be higher in the studies adjusting for individual smoking habits, whereas for EC, RRs were somewhat smaller among those adjusting for smoking. A formal assessment of the impact of risk of bias is included in Section 11.2.6.

As most studies have been published after 2008—the end of the search date for the 2010 Traffic Review, the meta-analysis results for recent publication years (or post 2008) are nearly identical to the primary meta-analysis (see Additional Materials to Chapter 11, available on the HEI website).

Some studies reported two-pollutant models in which the traffic-related pollutant effect estimates were adjusted for traffic noise (Appendix Table 11A-1). Four studies reported associations with TRAP adjusted for road traffic noise. In three studies air pollution RRs were not or very mildly attenuated (Nieuwenhuijsen et al. 2018; Raaschou-Nielsen et al. 2012; Tonne et al. 2016). In the most recent DDCH study (Hvidtfeldt et al. 2019), effect estimates were substantially attenuated but still indicative of an association with all-cause mortality. In the studies the correlation between air pollutants and noise was generally low to moderate (~0.2. to 0.6).

Only a single study corrected the $PM_{2.5}$ effect estimate in Los Angeles for ozone (Krewski et al. 2009) reporting stable results. Another single study corrected the BC and NO_2 effect estimates for general $PM_{2.5}$, with virtually similar results (Yang et al. 2018).

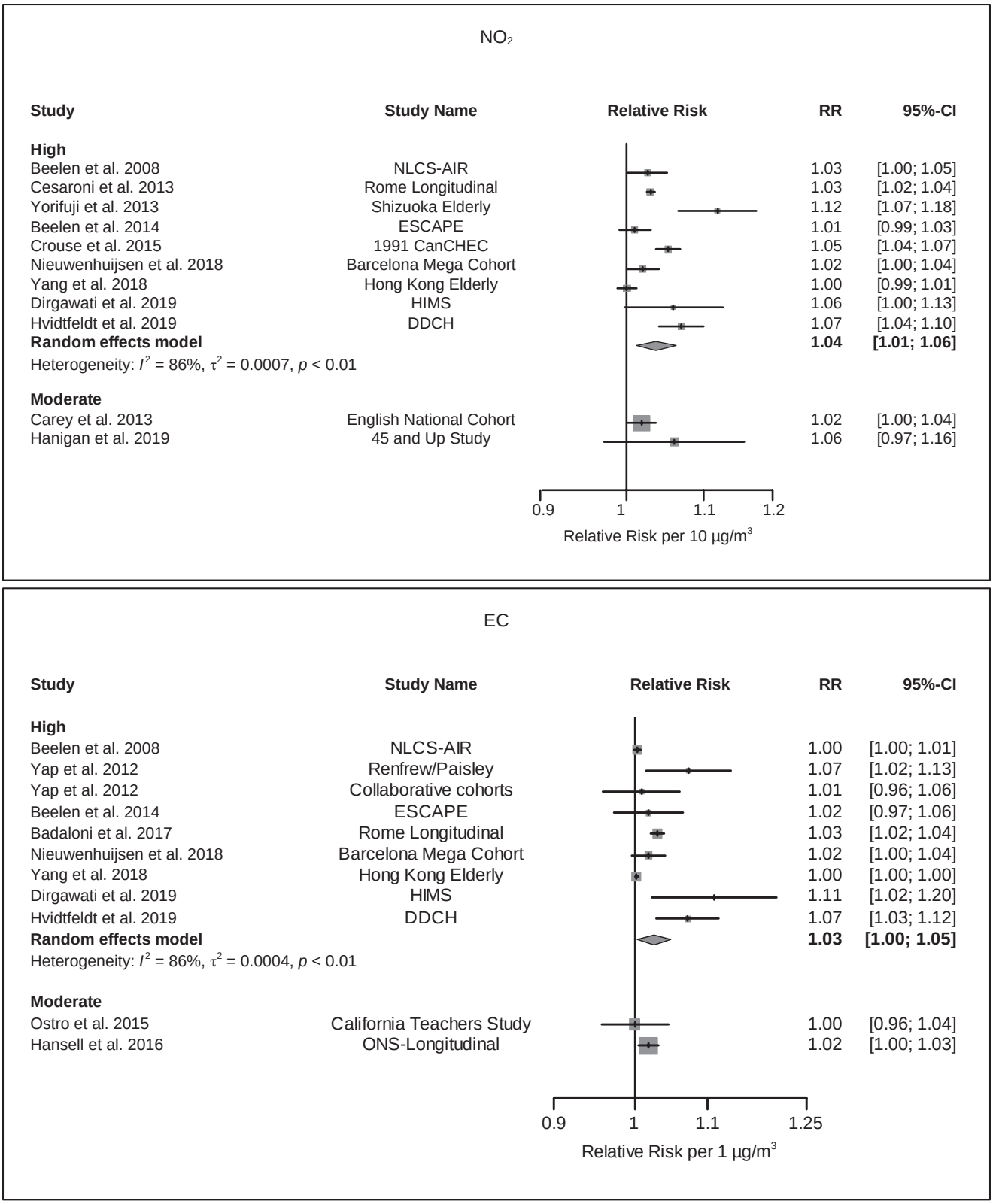

Figure 11.3. Association between NO_2 and EC and all-cause mortality: meta-analysis by traffic specificity.

11.2.4 ASSOCIATIONS WITH INDIRECT TRAFFIC MEASURES

Table 11.3 lists the studies with indirect traffic measures based on distance to major roads or traffic density. The effect estimates of the studies are also shown in Figure 11.4.

The studies on indirect traffic measures provide some further support for an association of TRAP with all-cause mortality. The indirect traffic measures were too heterogeneous in definitions to allow meta-analysis. For the distance measures, eight of the nine studies comparing a short distance category (e.g., <50 m from a major road) with the largest distance category, reported higher all-cause mortality for subjects living at short distances from major roads. The magnitude of the associations varied substantially between studies. Associations were weaker for the distance categories larger than 100 meters, in agreement with the generally steep decline of TRAP with increasing distance to major roads. The traffic density measures showed estimates slightly above unity in the three general population cohort studies, which evaluated these indirect traffic measures.

11.2.5 NARRATIVE ASSESSMENT

The primary meta-analysis showed consistent associations between multiple pollutants and all-cause mortality. The large majority of studies reported associations with all-cause mortality. All studies used the cohort study design, used registries to assess the health outcome (Sidebar 11.1), and adjusted for major potential confounders directly or indirectly, as argued in more detail in Section 11.2.2. The four studies that have considered potential confounding by traffic noise have found that TRAP remains associated with all-cause mortality after adjustment for road-traffic noise, typically with only small changes in effect estimates. The same conclusion was obtained in studies discussed in Section 11.3 regarding circulatory mortality; additional studies on mortality not included in the current review (Section 11.4) and cardiometabolic morbidity (Chapter 10). The generally modest attenuation on adjustment for traffic noise for all-cause mortality is consistent with traffic noise being a risk factor for only a selection of (cardiometabolic) diseases. Furthermore, traffic noise is typically a weak risk factor for all-cause mortality. Finally, in the included studies, the correlation between TRAP and noise was generally low to moderate. Despite the relatively small number of studies that have evaluated potential confounding by traffic noise, the Panel therefore judged that it is unlikely that traffic noise has substantially affected TRAP associations with all-cause mortality.

The finding of associations between TRAP and all-cause mortality in substantially different populations, across different geographical regions, and by multiple research groups using a variety of exposure-assessment strategies, lends further support to the presence of an association. If different approaches—with different types of biases—all point to the same conclusion, the confidence is strengthened, which is defined as *triangulation* in epidemiology (Pearce et al. 2019). Studies have addressed temporal trends in air pollution and mortality using a variety of approaches, including time-varying exposure models and assessment of the stability of exposure surfaces in those studies that relied on exposure in specific years. Stability of spatial contrast in exposure in periods of over a decade has been documented in several studies in Europe and North America (Cesaroni et al. 2012; Eeftens et al. 2011; Pope et al. 2002). The large majority of studies for NO_2 and EC were rated as high traffic specificity studies. RRs were elevated for both the high and moderate traffic specificity studies, with somewhat higher RRs for the high traffic specificity studies. Other additional subgroup analyses (e.g., on whether adjustment for smoking was performed) supported the robustness of the findings. The 11 studies on indirect traffic measures (distance and density) were consistent with the presence of an association of TRAP with all-cause mortality. Considering the summary estimates of the meta-analysis, the robustness of the findings, the number of well-designed studies accounting for important biases, and the consistency of findings across geographical areas, the Panel judged a high level of confidence in the presence of an association between TRAP and all-cause mortality.

Summary of Narrative Assessment for TRAP and All-Cause Mortality

The primary meta-analysis supplemented with additional analyses provided clear evidence of the presence of an association between TRAP and all-cause mortality. The studies on pollutants not included in the meta-analyses and the studies with indirect traffic measures (distance and density measures) supported this association. The Panel therefore had high confidence in an association between long-term exposure to TRAP and all-cause mortality.

11.2.6 RISK OF BIAS ASSESSMENT

Table 11.4 shows a summary of the results of the risk of bias assessment for the studies that were included in the primary meta-analysis. Appendix Table 11A-2 shows the risk of bias assessment for individual studies. Table 11.4 summarizes the risk of bias assessment on a study level and for all pollutant–study pairs. In total, 20 studies were identified with generally multiple pollutants per study, resulting in a total of 51 pollutant–all-cause mortality pairs. For most domains, most studies were rated as low to moderate risk of bias. The exception was the confounding domain where about 25% of the studies were rated as high risk of bias. This was due to the

Table 11.3. Key Study Characteristics of Cohort Studies Included in the Systematic Review for All-Cause Mortality—Indirect Traffic Measures

Reference	Study Name	Location	Study Period	Sample Size	Age (years)	Sex	Traffic Measure	Effect Estimate (95% CI)[a]	Increment
Beelen 2008	NLCS-AIR	The Netherlands	1987–1996	117,528	Adults (18+)	Both	Density	1.05 (0.97–1.12)	335,000 vehicles/day
							Distance	1.02 (0.97–1.07)	<100 m to highway or <50 m to major road vs. higher
Beelen 2014	ESCAPE	Multiple cities, multiple countries	1985–2008	357,380	Adults (18+)	Both	Density	1.01 (0.98–1.05)	4,000 vehicle-km/day
Cakmak 2019	1991 CanCHEC	Canada	1991–2011	2,644,370	Adults (18+)	Both	Distance	1.57 (1.44–1.72)	<475 vs. >1,583 m
								1.10 (1.07–1.13)	475–1,152 vs. >1,583 m
								1.04 (1.03–1.05)	1,152–1,583 vs. >1,583 m
Cesaroni 2013	Rome Longitudinal	Rome, Italy	2001–2010	1,265,058	Adults (18+)	Both	Density	1.01 (0.99–1.03)	>6,650 vs. <250 vehicle-km/day
								1.01 (0.99–1.02)	3,230–6,650 vs. <250 vehicle-km/day
								0.99 (0.98–1.01)	1,630–3,220 vs. <250 vehicle-km/day
								1.04 (1.03–1.06)	250–1,620 vs. <250 vehicle-km/day
					Adults (18+)	Both	Distance	1.03 (1.01–1.05)	50–100 vs. >250 m
								1.03 (1.01–1.05)	100–150 vs. >250 m
								1.02 (1.00–1.04)	150–250 vs. >250 m
Finkelstein 2005	Hamilton Pulmonary Cohort[b]	Hamilton, Ontario, Canada	1985–2001	5,228	Adults (18–64)	Both	Distance	1.18 (1.02–1.38)	<50 m from major road or <100 m from highway vs. higher
Gehring 2006	SALIA	North Rhine-Westphalia, Germany	1985–2003	4,230	Adults (18–64)	Female	Distance	1.29 (0.93–1.78)	<50 vs. >50 m
Heinrich 2013	SALIA	North Rhine-Westphalia, Germany	1985–2008	4,615	Adults (18–64)	Female	Distance	1.42 (1.12–1.79)	<50 vs. >50 m

Continues next page

Table 11.3 (*Continued*). Key Study Characteristics of Cohort Studies Included in the Systematic Review for All-Cause Mortality—Indirect Traffic Measures

Reference	Study Name	Location	Study Period	Sample Size	Age (years)	Sex	Traffic Measure	Effect Estimate (95% CI)[a]	Increment
Jerrett 2009	Toronto Respiratory Cohort[b]	Toronto, Canada	1992–2002	2,360	Adults (18+)	Both	Distance	1.19 (0.92–1.53)	<50 m from major road or <100 m from highway vs. higher
Medina-Ramón 2008	Worcester Heart Failure[b]	Worcester, Massachusetts, United States	2000–2005	1,389	Older Adults (65+)	Both	Density	1.15 (1.05–1.25)[c]	1,379 vehicle-km/day
								0.98 (0.91–1.05)[c]	2,008 m
Raaschou-Nielsen 2012	DDCH	Copenhagen and Aarhus, Denmark	1993–2009	52,061	Adults (18–64)	Both	Density	0.94 (0.85–1.05)[c]	1 vehicle-km/day
							Distance	1.01 (0.99–1.03)	<50 vs. >50 m
Wilker 2013	Boston Stroke Patients[b]	Boston, Massachusetts, United States	1999–2012	1,683	Adults (18+)	Both	Distance	1.20 (1.01–1.43)[c]	<100 vs. >400 m
								1.08 (0.88–1.31)[c]	100–200 vs. >400 m
								0.99 (0.82–1.2)[c]	200–400 vs. >400 m

[a] Effect estimates are expressed as relative risk or hazard ratio.

[b] Indicates a patient population.

[c] Log transformed.

subdomain adjustment for potential important confounders. Most of the administrative cohort studies were rated as high risk of bias because of a missing adjustment for individual smoking or BMI. Several studies provided additional support that smoking, BMI, or both were not important confounders, but this did not result in a moderate risk of bias assessment in most cases. This applies to the Rome Longitudinal study (Badaloni et al. 2017; Cesaroni et al. 2013), which did not have information on individual smoking and BMI. The Cesaroni study provided evidence that adjusting for pre-existing comorbidities related to smoking habits or BMI, based on hospital records of COPD and hypertensive heart disease (diabetes), did not affect the estimates. The Badaloni study used the same population and did not repeat this adjustment. Other studies with a high risk of bias were the Civitavecchia study (Bauleo et al. 2019), the Barcelona mega-cohort (Nieuwenhuijsen et al. 2018), and the English ONS-Longitudinal study (Hansell et al. 2016); although Hansell provided additional support that adjustment for small-area lung cancer rates did not affect the RRs. The rationale of the Panel for this strict assessment was to err on the side of caution with respect to confounding. The strict assessment allowed further analysis of effect estimates of studies rated low or moderate versus high risk of bias. It is important to stress that risk of bias assessment is an assessment of the potential risk of bias, not a determination of actual bias in an individual study (see Chapter 14). Risk of bias assessment for confounders furthermore does not specify in which direction the estimates may be biased, nor how large the bias might be if it exists at all. For example, in the Rome study, higher air pollution exposure was associated with a higher SES and therefore it is likely that a more favorable lifestyle is associated with higher air pollution exposure (Cesaroni et al. 2012). Bias due to insufficient adjustment for lifestyle is therefore likely toward the null in the Rome Longitudinal study.

The observation that only a small number of studies were deemed to be at high risk of bias for other domains is due to the similar design of the mortality cohort studies, which typically leverage existing registry data with little loss to

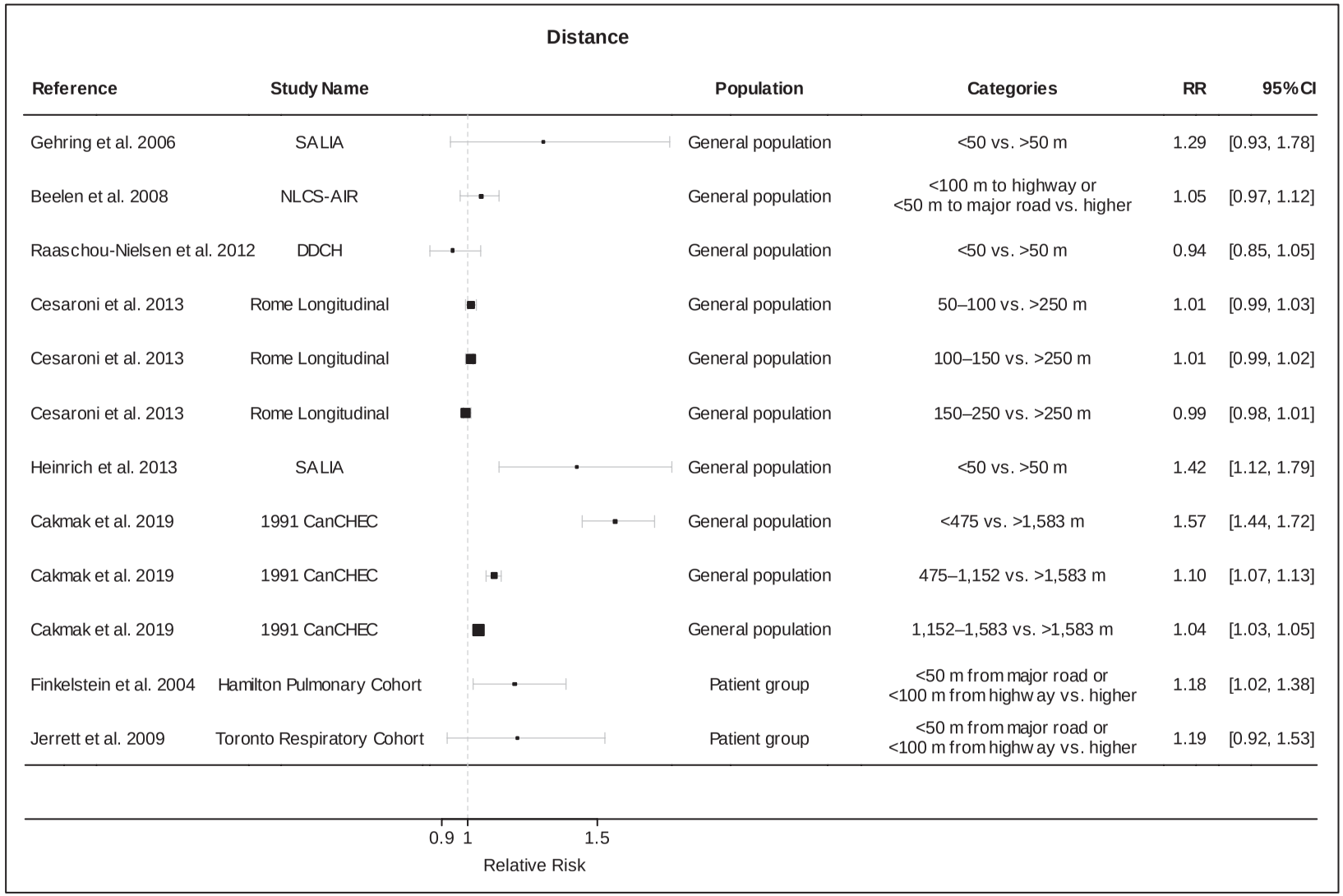

Figure 11.4. Association of distance to major roads and traffic density with all-cause mortality. Raaschou-Nielsen et al. (2012) (density) and Wilker et al. (2013) (distance) are not displayed in the plot because the estimates were log-transformed. The traffic density studies were all general population studies. *Figure continues next page.*

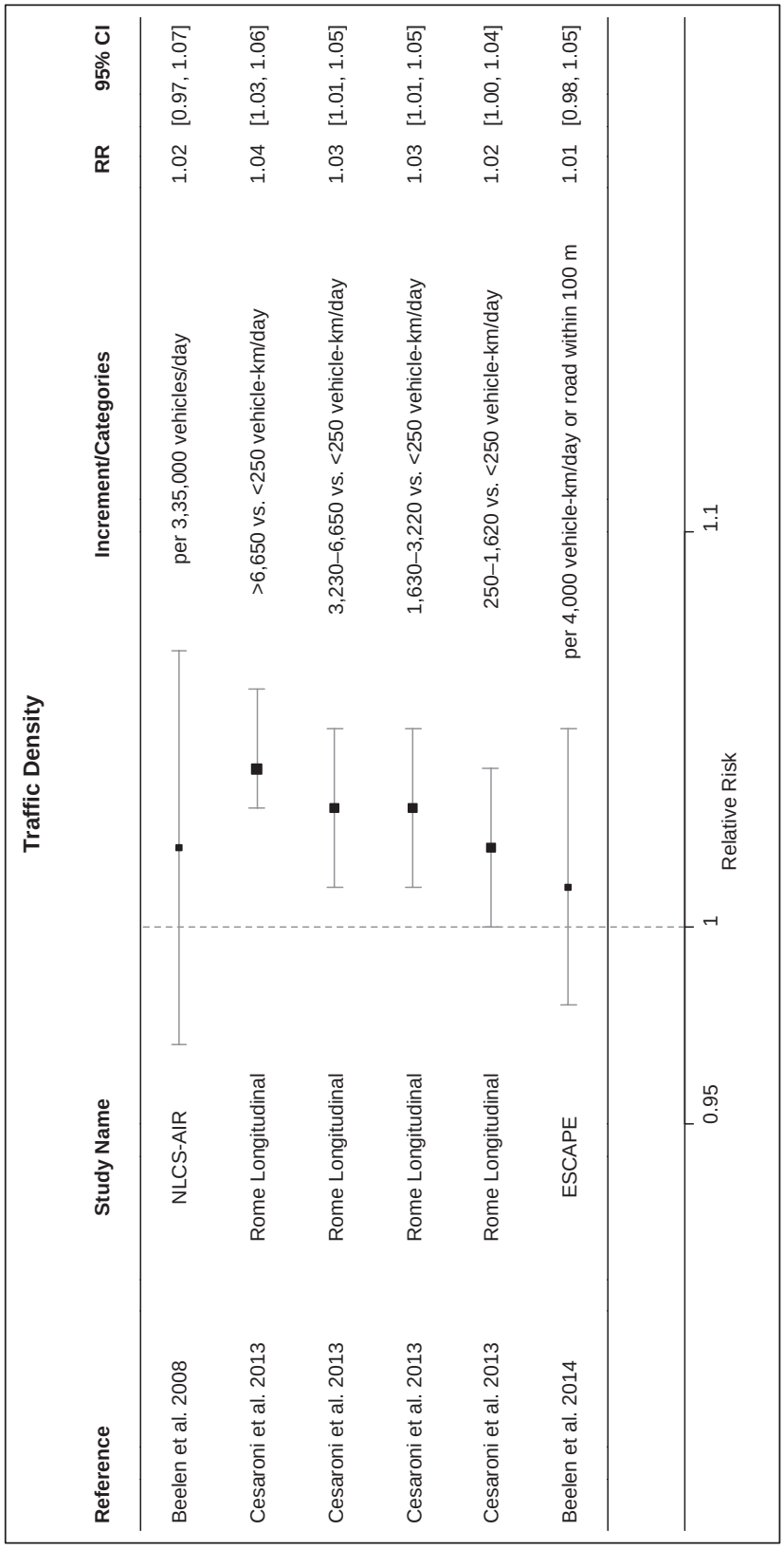

Figure 11.4. *(Continued).*

SIDEBAR 11.1 SUMMARY OF CRITICAL CONSIDERATIONS REGARDING THE SELECTED OUTCOMES AND STUDIES

- All selected studies on mortality were cohort studies, with outcome during follow-up determined by linkage to mortality registries. Mortality registries are generally complete, as is linkage of individuals to these registries. As a result, misclassification of outcome is not a major concern in studies of all-cause mortality.
- Studies of all-cause and nonaccidental (natural) mortality have been jointly analyzed. The rationale is that the fraction of nonaccidental causes of deaths is generally high (Chen and Hoek 2020).
- Despite the use of the standard International Classification of Diseases (ICD) in all studies, misclassification of cause of death has been documented to be potentially substantial. Misclassification may vary between countries, age groups (generally higher in older people), and cause of death (e.g., Alpérovitch et al. 2009; Ives et al. 2009). Difficulties in determining the underlying cause of death and the contributing causes is one reason for disagreement among different coders. Agreement among different coders has been shown to decrease with a more detailed level of ICD code (e.g., less agreement for ischemic stroke than for the broad circulatory mortality code). Misclassification between circulatory and respiratory mortality has been documented, leading some investigators to decide to analyze them together as cardiopulmonary mortality (Hawkins et al. 2009; Pope et al. 2004; Rutten and Broekhuizen 2018).
- The Panel analyzed mortality outcomes from broad disease groups (all circulatory, all respiratory diseases) and from more specific disease groups (IHD, stroke, COPD). The broad groups combine quite different diseases but are less prone to outcome misclassification.
- Many of the studies in the current review provide results related to more than one mortality outcome, and they report associations of the same outcome with multiple exposure measures related to TRAP (e.g., EC, NO_2). As such, the assessments are not fully independent.
- For all evaluated outcomes, underlying disease may have been present for many years prior to death. This applies to the respiratory and cardiovascular endpoints included in the review.

follow up for outcome measurement. As studies were evaluated extensively to ensure that their exposure assessment included a sufficiently specific TRAP exposure; all studies were rated as low risk of bias for the domain of exposure methods. About 40% of the studies were rated as moderate risk of bias, however, for a change in exposure status during the follow-up period. This assessment was typically applied when a study had a long follow-up period and exposure was assessed for only a limited part of the follow-up period, such as in the ESCAPE study where exposure was assessed for a year just after the end of follow-up. The assessment was moderate risk of bias on this domain for the ESCAPE study because additional support was provided that the spatial contrast was stable for periods of at least 10 years (Beelen et al. 2014).

11.2.7 CONFIDENCE ASSESSMENT OF THE BODY OF EVIDENCE

Table 11.5 provides the Panel's overall confidence assessment in the quality of the body of evidence. The table includes only the pollutants with three or more studies, namely those for which a meta-analysis was conducted. As all studies used the cohort study design, the Panel's initial confidence rating was moderate between mortality and all pollutants. Because only cohort studies were selected, no combined assessment across study designs was needed.

We first discuss four factors that may reduce confidence (downgrade factors). For the downgrade factor indirectness, all studies addressed the research question directly, and therefore no downgrade was applied. Next, factors that may increase confidence (upgrade factors) are discussed. The Panel decided a priori not to consider the upgrading factor large magnitude of the effect, as described in Chapter 5.

11.2.7.1 Downgrading Factor Risk of Bias

The overview of risk of bias ratings has been presented in Table 11.4. Appendix Table 11A-2 contains the risk of bias assessment for each individual study. Additional Materials to Chapter 11 contain all assessments.

Two of the eleven NO_2 studies included in the meta-analyses were listed as high risk of bias for confounding because of not adjusting for confounding by smoking and BMI, which the Panel deemed to be important a priori. The subgroup analysis with respect to risk of bias showed that robust associations between NO_2 and risk of mortality were found among those studies included in the low and moderate group combined (Figure 11.5). No remarkable difference between the low and moderate risk of bias subgroup and the high risk of bias group was found. As the high risk of bias group comprised only two studies, a formal comparison was not informative. For the other domains, including selection bias, even fewer studies were rated as high risk of bias; consequently analyses for the

Table 11.4. Summary of Risk of Bias Rating for Studies on All-Cause Mortality

Domain	Subdomain	Per Study			Per Pollutant–Study Pair		
		Low Risk	Moderate Risk	High Risk	Low Risk	Moderate Risk	High Risk
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	14	1	5	35	3	13
	Validity of measuring of confounding factors	18	2	0	44	7	0
	Control in analysis	18	2	0	49	2	0
	Overall	11	4	5	30	8	13
2. Selection bias	Selection of participants into the study	17	2	1	44	6	1
3. Exposure assessment	Methods used for exposure assessment	20	0	0	51	0	0
	Exposure measurement methods comparable across the range of exposure	20	0	0	51	0	0
	Change in exposure status	9	10	1	21	28	2
	Overall	9	10	1	21	28	2
4. Outcome measurements	Blinding of outcome measurements	20	0	0	51	0	0
	Validity of outcome measurements	20	0	0	51	0	0
	Outcome measurements	20	0	0	51	0	0
	Overall	20	0	0	51	0	0
5. Missing data	Missing data on outcome measures	19	0	1	50	0	1
	Missing data on exposures	19	0	1	49	0	2
	Overall	18	0	2	48	0	3
6. Selective reporting	Authors reported a priori primary and secondary study aims	20	0	0	51	0	0

low and moderate risk of bias subgroup showed similar associations as the primary meta-analysis including all studies.

Also, for the other pollutants, apart from the confounding domain, very few studies had a high risk of bias assessment; therefore the other domains are not discussed further. For $PM_{2.5}$ and EC two of twelve and three of eleven studies, respectively, in the meta-analysis were rated as high risk of bias due to missing important confounders in the analysis. In both cases, the estimates in the low and moderate subgroup were slightly higher than those in the high risk of bias subgroup.

For NO_x, one of the five studies in the meta-analysis was rated as high risk of bias due to missing important confounders in the analysis (Additional Materials to Chapter 11). The effect estimate in the low and moderate subgroup was above unity (RR 1.06; 95% CI: 0.97–1.17). The estimates in the low and moderate subgroup were higher than in the single high risk of bias study.

For PM_{10}, three of the six studies in the meta-analysis were rated as high risk of bias due to missing important confounders in the analysis. The effect estimates in the low and moderate risk of bias group were above unity, but with CIs including unity (RR 1.05; 95% CI: 0.92–1.19). The estimates in the low and moderate risk of bias group were only slightly smaller than in the high risk of bias subgroup, considering the CI (RR 1.08; 0.80–1.44).

For Cu and Fe in $PM_{2.5}$ there were just three studies, making the assessment difficult. For both components, the study carrying most of the weight was rated as high risk of bias (Badaloni et al. 2017). For Cu, this was the only study with a positive association, hence a downgrade was appropriate. For Fe, the high risk of bias study effect estimate did not differ substantially from those of the other two studies, although the Panel acknowledged that this assessment was uncertain.

Overall, the risk of bias assessment did not suggest a need to downgrade the confidence in the quality of the body of evidence between risk of mortality and exposure to these pollutants included in the meta-analysis, except for Cu. This judgment was supported by the previously discussed finding

Table 11.5. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and All-Cause Mortality[a]

	High ++++ Moderate +++ Low ++ Very low +		Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ (N = 11)	0	0	0	0	+	0	+	++++ (High)
	Rationale	Cohort design initially rated as moderate.	Few studies high RoB and robust effect estimates in low and moderate RoB studies.	High heterogeneity (I^2 = 83%) due to magnitude not direction.	Sample size met, and confidence interval does not include unity.	No evidence found in plot and test.	Clear evidence of plausible shape of ERF (Cesaroni 2013; Crouse 2015; Dirgawati 2019; Hvidtfeldt 2019; Raaschou-Nielsen 2012).	Confounding in both directions possible.	Across geographic regions robust effect.	
NO_x	Cohort	+++ (N = 5)	0	0	–	0	+	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	Few studies serious RoB and robust effect estimates in low and moderate RoB studies.	High heterogeneity (I^2 = 86%) mostly due to magnitude not direction.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible, no clear evidence.	Clear evidence of plausible shape of ERF (Beelen 2014; Dirgawati 2019; Nafstad 2004; Stockfelt 2015).	Confounding in both directions possible.	Too few studies to assess robustness across geographic regions.	
EC	Cohort	+++ (N = 11)	0	0	0	0	+	0	0	++++ (High)
	Rationale	Cohort design initially rated as moderate.	Few studies serious RoB and robust effect estimates in low and moderate RoB studies.	High heterogeneity (I^2 = 84%) due to magnitude not direction.	Sample size met and estimate consistent with an association.	Asymmetry in plot and test, unlikely due to publication bias.	Clear evidence of plausible shape of ERF (Dirgawati 2019; Hansell 2016; Hvidtfeldt 2019).	Confounding in both directions possible.	Across geographic regions insufficient evidence for a robust effect.	

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Table 11.5 (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and All-cause Mortality[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
PM_{10}	Cohort	+++ (N = 6)	0	0	–	0	+	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	Three of six studies high RoB. Fairly robust effect estimates in low and moderate RoB studies.	High heterogeneity (I^2 = 86%) due to magnitude not direction.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible, no clear evidence.	Clear evidence of plausible shape of ERF (Beelen 2014; Hvidtfeldt 2019).	Confounding in both directions possible.	All studies European, no consistency check possible.	
$PM_{2.5}$	Cohort	+++ (N = 12)	0	0	0	0	+	0	0	++++ (High)
	Rationale	Cohort design initially rated as moderate.	Few studies serious RoB and robust effect estimates in low and moderate RoB studies.	Moderate heterogeneity (I^2 = 51%) due to magnitude not direction.	Sample size met, and confidence interval does not include unity.	No evidence found in plot and only borderline significant test, unlikely due to publication bias.	Clear evidence of plausible shape of ERF (Beelen 2014; Cesaroni 2013; Dirgawati 2019; Hvidtfeldt 2019).	Confounding in both directions possible.	Insufficient evidence for robustness across geographic regions.	
Cu - $PM_{2.5}$	Cohort	+++ (N = 3)	–	0	0	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	One study with high RoB which is the only study with an effect estimate above unity.	Low heterogeneity (I^2 = 0%) mostly due to magnitude not direction.	Sample size met and confidence interval includes unity, but confidence interval precise.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	All studies European, no consistency check possible.	

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Table 11.5 (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and All-cause Mortality[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
Fe - $PM_{2.5}$	Cohort	+++ (N = 3)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	One study with high RoB with similar effect estimates as the two low - moderate RoB studies.	Low heterogeneity (I^2 = 46%) due to magnitude not direction.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	All studies European, no consistency check possible.	

ERF = exposure–response function; RoB = risk of bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

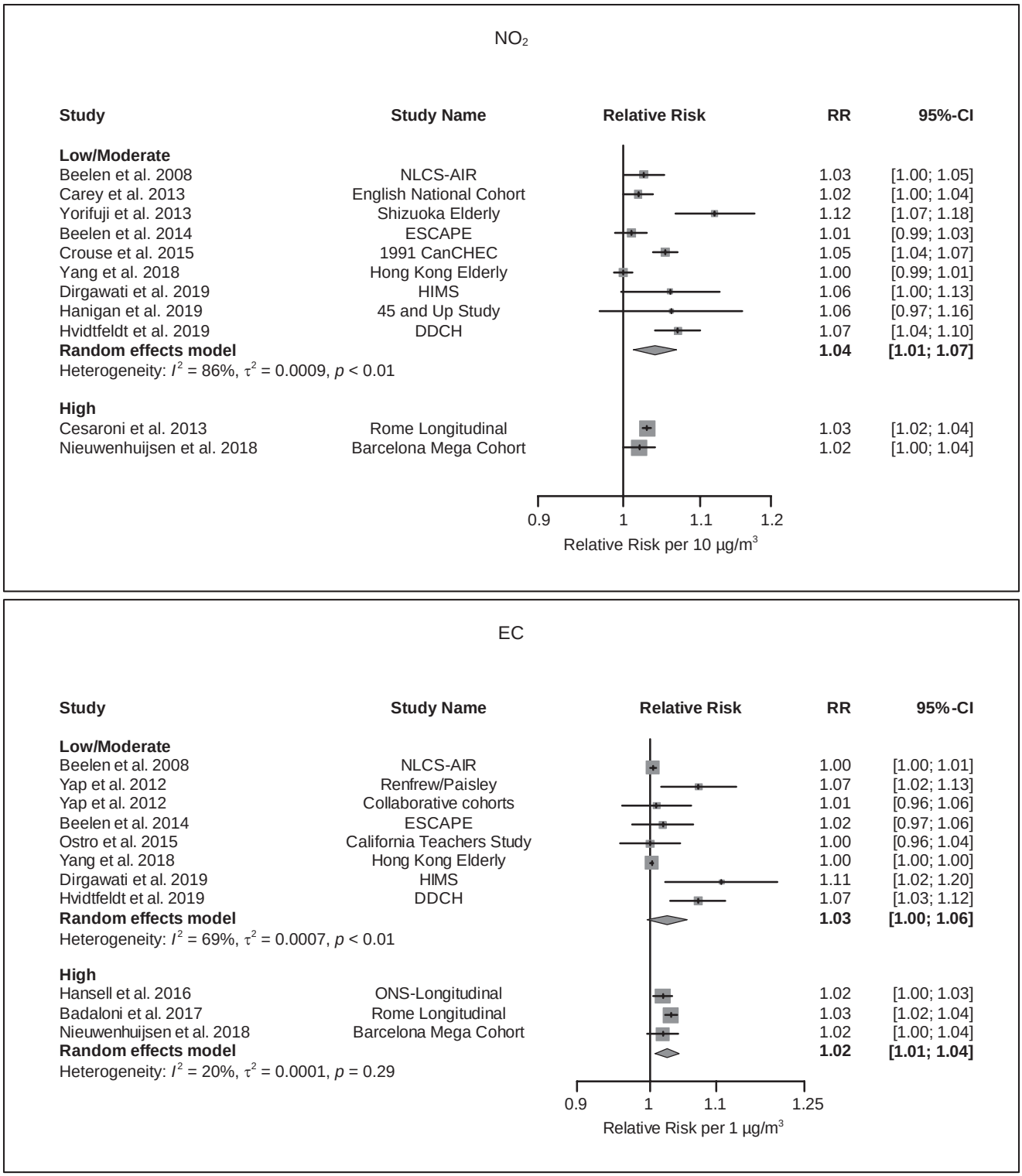


Figure 11.5. Association between NO_2, EC, and $PM_{2.5}$ and all-cause mortality: meta-analysis by risk of bias confounding. *Figure continues next page.*

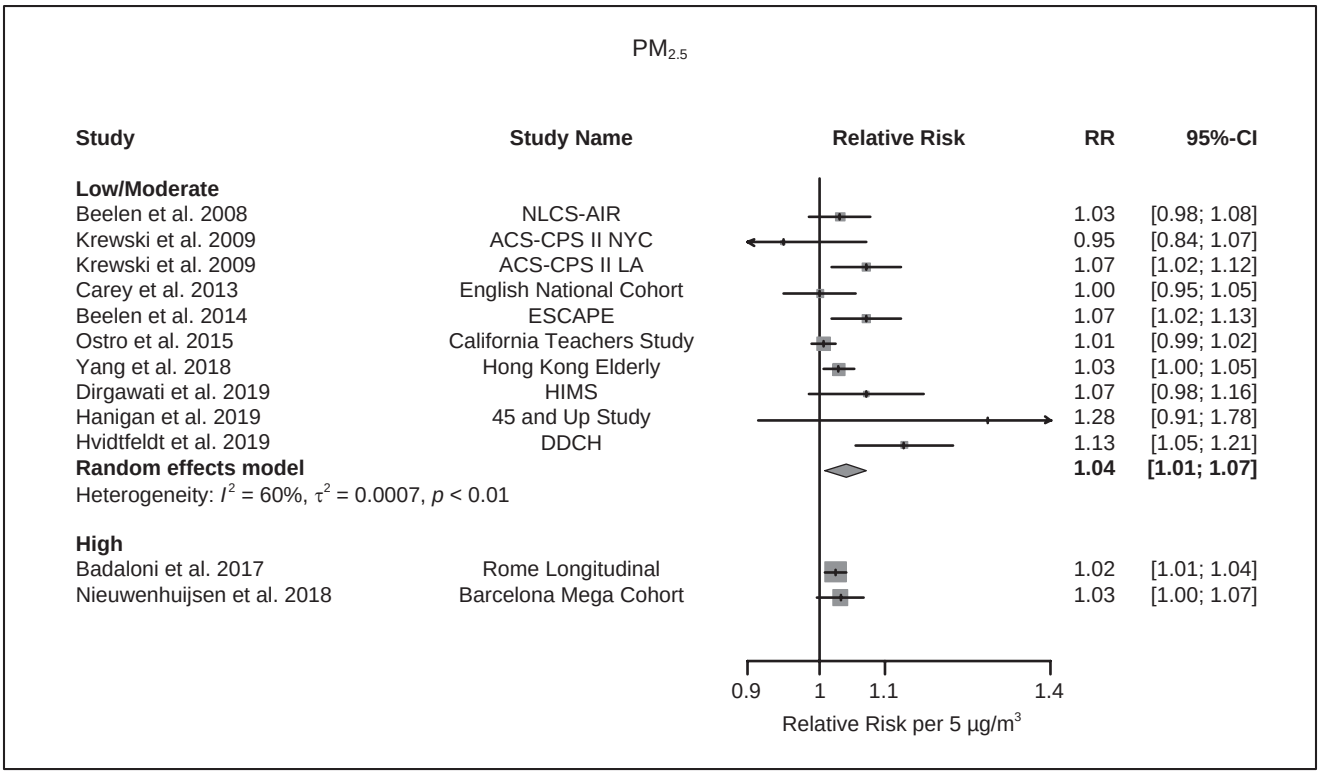


Figure 11.5. *(Continued).*

of robust associations in the group of studies with adjustment for individual smoking habits (Appendix Figure 11A-4).

11.2.7.2 Downgrading Factor Unexplained Inconsistency

The Panel observed a high degree of heterogeneity (I^2 = 83%) of effect estimates across studies for NO_2 (Figure 11.2). Several effect estimates were not included in the CIs of other studies. The high I^2 value derives from the nonoverlapping CIs for some very large studies. Effect estimates in individual studies ranged from 1.00 to 1.12, which can all be interpreted as small effect estimates. The RR for the Shizuoka Elderly study (1.12) is relatively high compared with the other studies (Yorifuji et al. 2013). RRs were all above unity, except for the Hong Kong Elderly study (Yang et al. 2018). The Panel did not downgrade the evidence for heterogeneity, because the heterogeneity derived from the variation between estimates and their precision and not the direction of the association. Furthermore, all effect estimates can be considered as small in magnitude. The I^2 statistic is high because it considers relative differences across effect estimates. Some of the heterogeneity was explained by the a priori chosen stratification variables, such as geographical region and risk of bias on selection bias. The heterogeneity measures were substantially smaller in the largest subgroup of studies for these stratifications: (European studies or low or moderate risk of bias) compared with values reported for the full population. The Panel further noted that the overall confidence assessment is about the confidence that an association between NO_2 and mortality is present, not about the exact magnitude of that association. In the latter case, a downgrade would be appropriate.

For EC, a high degree of heterogeneity (I^2 = 84%) of effect estimates across studies was found, similar to what was reported for NO_2. Effect estimates in individual studies ranged from 1.00 to 1.11, with several effect estimates not included in the CI of other studies. Some of the heterogeneity is likely due to the uncertainty due to the conversion of the different metrics used to represent EC. RRs were above unity, except for the California Teacher's study (Ostro et al. 2015), and the NLCS-Air study (Beelen et al. 2008). The Panel did not downgrade the evidence for heterogeneity, because the heterogeneity derived primarily from the magnitude of the effect estimates and not the direction of the association.

For $PM_{2.5}$ a moderate degree of heterogeneity (I^2 = 51%) of effect estimates across studies was found, much smaller than for NO_2. Effect estimates in individual studies ranged from 0.95 to 1.28, with several effect estimates not included in the CI of other studies. RRs were above unity, except for the New York ACS-CPS II (Krewski et al. 2009) and the English National cohort (Carey et al. 2013). The Panel did not downgrade the evidence for heterogeneity, because the heterogeneity is moderate and derives primarily from the

variation between predominantly positive estimates and their precision—not from the direction of the association.

For NO_x, PM_{10}, and Fe a high degree of heterogeneity of effect estimates across studies was found, for Cu a moderate degree. Because of the small number of studies, further evaluation is difficult. For NO_x, four of five studies showed positive associations with different magnitude. The Panel did not downgrade the evidence for heterogeneity for any of these pollutants, because the heterogeneity derived primarily from the magnitude of the effect estimates and not from the direction of the association. For NO_x and PM_{10} heterogeneity was explained for a large part by year of publication and risk of bias related to confounding (Additional Materials to Chapter 11).

11.2.7.3 Downgrading Factor Imprecision

For all pollutants included in the meta-analyses, the overall sample size (number of people) of all studies was much larger than the minimum sample size specified in the protocol as being needed for an informative judgement. Several individual studies already included more people. For NO_2, $PM_{2.5}$, and EC several large cohort studies with very narrow CIs were included (Figure 11.2). The combined meta-analytic estimates for NO_2, $PM_{2.5}$, and EC had narrow CIs not including unity as well, although they were wider than for some of the individual studies such as the Rome Longitudinal study (Cesaroni et al. 2013) and the English National Cohort (Carey et al. 2013). The wider CI of the combined summary estimate reflects heterogeneity. For NO_x, PM_{10}, and the nontailpipe pollutant Fe the combined meta-analytic estimates had wide CIs related to the smaller number of studies for these components, and all CIs clearly included unity. Therefore, the Panel downgraded the evidence because of imprecision for NO_x, PM_{10}, and Fe. The Panel noted that this choice to downgrade is debatable, as the width of the meta-analytical CI is more affected by heterogeneity than by lack of precision of individual studies. However, as the Panel did not downgrade for heterogeneity, the Panel thought it would be appropriate to downgrade for imprecision instead. The rationale was that if the heterogeneity was so large that the summary estimate could be consistent with an estimate above and below unity, the confidence in an association was less. The evaluation was therefore focused on the summary estimate. No downgrade was applied for NO_2, $PM_{2.5}$, and EC because CI did not include unity, or the estimate was borderline significant (EC). The nontailpipe pollutant Cu was not downgraded because the CI was considered narrow according to the protocol, although it included unity.

11.2.7.4 Downgrading Factor Publication Bias

There were more than 10 studies for NO_2, EC, and $PM_{2.5}$; hence, funnel plots and Egger tests were produced (Figure 11.6). For NO_2, there was one study with a relatively large RR (Yorifuji et al. 2013). The largest RR was observed for a study with an average CI. The Egger test was nonsignificant. For EC, the funnel plot shows a nonsymmetric distribution and the Egger test was highly significant. There was one study with a relatively large effect estimate that also had the widest CI (Dirgawati et al. 2019). Studies with relatively wide CIs reported both significant (Dirgawati et al. 2019; Hvidtfeldt et al. 2019; Yap et al. 2012) and nonsignificant findings (Beelen et al. 2014; Ostro et al. 2015; Yap et al. 2012). For $PM_{2.5}$ there was one study with a large effect estimate, which also had a wide CI (Hanigan et al. 2019). The study with the second widest CI was the only study with a RR below unity. The funnel plot was more symmetric than that for NO_2, reflecting the lower heterogeneity. The Egger test was borderline significant. The hypothesis for publication bias is that statistically significant positive studies have a larger likelihood of being published. It is important, therefore, to note that the $PM_{2.5}$ RR in the 45 Year and Up study was actually not statistically significant (Hanigan et al. 2019).

It is difficult to judge whether observed asymmetry and a significant Egger test for EC are due to the high heterogeneity or to publication bias. Overall, the Panel judged that the observed asymmetry is more likely due to heterogeneity than to publication bias and did not downgrade for publication bias. This judgement is informed by the described pattern observed for the three pollutants. For EC, the study with the largest RR was a small study with a significant estimate (Dirgawati et al. 2019). For $PM_{2.5}$, a single study had a higher RR but as the RR from that study is nonsignificant, publication bias hardly explains that this study was published. The Panel noted that seven of the 11 EC studies also reported an NO_2 RR for which the Egger test was highly nonsignificant. The HIMS study had a nonremarkable NO_2 RR (Dirgawati et al. 2019). It is difficult to imagine a stronger mechanism for publication bias for EC studies compared with NO_2 and $PM_{2.5}$. The Panel a priori did not expect that in cohort studies publication bias would be a major issue, given the effort it requires to perform cohort studies, often including collaboration between different research groups including cohort owners, environmental epidemiologists, statisticians, and exposure scientists, an argument made in a recent World Health Organization (WHO) systematic review as well (Chen and Hoek 2020). This may be different when a new pollutant (e.g., UFPs) is added to an already fully developed study of exposure, covariate, and health outcome data.

For NO_x, PM_{10}, Cu, Fe, NO, UFPs, benzene, PM_{coarse}, and distance and traffic density measures, a formal assessment was not possible, because fewer than 10 studies were available. The pattern of associations does not suggest substantial publication bias. This judgement is also informed by the assessment for $PM_{2.5}$ and NO_2, pollutants with more studies.

11.2.7.5 Upgrading Factor Monotonic Exposure–Response Function

Appendix Table 11A-3 provides for all studies an assessment of the evidence about the exposure–response function. For

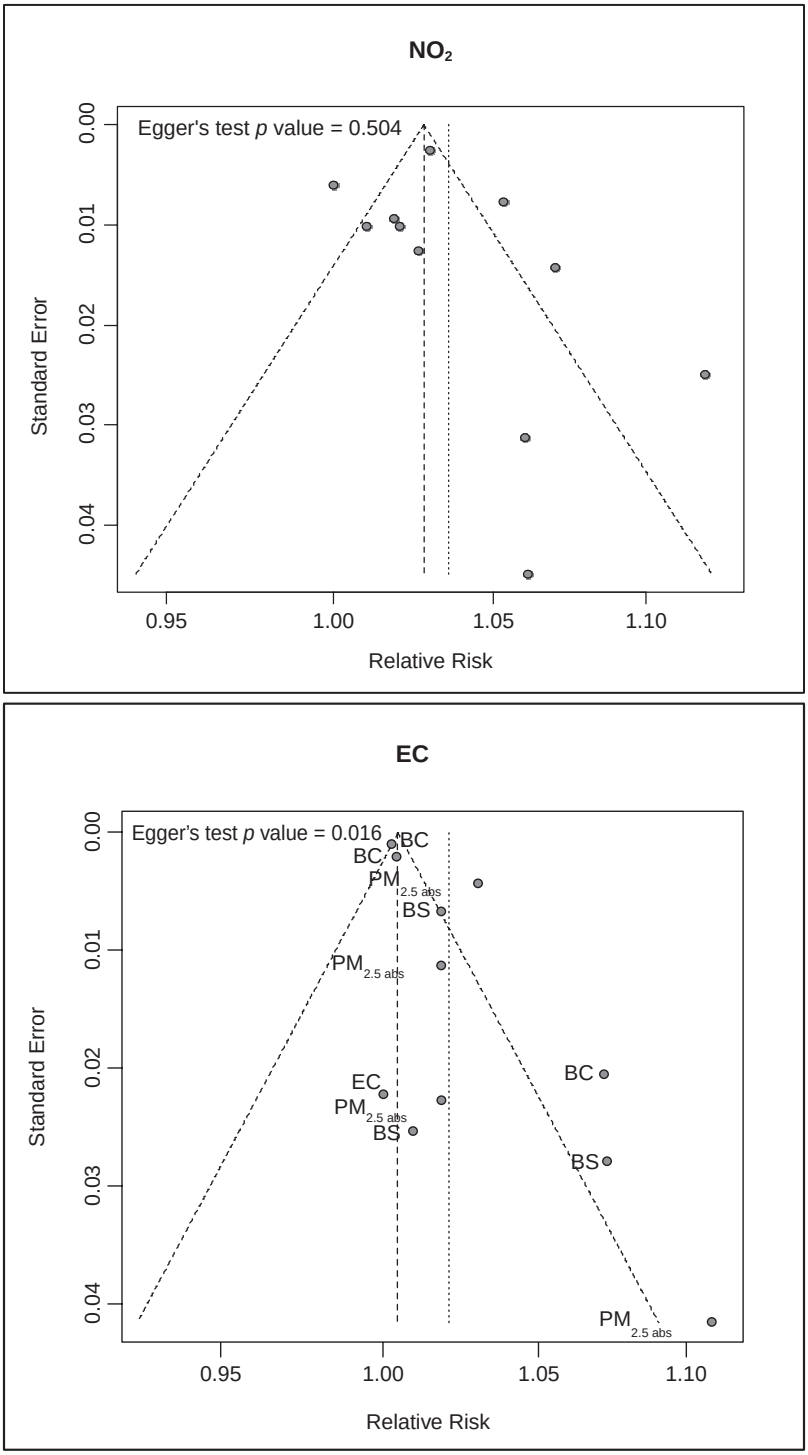


Figure 11.6. Funnel plots for NO_2, EC, and $PM_{2.5}$ and all-cause mortality. The vertical dashed line in the middle of the funnel shows the pooled fixed-effect estimate. As the Panel applied a random-effects model, the funnel plot also presents the pooled random-effects estimate with the dotted line. *Figure continues next page.*

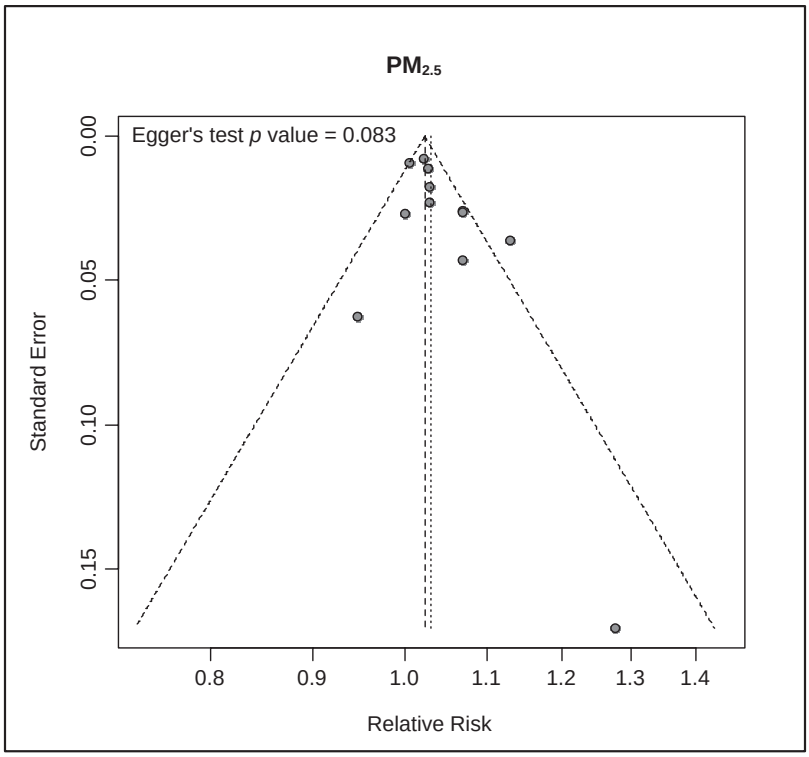


Figure 11.6. *(Continued).*

NO_2, NO_x, EC, PM_{10}, and $PM_{2.5}$, there was sufficient evidence of a plausible monotonic exposure–response function and hence an upgrade was applied. Table 11.5 documents which studies were considered to provide positive evidence for each pollutant. Sufficient evidence was interpreted as evidence from at least two studies in addition to a (borderline) significant meta-analytical summary estimate. Studies not included in the meta-analysis were also used for this judgment; for example, for the Rome Longitudinal cohort studies, an analysis of the shape of the concentration–response function was evaluated by Cesaroni and colleagues (Cesaroni et al. 2013), but not in Badaloni (2017) in the same study population. The Panel first assessed evidence from spline functions, supplemented with a statistical test of deviation from linearity when available. If splines were not presented, the Panel assessed categorical exposure analyses, preferably including a trend test to support a judgment of a plausible exposure–response function. Finally, the Panel accepted a statement of no deviation from a linear function in the text obtained with an appropriate nonparametric procedure. The Panel did not accept a statement of no deviation from linear if the linear association was null (e.g., in the ESCAPE study [Beelen et al. 2014], we did not consider NO_2, EC, and PM_{coarse} as contributing evidence of a monotonic exposure–response function).

11.2.7.6 Upgrading Factors Potentially Shifting the RR Toward the Null

Associations between lifestyle covariates, such as smoking and BMI, and air pollution differ in direction in specific populations. In Canadian national surveys, participants with higher air pollution exposures tended to have healthier lifestyles; and therefore, RRs for mortality may be underestimated when no adjustment is made for lifestyle covariates (Shin et al. 2014). In a Netherlands national survey, smoking and being overweight were more prevalent among participants with high air pollution exposure (Strak et al. 2017), resulting in an upward bias when no adjustment is made for smoking and BMI. In a survey within the U.S. Medicare study, air pollution exposure was not related to smoking (Di et al. 2017). Some studies noted an increase of effect estimates after adjusting more fully for available confounders in the cohort such as the Rome Longitudinal cohort studies (Cesaroni et al. 2013), whereas other studies reported smaller RRs after adjusting for more confounders at an individual- or area-level (Beelen et al. 2014; Carey et al. 2013; Hvidtfeldt et al. 2019). Because of the difference in direction of potential bias across populations, the Panel did not upgrade the evidence.

We considered the impact of measurement error in exposure on RRs to be too complex to consider an upgrade. Outcome misclassification is difficult to judge, but as outcome determination is based on registries, it is unlikely to be associated with important bias. An upgrade was, however, not considered appropriate.

11.2.7.7 Upgrading Factor Consistency

The Panel found positive associations for NO_2 in the four identified geographical areas (Western Europe, Asia, North America, and Australia–New Zealand), although the combined estimate differed in magnitude across regions. In areas with fewer than three studies (North America and Australia–New Zealand), the Panel assessed the individual studies. The Panel upgraded the evidence for consistency for NO_2. The Panel did not require identical effect estimates across regions, as it is plausible that differences in population and mean TRAP levels, among other factors, contributed to differences in magnitude. Most NO_2 studies were published after 2008; hence the Panel could not assess consistency across time periods. Generally positive associations were found in the five patient studies representing a potentially sensitive subgroup, but they had wider CIs compared with the general population studies related to the smaller sample size.

For EC, nine out of the 11 studies were conducted in Europe (Yap et al. 2012 contributed two cohort-specific estimates). In the three remaining studies, positive associations were only found in the Australian study but not in the Hong Kong and the United States studies. The Panel did not think an upgrade of the evidence based on consistency was appropriate for EC.

For $PM_{2.5}$, the Panel found generally positive associations in the four identified geographical areas, but the evidence was not compelling, especially in the three North American studies. The small number of $PM_{2.5}$ studies from North America may seem counterintuitive, as the majority of generic $PM_{2.5}$ studies were conducted in North America (Chen and Hoek 2020; Pope et al. 2020). However, most of these studies exploited between-city contrasts of exposure and were considered not informative for assessing TRAP when applying our exposure framework. The small number of studies outside Europe limits the interpretation of differences across regions. The Panel did not upgrade the evidence for consistency for $PM_{2.5}$. More variable RRs with wider CIs compared with the general population studies were found in the few patient studies available.

11.2.7.8 Evaluation of Confidence for Combined Measures of TRAP

The Panel conducted separate assessments of the seven pollutants for which there were sufficient studies to conduct meta-analyses. Three assessments were high (NO_2, EC, and $PM_{2.5}$), two moderate (NO_x and PM_{10}), and two were low (Cu and Fe). Our overall confidence assessment for TRAP is high because the highest rating is high. The Panel noted that the pollutants with the largest number of studies (NO_2, EC, and $PM_{2.5}$) had the high confidence rating. The lower confidence assessments were derived for pollutants with substantially fewer than 10 studies. The meta-analytic summary estimates of these pollutants were also above unity, although with less precision. These other pollutants, as well as the indirect traffic measure studies, thus provided some additional support for the high confidence assessment between TRAP and all-cause mortality. In conclusion, the confidence in the quality of the body of evidence between TRAP exposure and all-cause mortality is high.

11.2.8 OVERALL CONFIDENCE ASSESSMENT

The confidence assessment of the narrative and the modified OHAT assessment both resulted in an assessment of high confidence. The overall evaluation of the Panel is therefore high confidence in the evidence for an association between TRAP and all-cause mortality.

11.3 CAUSE-SPECIFIC MORTALITY

This section follows the same structure as Section 11.2, that is, after documentation of results from primary and additional meta-analyses and indirect traffic measures, a narrative assessment is presented to assess confidence in the presence of an association. Informed by the risk of bias assessment, a modified OHAT assessment is presented, followed by the overall confidence assessment. This section is more concise, as many of the issues discussed in Section 11.2 also apply to the assessment of cause-specific mortality studies.

11.3.1 PRIMARY META-ANALYSIS

Appendix Tables 11B-1 to 11B-6 present a description of the studies on cause-specific mortality. Most studies have also reported associations for all-cause mortality (Table 11.2). As noted in Section 11.2, the evidence base includes cohort studies by multiple research groups in a wide variety of geographical locations and population groups. Sidebar 11.1 discusses methodological issues related to the outcome definitions. The definitions of the outcomes in terms of ICD codes have been provided in Chapter 5. In individual studies, the definitions of circulatory and respiratory mortality were consistent with these definitions, although not necessarily identical. IHD and stroke deaths were included in circulatory deaths in most studies. COPD is included in respiratory mortality in all studies.

Figure 11.7 shows the meta-analytical summary estimates for circulatory, respiratory, and lung cancer mortality for all pollutants with three or more studies. The number of studies included in the meta-analysis was about the same for circulatory ($N = 19$) and smaller for respiratory mortality ($N = 14$) compared with all-cause mortality ($N = 20$). Fewer studies

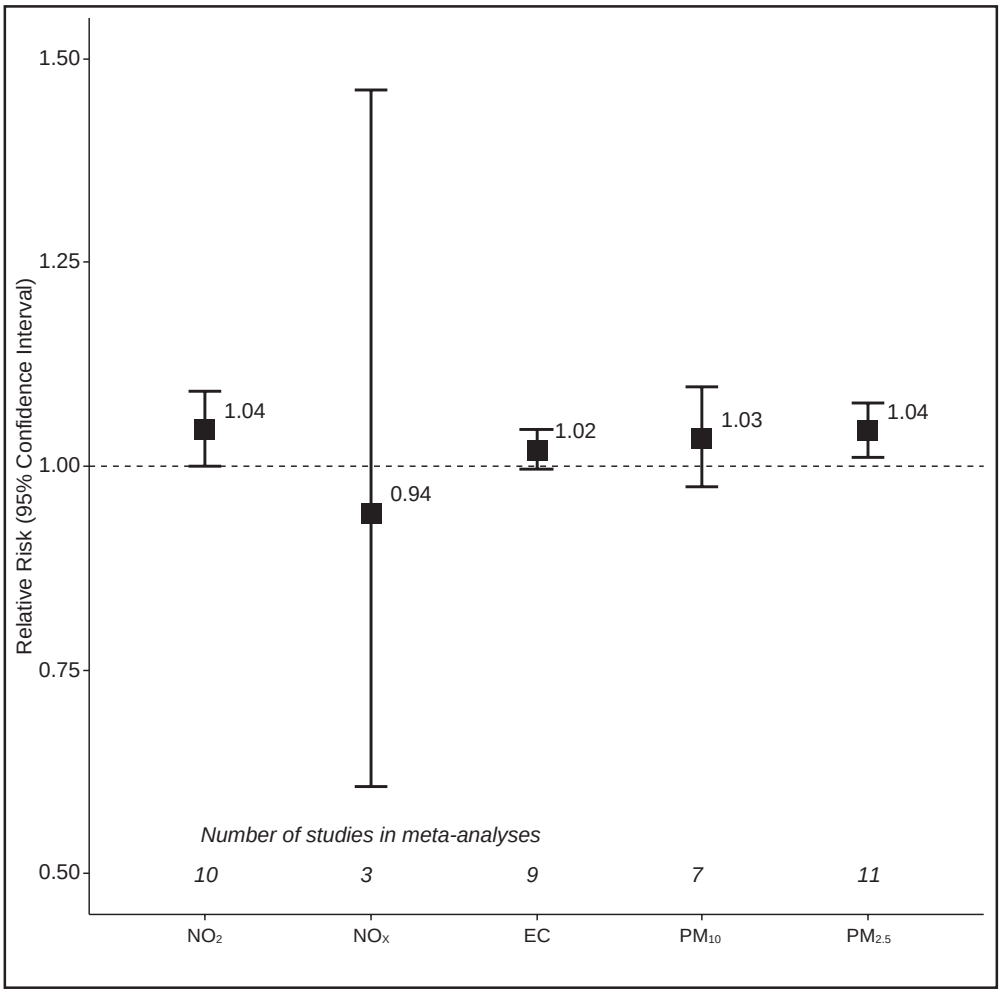


Figure 11.7. Meta-analysis of associations between traffic-related air pollutants and (A) circulatory, (B) respiratory, and (C) lung cancer mortality. The following increments were used: 10 µg/m^3 for NO_2, 20 µg/m^3 for NO_x, 1 µg/m^3 for EC, 10 µg/m^3 for PM_{10}, and 5 µg/m^3 for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure. *Figure continues next page.*

B. Respiratory Mortality

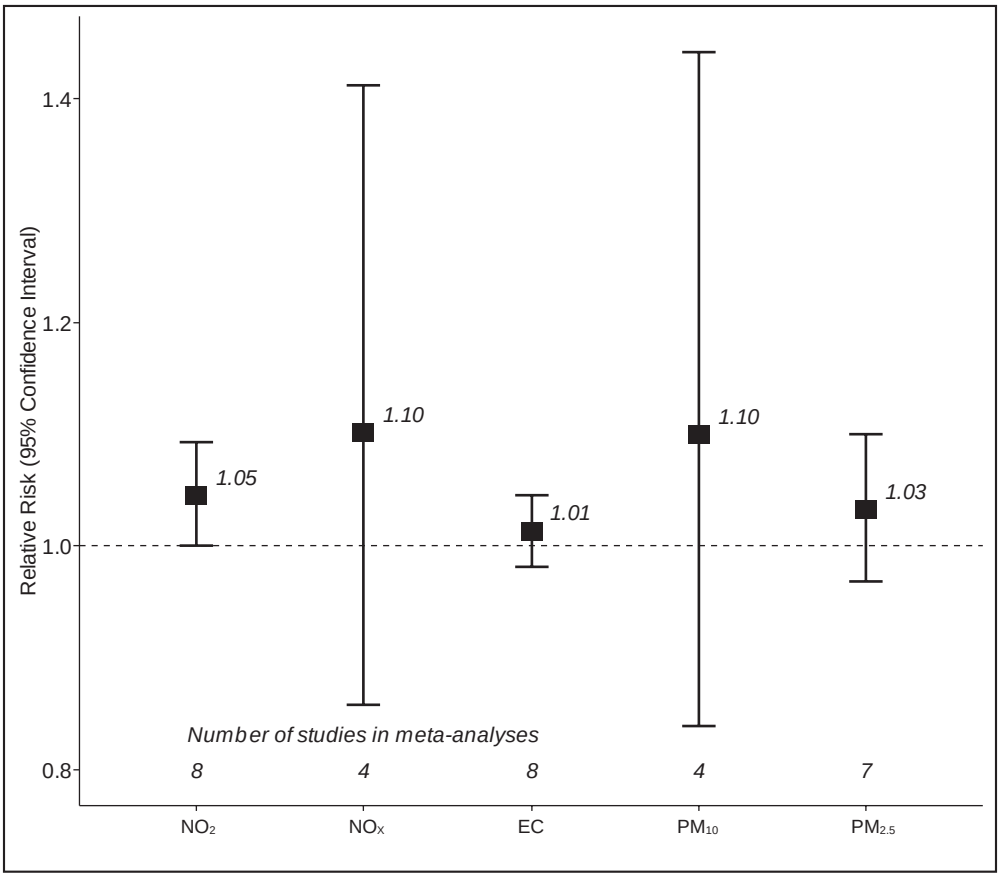


Figure 11.7. *(Continued).*

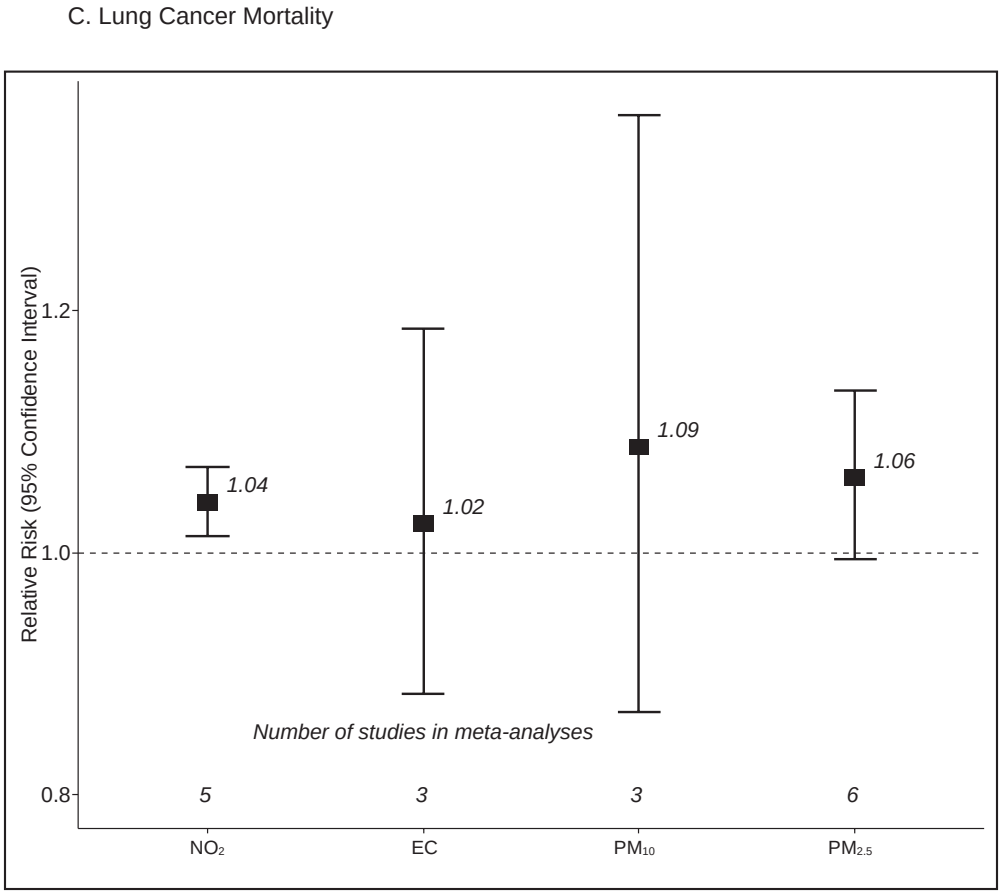


Figure 11.7. *(Continued).*

assessed lung cancer mortality ($N = 8$). Studies often reported effect estimates for multiple pollutants.

Most meta-analytical summary effect estimates were above unity for multiple pollutants for these three health outcomes. For circulatory mortality, the meta-analytical summary effect estimate was statistically significant for NO_2, EC, and $PM_{2.5}$, the pollutants with the largest number of studies, similar to all-cause mortality. For respiratory mortality, the meta-analytical summary effect estimate was (borderline) statistically significant only for NO_2. For lung cancer mortality, the meta-analytical summary effect estimate was statistically significant for NO_2 and (borderline) $PM_{2.5}$, pollutants with the largest number of studies. The meta-analytical summary effect estimate for NO_2 was 1.04 (95% CI: 1.00–1.09) for circulatory mortality, 1.05 (1.00–1.09) for respiratory mortality and 1.04 (1.01–1.07) for lung cancer mortality, expressed per 10-μg/m^3. The wider CIs compared with the all-cause mortality analyses may be partly related to the smaller number of studies and events per study in the cause-specific mortality analysis.

Figures 11.8 through 11.10 show the forest plots for NO_2, EC, and $PM_{2.5}$ for circulatory, respiratory, and lung cancer mortality. In Appendix Figure 11B-1 to 11B-3 forest plots are included for the other pollutants for which a meta-analysis was performed.

Most studies of NO_2, EC, and $PM_{2.5}$ and **circulatory mortality** showed positive associations, with RRs typically below 1.10 (Figure 11.8). Overall heterogeneity was high for NO_2 and moderate for EC and $PM_{2.5}$, related more to different RR magnitudes and less for the direction of the association. The Panel noted that the designation of high heterogeneity is related to expressing the heterogeneity metric on a relative scale. One could argue that all studies are consistent with a small relative risk estimate. None of the studies had a large impact on the meta-analytical summary effect estimate, as documented by the small weights in the forest plots. An additional

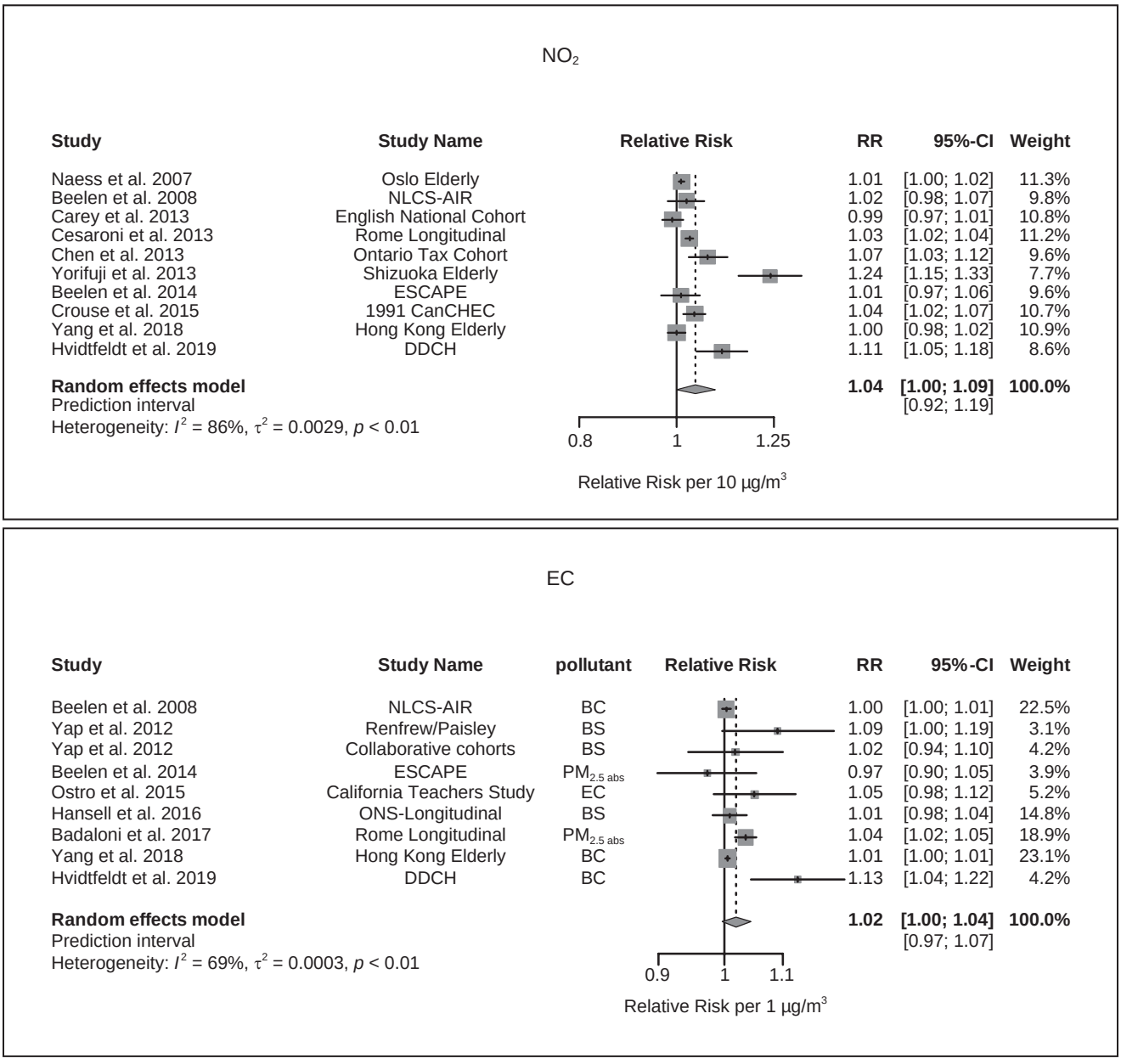


Figure 11.8. Association between NO_2, EC, and $PM_{2.5}$ and circulatory mortality: meta-analysis. *Figure continues next page.*

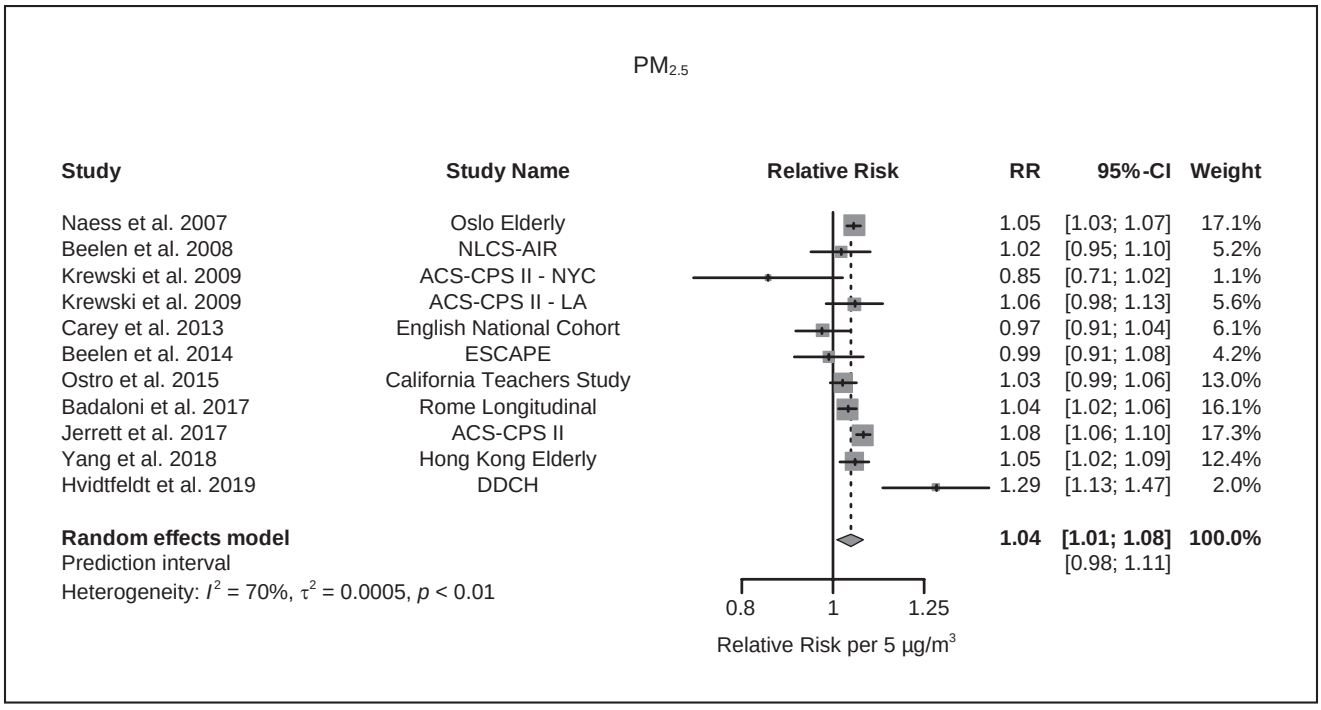


Figure 11.8. *(Continued).*

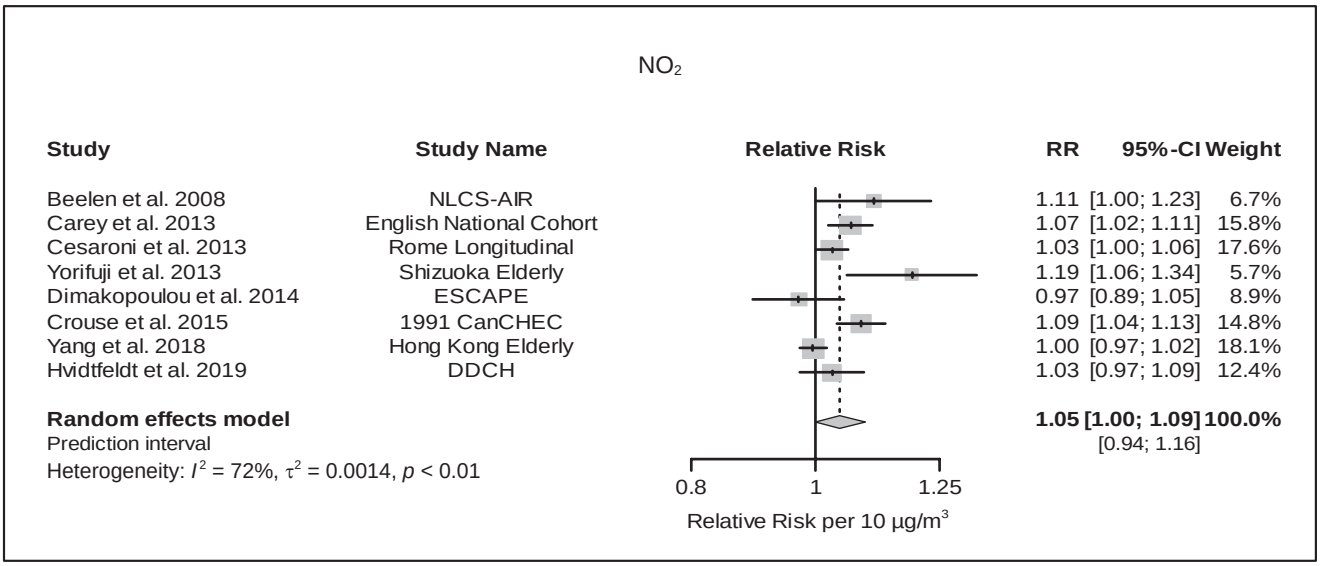
sensitivity analysis was conducted for $PM_{2.5}$ where the two city-specific ACS-CPS II estimates were removed (Krewski et al. 2009) because they overlap slightly with the nationwide ACS-CPS II analysis (Jerrett et al. 2017). The results were fairly similar (RR 1.06; 95% CI: 1.01–1.08) compared with the main results (1.04; 1.01–1.08) (Additional Materials to Chapter 11). As described in Chapter 5, the Panel decided to be inclusive; thus, the default was that studies were included unless the same study population was used in several publications on the same exposure–outcome pair. In the ACS-CPS II case, the two studies used a different exposure assessment.

Studies of **respiratory mortality** showed positive associations for NO_2 (Figure 11.9). Seven of the eight NO_2 studies showed positive associations; although several had wide CIs. Overall, heterogeneity was moderate, related primarily to magnitude of the RRs. Only three of the eight studies of EC and respiratory mortality showed positive associations. Three studies carried a large weight in the meta-analysis (Beelen et al. 2008; Hansell et al. 2016; Yang et al. 2018). Five of the seven $PM_{2.5}$ studies showed positive associations. Overall heterogeneity was moderate, despite a large estimate for the English National cohort (Carey et al. 2013).

Most studies of NO_2 and $PM_{2.5}$ and **lung cancer mortality** showed positive associations (Figure 11.10); although there were fewer studies than for circulatory mortality. Overall heterogeneity was low for NO_2 and moderate for $PM_{2.5}$, related more to RR magnitude and less so to direction. There were only three studies of EC and lung cancer mortality and only one of these showed a positive association.

Appendix Figures 11B-4 to 11B-6 show the summary plots and forest plots for IHD, stroke, and COPD mortality. These effect estimates were not included in the broad circulatory and respiratory mortality results discussed earlier. Meta-analytical summary effect estimates were positive for all pollutants included in the meta-analysis of **IHD mortality** (Appendix Figure 11B-4). The meta-analytical summary estimate for the six studies of NO_2 and IHD mortality was 1.05 (95% CI: 1.03–1.08) per 10-µg/m^3, with all studies except the ESCAPE study (Beelen et al. 2014) showing RRs above 1. Overall heterogeneity was moderate and the large Rome Longitudinal study contributed 69% to the meta-analytical summary effect estimate for NO_2 (Cesaroni et al. 2013). The meta-analytical summary effect estimate for the five studies of EC was 1.05 (0.99–1.11) per 1-µg/m^3. The meta-analytical summary estimate for the seven studies of $PM_{2.5}$ was 1.07 (1.04–1.10) per 5-µg/m^3. For $PM_{2.5}$ and EC, all studies except the ESCAPE study (Beelen et al. 2014), showed RRs above 1. Overall heterogeneity was high for EC and low for $PM_{2.5}$.

The meta-analytical summary estimate for the six studies of NO_2 and **stroke mortality** was 1.01 (95% CI: 0.98–1.04) per 10-µg/m^3, with most studies showing estimates close to unity (Appendix Figure 11B-5). The three studies of $PM_{2.5}$ and stroke mortality showed positive associations, with a combined RR of 1.04 (1.01–1.07) per 5-µg/m^3. The large Rome



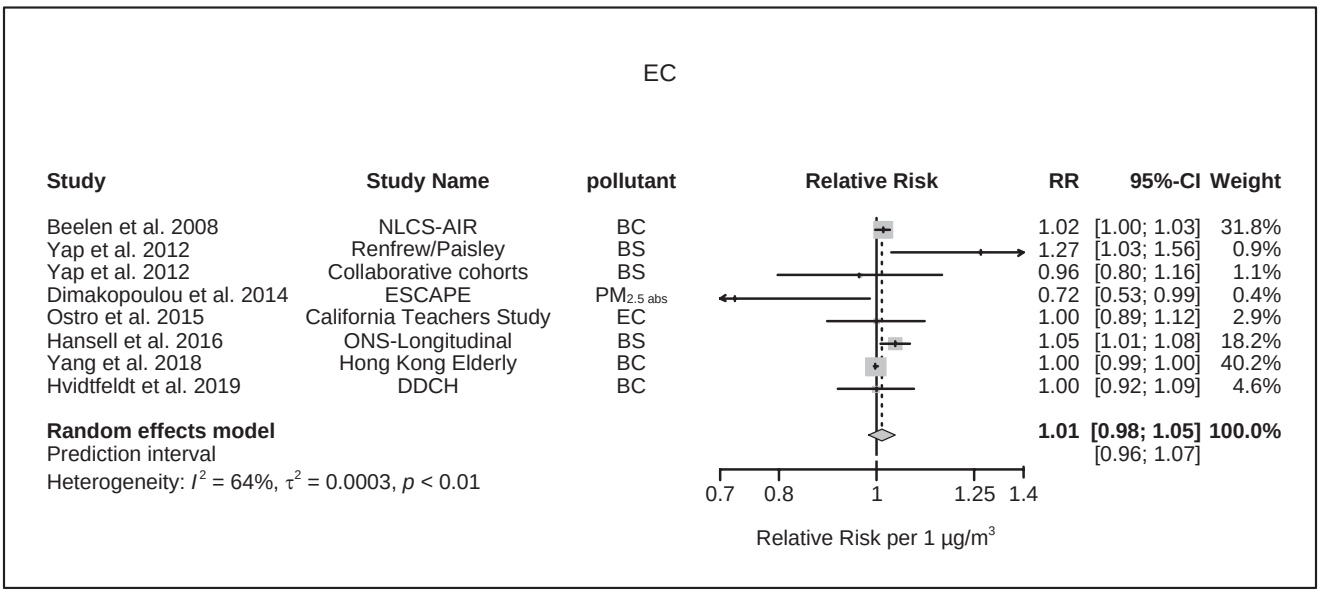


Figure 11.9. Association between NO_2, EC, and $PM_{2.5}$ and respiratory mortality: meta-analysis. *Figure continues next page.*

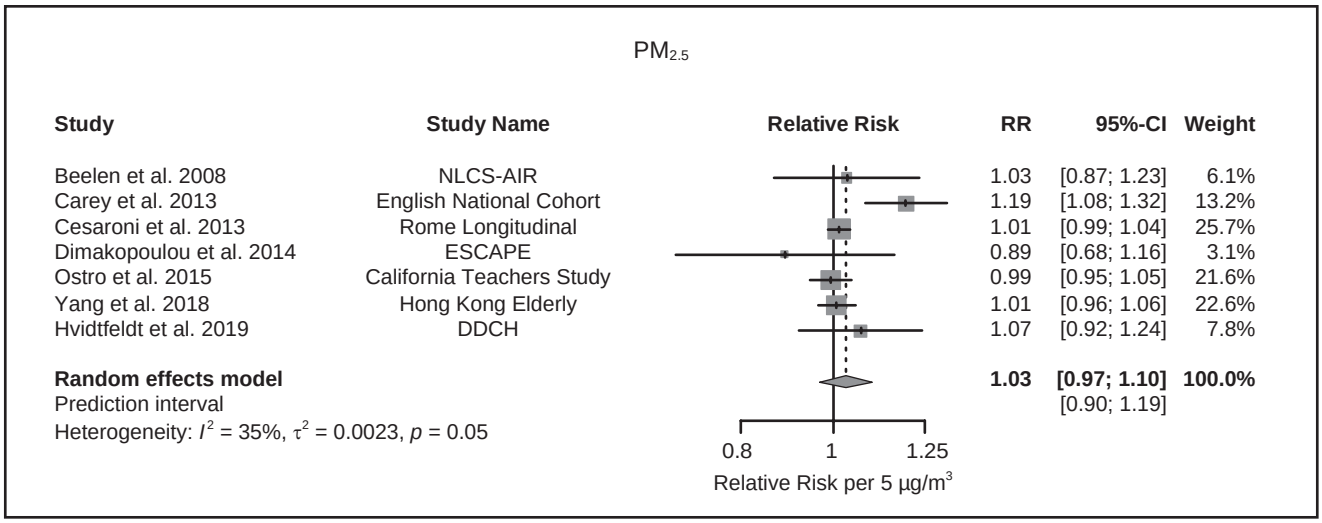


Figure 11.9. *(Continued).*

Longitudinal cohort study contributed 62% and 89% of the weight of the meta-analytical summary effect estimate for NO_2 and $PM_{2.5}$, respectively (Cesaroni et al. 2013).

Few studies have assessed **COPD mortality** (Appendix Figure 11B-6). Only for NO_2 were three studies available for meta-analysis. Two of the three studies showed a positive association. The meta-analytical summary effect estimate was 1.03 (95% CI: 1.00–1.05) per 10-µg/m^3, but this was almost completely driven (84%) by the large Norwegian study (Naess et al. 2007).

There were two papers on **ALRI mortality**, both in the Shiuzoaka Elderly cohort (Yorifuji et al. 2010, 2013). Both papers reported a positive association with LUR modeled NO_2 (Appendix Table 11B-3).

The discussion in Section 11.2.2 regarding the body of the evidence applies especially to circulatory, IHD, respiratory, and lung cancer mortality. Strengths of the evidence include different geographical locations, several large studies, and adjustment for major potential confounders. For the other mortality causes the number of studies was smaller and some of the strengths were less evident. All outcomes had one or more studies with precise effect estimates. Meta-analytical summary estimates often had wider CIs than some individual studies, which reflects heterogeneity.

11.3.2 ADDITIONAL META-ANALYSES

For **circulatory, respiratory, and lung cancer mortality**, most studies on NO_2 and EC were judged to be of high traffic specificity. Effect estimates were not remarkably different in the high traffic specificity group of studies compared with the few moderate traffic specificity studies (Figure 11.11). The summary effect estimates were therefore consistent with the effect estimates for the full group of studies (Figures 11.8 to 11.10). All $PM_{2.5}$ studies were a priori rated as moderate traffic specificity for all outcomes.

11.3.3 ASSOCIATIONS WITH INDIRECT TRAFFIC MEASURES

Figure 11.12 shows the associations between roadway distance measures and circulatory, respiratory, and lung cancer mortality. Appendix Figure 11B-7 shows the associations with the less reported traffic density measures. All except one study (Raaschou-Nielsen et al. 2012) comparing a short distance category with the largest distance category, reported higher circulatory mortality at shorter distances to major roads. Fewer distance studies were available for respiratory and lung cancer mortality, and no consistent association was found in the five studies available for both these outcomes. Traffic density was not consistently associated with circulatory mortality (three studies), whereas a suggestion of associations was found for respiratory and lung cancer mortality; although the number of studies was small (three and two, respectively). Associations were found in the five studies of distance to major road and the three studies of traffic density and IHD mortality. No clear pattern of associations emerged in the seven studies of distance to major road and the three studies of traffic density and stroke mortality.

11.3.4 NARRATIVE ASSESSMENT

The evaluation followed the same reasoning as outlined for all-cause mortality (Section 11.2.5), as the evidence base of studies on cause-specific mortality overlapped substantially with the studies of all-cause mortality. Specifically,

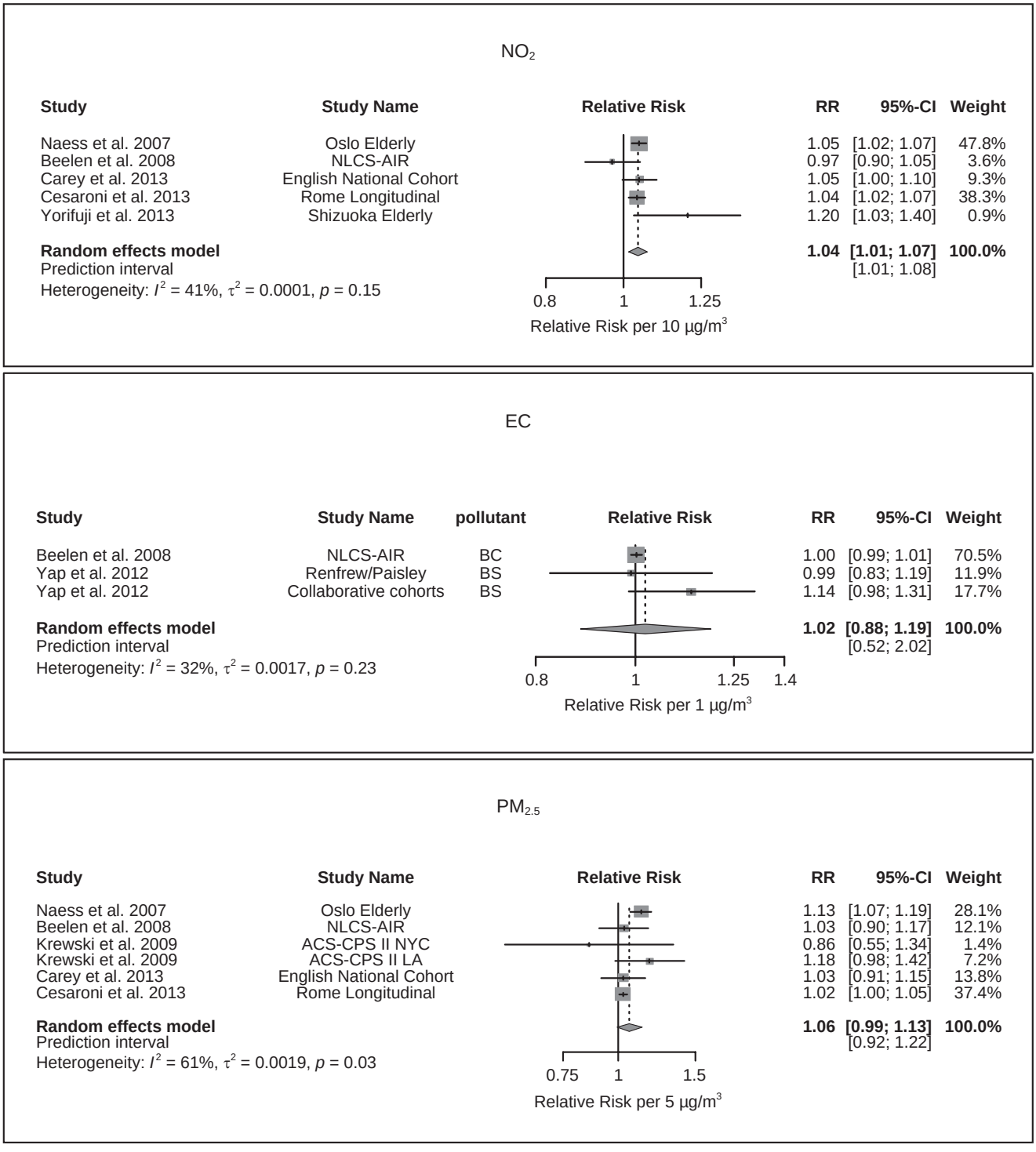
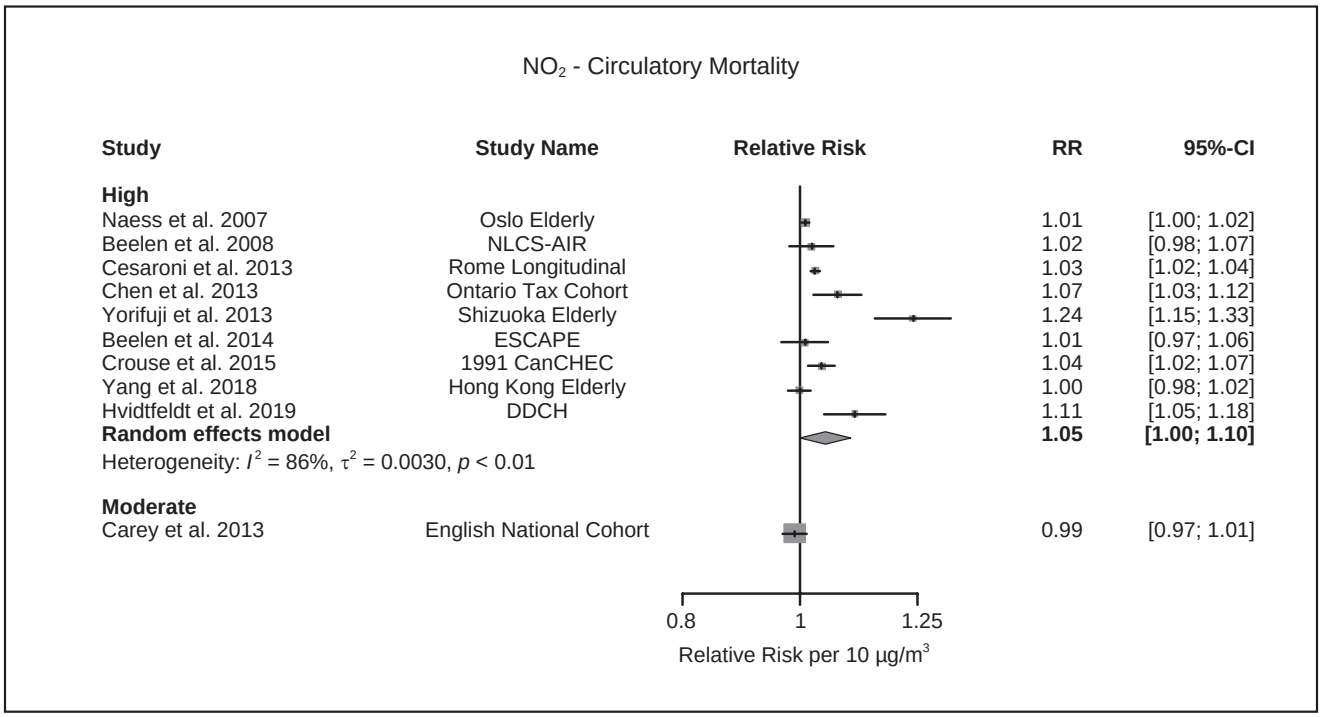


Figure 11.10. Association between NO_2, EC, and $PM_{2.5}$ and lung cancer mortality: meta-analysis.



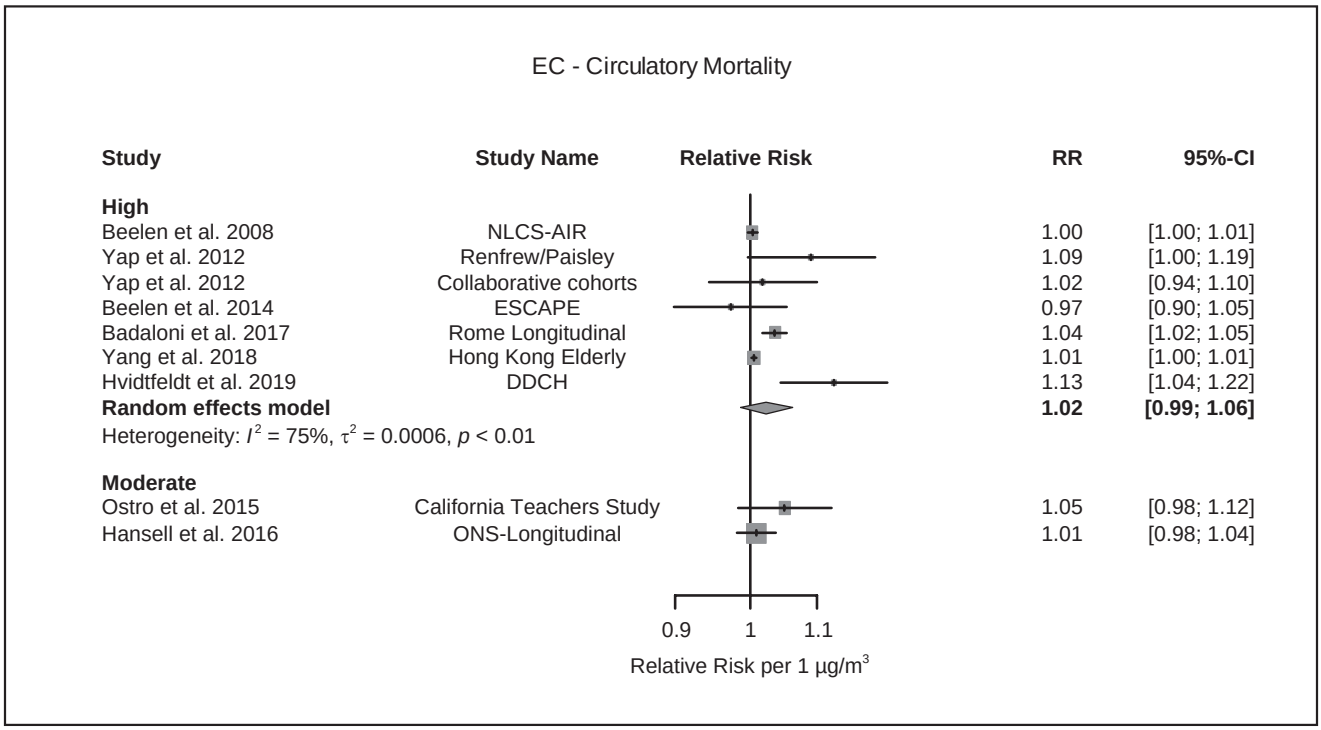
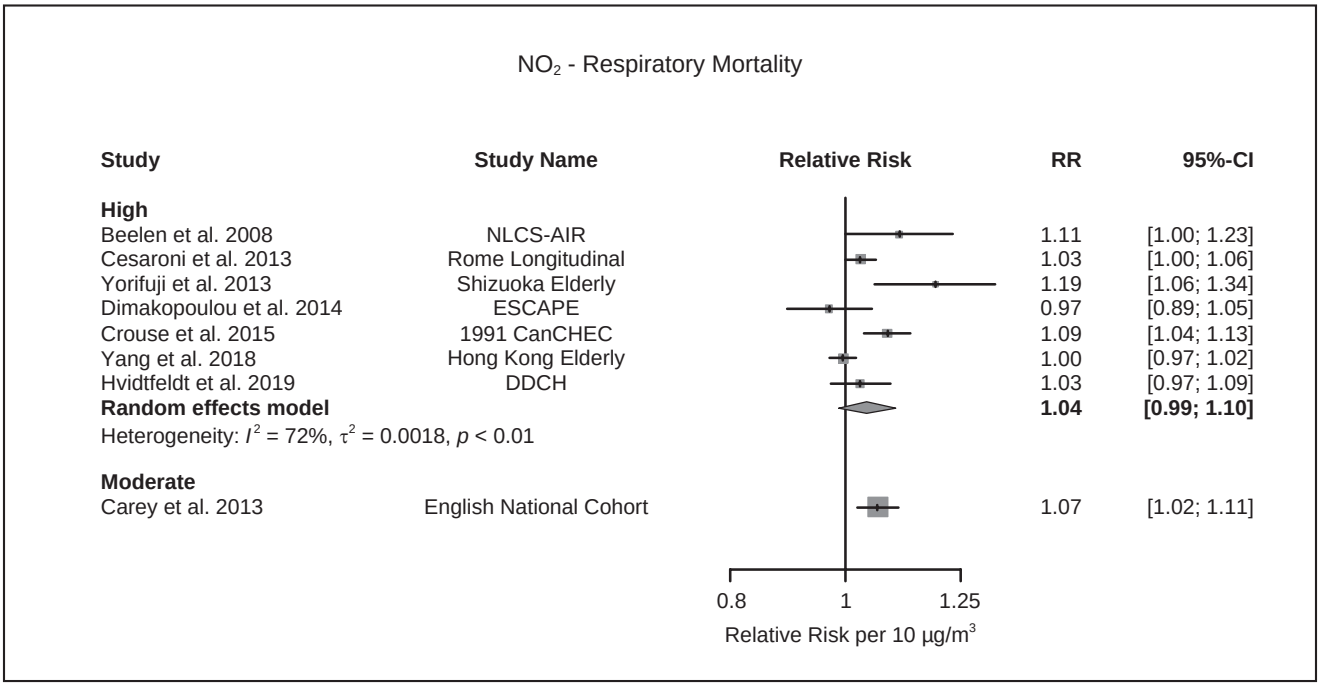


Figure 11.11. Association between NO_2 and EC and circulatory mortality, respiratory mortality, and lung cancer mortality: meta-analysis by traffic specificity. All three EC studies for lung cancer mortality were high traffic specificity. *Figure continues next page.*



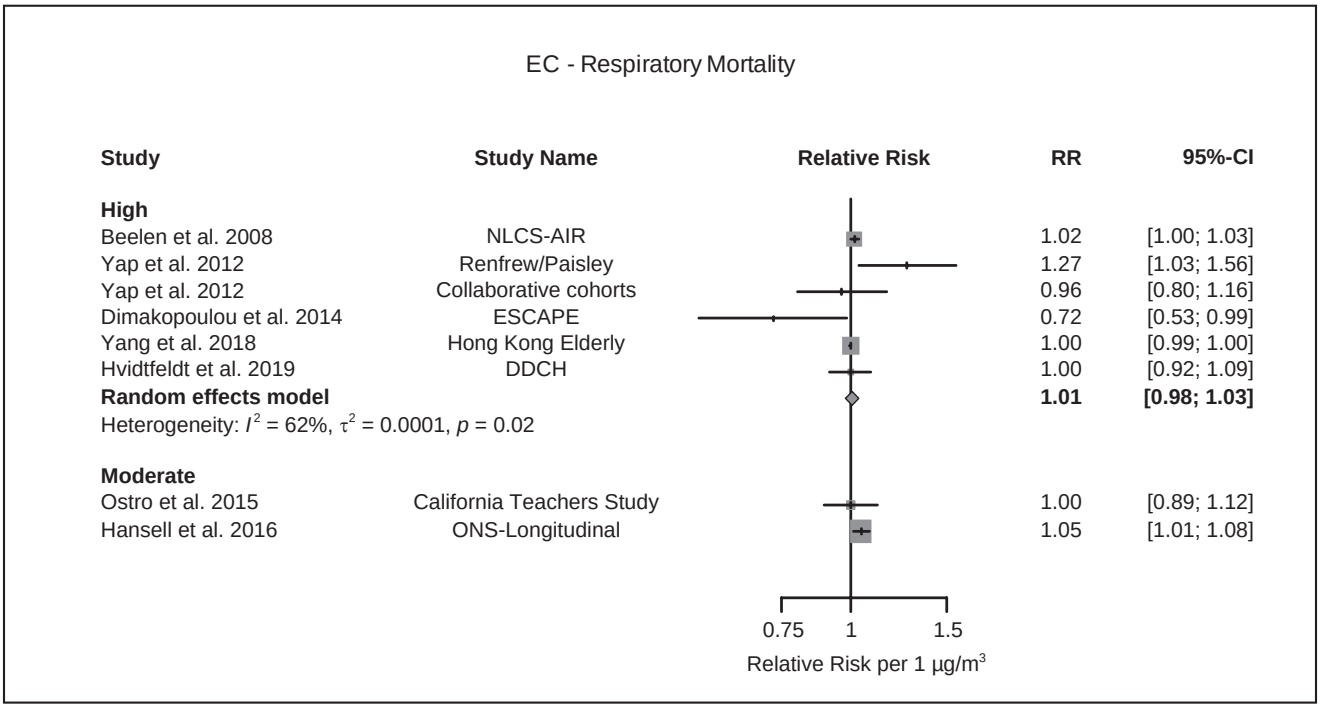


Figure 11.11. *(Continued).*

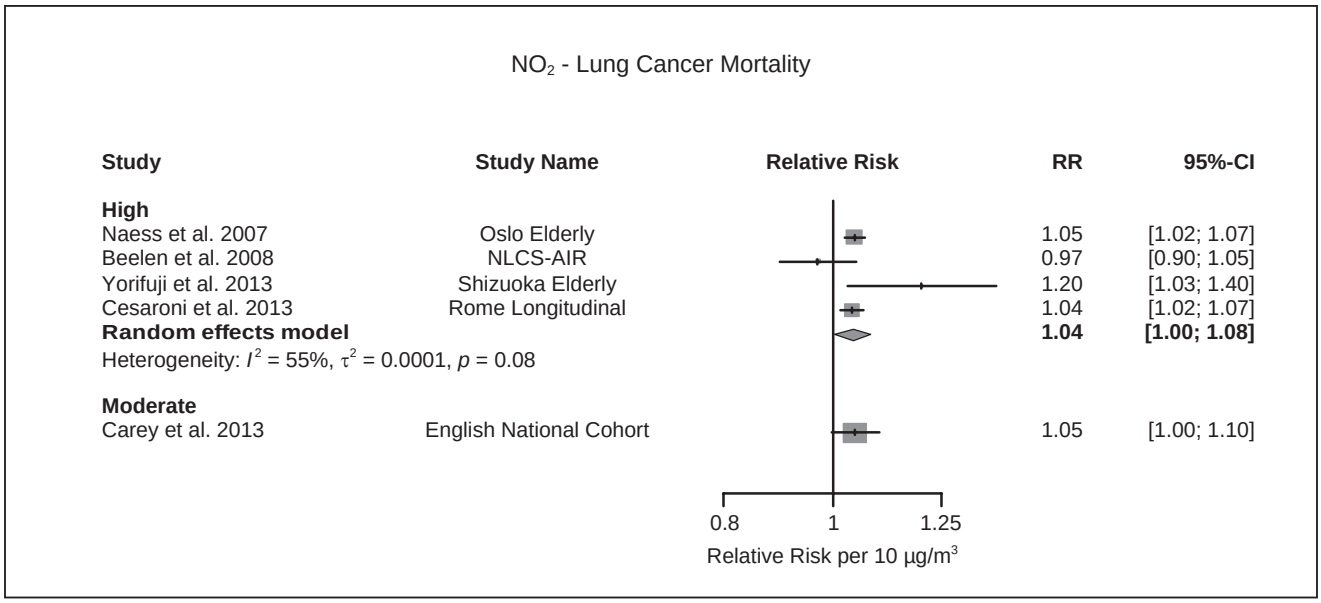


Figure 11.11. *(Continued).*

several large studies with precise effects estimates have been conducted by multiple research groups. The included studies accounted for major biases and were conducted in diverse populations, although mostly in Europe for outcomes other than circulatory mortality. However, the number of studies for some causes (stroke, COPD) were much lower than for all-cause mortality, resulting in a more difficult evaluation.

A high confidence judgement for the presence of an association was derived for circulatory and IHD mortality, based on the predominantly positive associations for most of the pollutants for which a meta-analysis was possible. The meta-analysis resulted in a (borderline) significant combined RR for the three most studied pollutants NO_2, EC, and $PM_{2.5}$. There was additional support from other pollutants or indirect traffic measures. For high traffic specificity studies, RRs were generally mildly higher or equal compared with the moderate traffic specificity studies. The included studies accounted for major confounders and were conducted in diverse populations. In a study in the Netherlands, associations between TRAP and circulatory, stroke, and IHD mortality remained after adjustment for traffic noise (Beelen et al. 2009). In a Danish study, the association of circulatory, stroke, and IHD mortality with NO_2 remained indicative of an association; although modest to sizable (IHD) attenuation was found after adjustment for traffic noise (Raaschou-Nielsen et al. 2012). In a later study in the same Danish cohort, associations between circulatory mortality and $PM_{2.5}$, PM_{10}, and NO_2 were mildly affected by adjustment for traffic noise (Hvidtfeldt et al. 2019). The EC association was attenuated more but also remained indicative of an association with circulatory mortality. Despite the relatively small number of studies that have evaluated potential confounding by traffic noise, the Panel therefore judged that it is unlikely that traffic noise has substantially affected TRAP associations with circulatory mortality (see Section 11.2.5 for a similar conclusion for all-cause mortality).

For lung cancer mortality, the Panel derived a moderate confidence in the presence of an association based on the predominantly positive associations for all meta-analyzed pollutants. The meta-analytic summary estimate was (borderline) significant for NO_2 and $PM_{2.5}$. There was limited support from indirect traffic measures. For high traffic specificity studies, the estimates were equal compared with the moderate traffic specificity study. The Panel arrived at a lower judgement compared with circulatory and IHD mortality, primarily because the evidence was not convincing for EC, and the number of studies was lower than for circulatory mortality.

The judgement of moderate confidence in the presence of an association for respiratory mortality was based on the less consistent associations found across pollutants. For NO_2 a consistent association was found, but only weak evidence was found for $PM_{2.5}$ and especially for EC. There was also only weak support from the few indirect traffic measure studies and other pollutants.

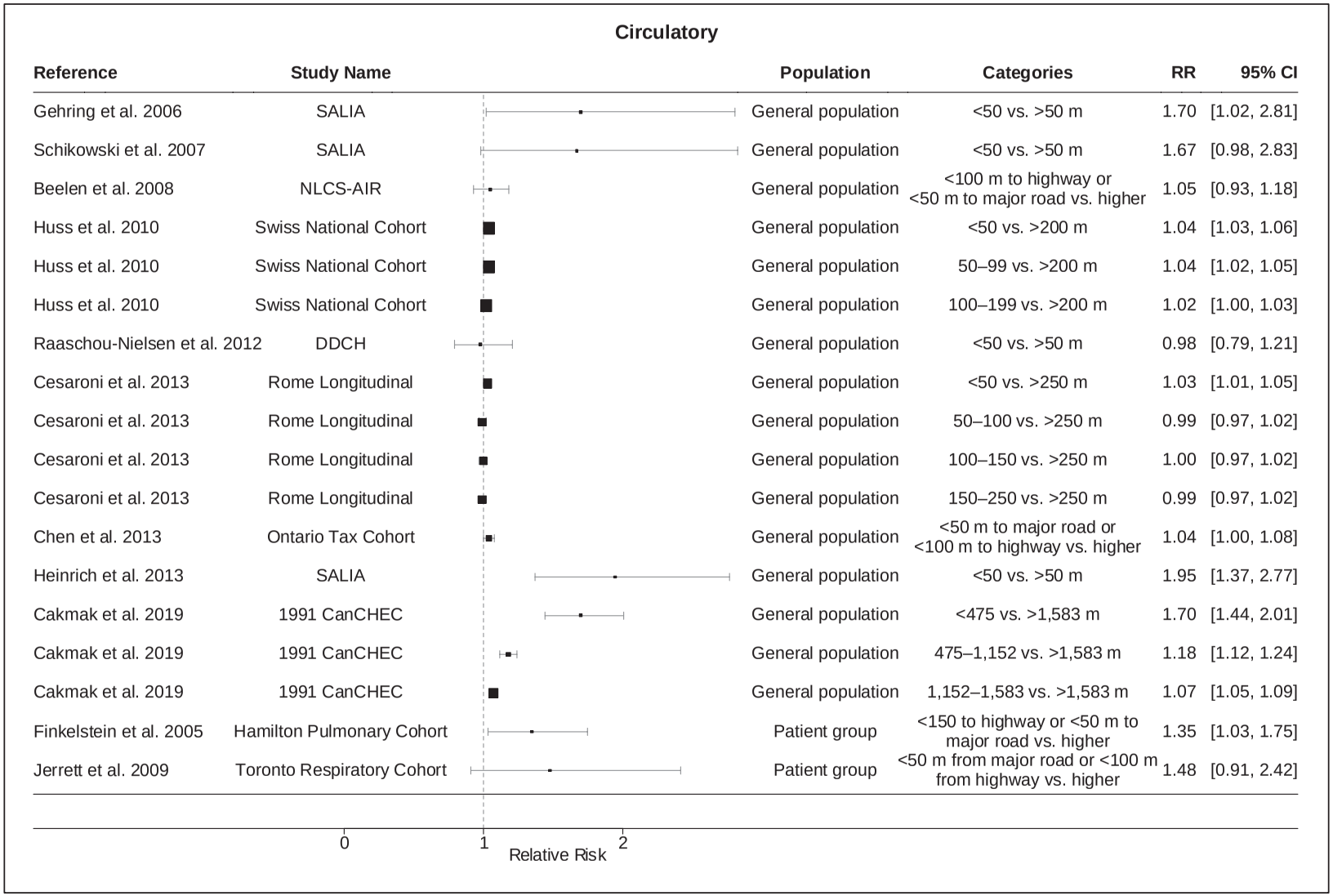


Figure 11.12 Associations between distance measures and circulatory mortality, respiratory mortality, and lung cancer mortality. *Figure continues next page.*

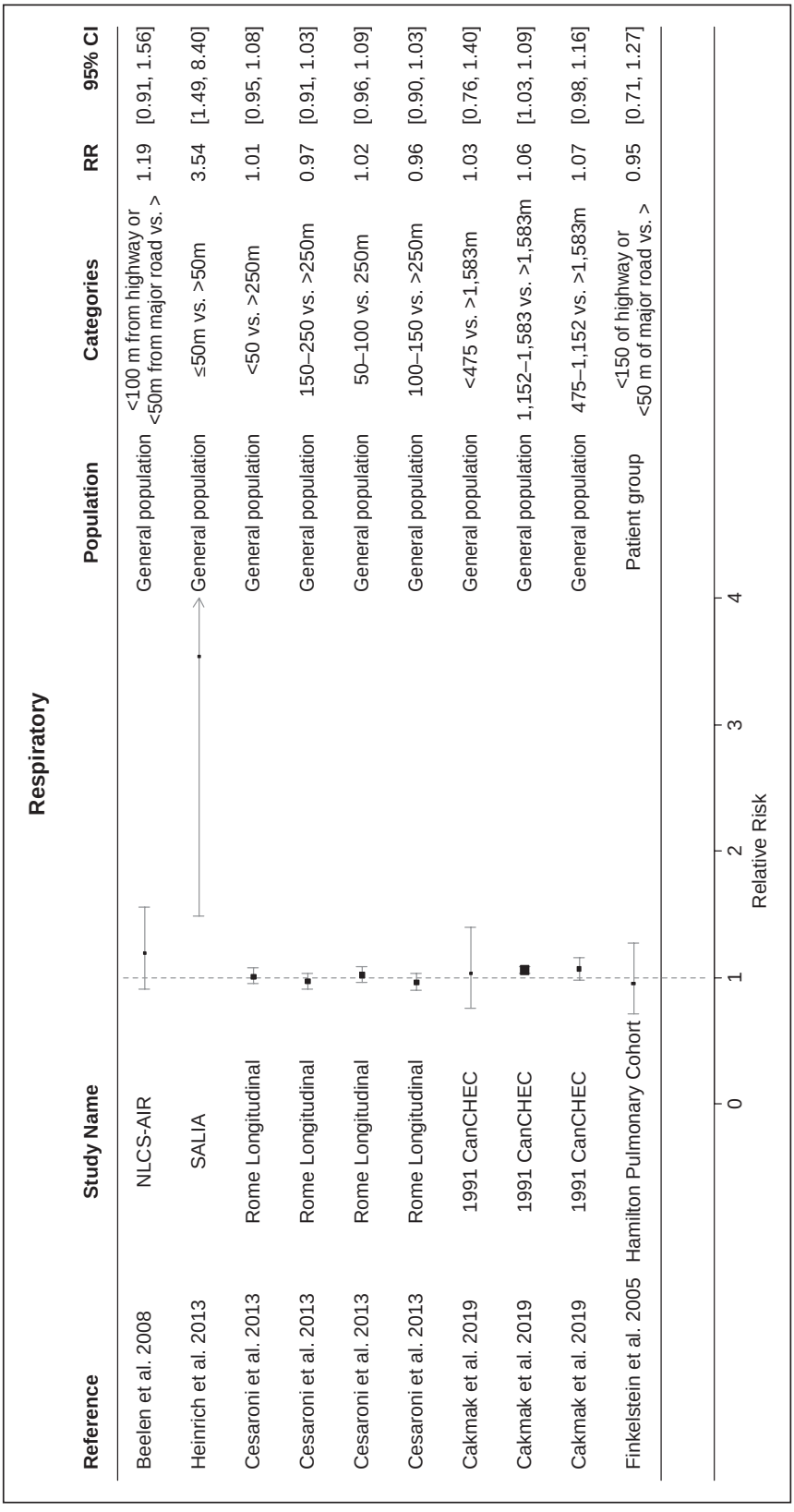


Figure 11.12 *(Continued).*

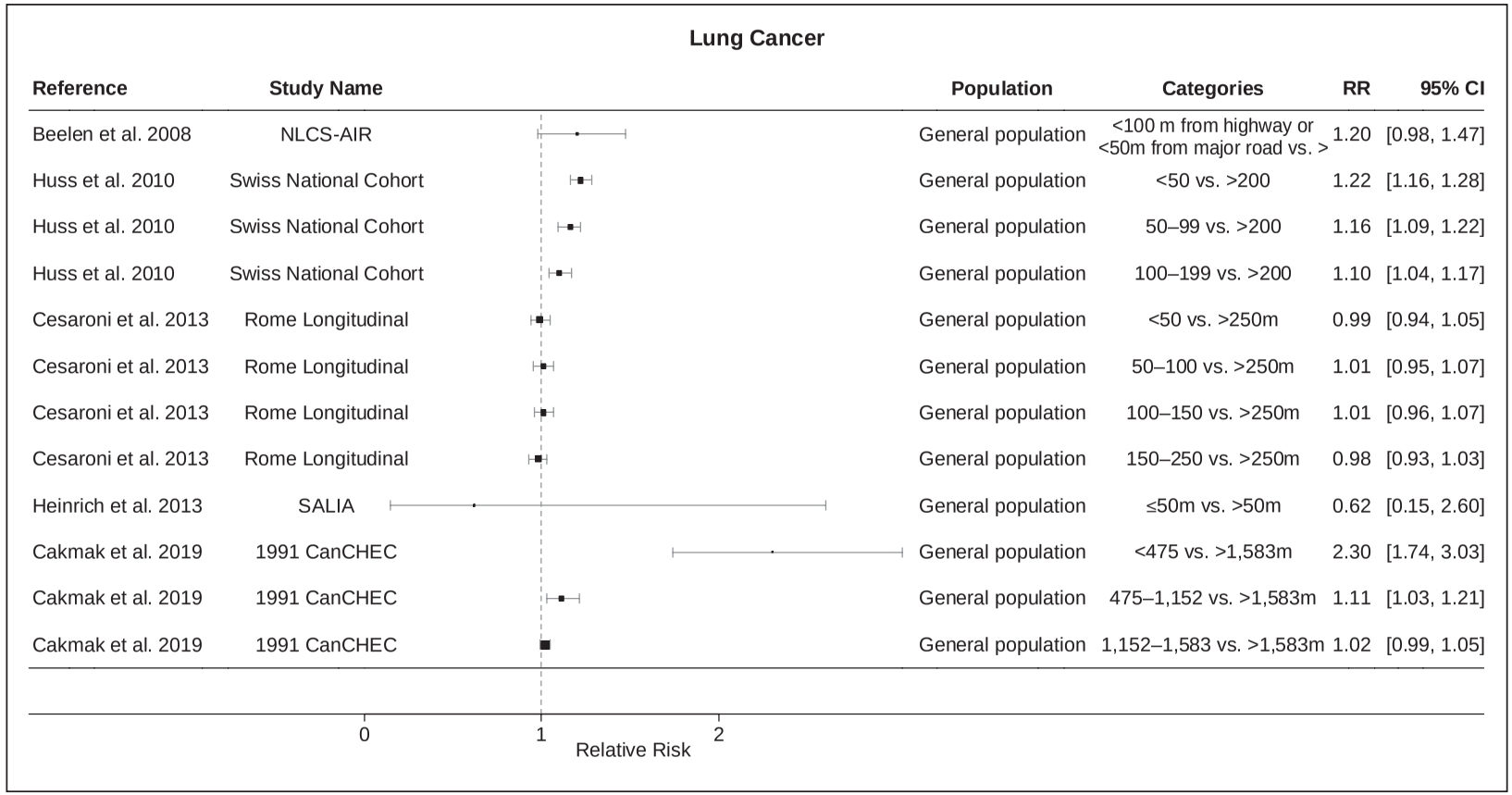


Figure 11.12 *(Continued).*

The assessment of low confidence for stroke and COPD was based on the small number of studies for these outcomes and the inconsistent associations for most pollutants. There were only two papers in one study population that assessed ALRI mortality, hence an assessment was not provided.

Summary of Narrative Assessment for TRAP and Cause-Specific Mortality

- High confidence for circulatory and IHD mortality
- Moderate confidence for respiratory and lung cancer mortality
- Low confidence for stroke and COPD mortality
- No assessment for ALRI mortality because of too few studies
- The differences among these assessments were primarily due to the evidence from the meta-analysis and the consistency across pollutants and indirect traffic measures.

11.3.5 RISK OF BIAS ASSESSMENT

The pattern of risk of bias assessment for the different domains was similar as presented for all-cause mortality. Appendix Tables 11B-7 to 11B-9 summarize the risk of bias assessment on a study level and for all pollutant–study pairs for circulatory, respiratory, and lung cancer mortality. Appendix Tables 11B-10 to 11B-12 contain the risk of bias assessment for each individual study.

11.3.6 CONFIDENCE ASSESSMENT OF THE BODY OF EVIDENCE

The Panel applied the same reasoning as outlined in Section 11.2.7 for all-cause mortality. Hence this section is more concise. Table 11.6 shows the final confidence assessment for all causes of death considered. Tables 11.7 to 11.12 show the motivation of the confidence assessment for the specific causes of death. The key analyses used in the confidence assessment are shown in Appendix Figures 11B.8 to 11B.14. Additional Materials to Chapter 11 shows all analyses conducted. As all studies used the cohort study design, the initial rating was moderate.

For **circulatory mortality**, the Panel derived a high confidence level in the quality of the body of evidence between TRAP and mortality (Table 11.7). This assessment is supported by high confidence judgements for NO_2, $PM_{2.5}$, and EC and support from distance traffic measures. These judgements were derived by a combination of downgrades because of unexplained inconsistency and imprecision and upgrades for a monotonic exposure–response and consistency across regions.

For **respiratory mortality**, the Panel derived a moderate level of confidence in the quality of the body of evidence with TRAP (Table 11.8). This assessment was supported by high confidence judgements for NO_2, moderate confidence

Table 11.6. Summary of Final Confidence Ratings in the Quality of the Body of Evidence for TRAP and All-Cause and Cause-Specific Mortality (Modified OHAT Assessment)[a]

Pollutant	All-Cause	Circulatory	Respiratory	Lung Cancer	IHD	Stroke	COPD
NO_2	High	High	High	High	High	Moderate	Low
NO_x	Moderate	Very low	Very low	Fewer than three studies	Low	Low	Fewer than three studies
EC	High	High	Moderate	Low	Moderate	Fewer than three studies	Fewer than three studies
PM_{10}	Moderate	Low	Low	Very low	Fewer than three studies	Fewer than three studies	Fewer than three studies
$PM_{2.5}$	High	High	Low	High	Moderate	Moderate	Fewer than three studies
Cu - $PM_{2.5}$	Low	Fewer than three studies	Fewer than three studies	Fewer than three studies	Fewer than three studies	Fewer than three studies	Fewer than three studies
Fe - $PM_{2.5}$	Low	Fewer than three studies	Fewer than three studies	Fewer than three studies	Fewer than three studies	Fewer than three studies	Fewer than three studies
TRAP	**High**	**High**	**Moderate**	**High**	**High**	**Moderate**	**Low**

[a] Only completed for meta-analyzed pollutants. ALRI not included as only two papers available.

Table 11.7. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Circulatory Mortality[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ (N = 10)	0	0	0	0	+	0	0	++++ (High)
	Rationale	Cohort design initially rated as moderate.	Few studies high RoB and robust effect estimates in low and moderate RoB studies.	High heterogeneity (I^2 = 86%) due to magnitude not direction.	Sample size met and estimate consistent with an association.	Some evidence found in plot and test, but not sufficient for a downgrade.	Clear evidence of plausible shape of ERF (Cesaroni 2013; Chen 2013; Crouse 2015).	Confounding in both directions possible.	Across geographic regions consistent associations, but most studies in Europe.	
NO_X	Cohort	+++ (N = 3)	0	–	–	0	0	0	0	+ (Very low)
	Rationale	Cohort design initially rated as moderate.	All studies low and moderate RoB.	High heterogeneity (I^2 = 84%) due to magnitude and direction.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	Little evidence of plausible shape of ERF (Stockfelt 2015).	Confounding in both directions possible.	Too few studies to assess consistency across populations.	
EC	Cohort	+++ (N = 9)	0	0	0	0	+	0	0	++++ (High)
	Rationale	Cohort design initially rated as moderate.	Few studies high RoB and robust effect estimates in low and moderate RoB studies.	Moderate heterogeneity (I^2 = 69%) due to magnitude not direction.	Sample size met and estimate consistent with an association.	No formal evaluation possible.	Some evidence of plausible shape of ERF (Hansell 2016; Hvidtfeldt 2019)	Confounding in both directions possible.	Most studies in Europe, no consistency check possible.	

Continues next page

Table 11.7 (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Circulatory Mortality[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
PM_{10}	Cohort	+++ ($N = 7$)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	Four of seven studies high RoB, but RR in low-moderate RoB group larger than in full group.	High heterogeneity ($I^2 = 82\%$) due to magnitude not direction.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	Little evidence of plausible shape of ERF (Hvidtfeldt 2019).	Confounding in both directions possible.	All studies European, no consistency check possible.	
$PM_{2.5}$	Cohort	+++ ($N = 11$)	0	0	0	0	+	0	+	++++ (High)
	Rationale	Cohort design initially rated as moderate.	Few studies high RoB and robust effect estimates in low and moderate RoB studies.	Moderate heterogeneity ($I^2 = 70\%$) due to magnitude not direction.	Sample size met, and confidence interval does not include unity.	No evidence found in plot and test.	Clear evidence of plausible shape of ERF (Hvidtfeldt 2019; Jerrett 2017; Naess 2007).	Confounding in both directions possible.	Evidence for consistency across geographic regions and populations.	

ERF = exposure–response function; RoB = risk of bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

Table 11.8. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Respiratory Mortality[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ (N = 8)	0	0	0	0	+	0	0	++++ (High)
	Rationale	Cohort design initially rated as moderate.	Only one high RoB study, RR in low-moderate RoB group similar to full group.	Moderate heterogeneity (I^2 = 72%) due to magnitude not direction.	Sample size met and estimate consistent with an association.	No formal evaluation possible.	Some evidence of a plausible shape of ERF (Cesaroni 2013; Crouse 2015).	Confounding in both directions possible.	Too few studies outside Europe to assess consistency.	
NO_X	Cohort	+++ (N = 4)	0	–	–	0	0	0	0	+ (Very low)
	Rationale	Cohort design initially rated as moderate.	Only one high RoB study, RR in low-moderate RoB group similar to full group.	Moderate heterogeneity (I^2 = 71%). Two large positive, two null findings.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	Little evidence of a plausible shape of ERF (Nafstad 2004).	Confounding in both directions possible.	No studies outside Europe.	
EC	Cohort	+++ (N = 8)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	Only one high RoB study, RR in low-moderate RoB group similar to full group.	Moderate heterogeneity (I^2 = 64%) due to magnitude not direction. Also, the three studies with large weights consistent estimates.	Sample size met and confidence interval includes unity, but precise.	No formal evaluation possible.	Little evidence of a plausible shape of ERF (Hansell 2016).	Confounding in both directions possible.	Too few studies outside Europe to assess consistency.	

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Table 11.8 (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Respiratory Mortality[a]

	High ++++ Moderate +++ Low ++ Very low +		Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
PM_{10}	Cohort	+++ ($N = 4$)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	Only one high RoB study, fairly robust effect estimates in low and moderate RoB studies.	Moderate heterogeneity ($I^2 = 71\%$) due to magnitude not direction.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of a plausible shape of ERF.	Confounding in both directions possible.	No studies outside Europe.	
$PM_{2.5}$	Cohort	+++ ($N = 7$)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	One high RoB study, RR in low-moderate RoB group larger than in full group.	Moderate heterogeneity ($I^2 = 53\%$) due to magnitude not direction.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	Little evidence of a plausible shape of ERF (Cesaroni 2013)	Confounding in both directions possible.	Too few studies outside Europe to assess consistency.	

ERF = exposure–response function; RoB = risk of bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

assessment for EC, low confidence judgements for $PM_{2.5}$ and PM_{10}, and some support from the three traffic density studies. These judgements were derived by a combination of downgrades because of imprecision, unexplained inconsistency, and upgrades for a monotonic exposure–response. The Panel thought that a moderate overall judgment for TRAP was more appropriate than a high confidence judgement because the confidence for an association with TRAP was primarily based on the high confidence judgement for NO_2, with little support from other pollutants and indirect traffic measures.

For **lung cancer mortality**, the Panel derived a high confidence level in the quality of the body of evidence with TRAP (Table 11.9). This assessment was supported primarily by high confidence judgements for NO_2 and $PM_{2.5}$. These judgements were derived by a combination of downgrades because of imprecision, risk of bias, and upgrades for a monotonic exposure–response function.

For **IHD mortality**, the Panel derived a high confidence level in the quality of the body of evidence with TRAP (Table 11.10). This assessment was supported by high confidence judgements for NO_2, a moderate judgment for EC and $PM_{2.5}$, and support from distance metric studies. These judgements were derived from a combination of downgrades because of imprecision and upgrades for exposure–response.

For **stroke mortality**, the Panel derived a moderate confidence level in the quality of the body of evidence with TRAP (Table 11.11). This assessment was supported by moderate confidence judgements for NO_2 and $PM_{2.5}$, and low for NO_x. Only a single downgrade was applied because of imprecision (NO_x).

For **COPD mortality**, the Panel derived a low confidence level in the quality of the body of evidence with TRAP (Table 11.12). Only for NO_2 were three studies identified. The low confidence judgement was derived by a downgrade because of risk of bias. There was no support from other pollutants or indirect traffic measures for the confidence assessment.

11.3.7 OVERALL CONFIDENCE ASSESSMENT

The narrative and modified OHAT confidence assessment resulted in the same assessment, except for lung cancer and stroke. For lung cancer the Panel arrived at a moderate confidence judgment in the narrative and a high confidence in the modified OHAT-based assessment because, for the narrative assessment, there was limited support from indirect traffic measure studies, and the evidence was not convincing for EC. For stroke mortality the Panel arrived at a low confidence in the narrative assessment and a moderate confidence using the modified OHAT assessment because, for the narrative assessment, the meta-analysis for NO_2 showed little evidence of an association and there were too few studies on EC to conduct a meta-analysis.

Summary of Overall Confidence Assessment for TRAP and Cause-Specific Mortality

- High confidence for circulatory and IHD mortality
- Moderate to high confidence for lung cancer mortality
- Moderate confidence for respiratory mortality
- Low to moderate confidence for stroke mortality
- Low confidence for COPD mortality

11.4 OVERALL DISCUSSION

11.4.1 SUMMARY OF MAIN FINDINGS

Considering the results of the meta-analysis, robustness of the findings, the number of well-designed studies accounting for important biases, and the consistency of findings across geographical areas, the Panel judged there was high confidence in the presence of an association between TRAP and all-cause, circulatory, and IHD mortality. The confidence assessment using the modified OHAT methods resulted in a high level of confidence in the quality of the body of evidence with TRAP for these outcomes and for lung cancer mortality. For respiratory mortality, the narrative and modified OHAT assessment resulted in a moderate confidence assessment. The Panel judged that there was low to moderate or low confidence in the presence of an association between TRAP and stroke and COPD mortality, respectively.

11.4.2 FINDINGS IN RELATION TO OTHER ASSESSMENTS AND STUDIES

The overall judgment of high confidence in an association between TRAP and all-cause, circulatory, IHD, and lung cancer mortality represents a significant increase in confidence compared with that reported in the 2010 HEI Traffic Review (HEI 2010). Although the methodologies of the two reviews differed, the Panel judged that the main reason for the increased confidence is the larger number of studies published since the 2010 review. The current review also included studies at a larger spatial scale than those in the 2010 review, but a subgroup analysis of the more local high-traffic specificity studies resulted in effect estimates similar to the overall effect estimates.

The Panel's judgement generally agrees with other recent assessments of the evidence for two main pollutants included in this review (NO_2 and $PM_{2.5}$). The Panel notes that in these other assessments, the pollutant itself was evaluated,

Table 11.9. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Lung Cancer Mortality[a]

	High ++++ Moderate +++ Low ++ Very low +		Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ (N = 5)	0	0	0	0	+	0	0	++++ (High)
	Rationale	Cohort design initially rated as moderate.	Two studies high RoB, RR similar in low/moderate RoB group compared to full group.	Low heterogeneity (I^2 = 41%).	Sample size met, and confidence interval does not include unity.	No formal evaluation possible.	Some evidence of a plausible shape of ERF (Cesaroni 2013; Naess 2007).	Confounding in both directions possible.	Too few studies to assess consistency across populations.	
EC	Cohort	+++ (N = 3)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	All low RoB.	Low heterogeneity (I^2 = 32%).	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of a plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency across populations.	
PM_{10}	Cohort	+++ (N = 3)	–	0	–	0	0	0	0	+ (Very low)
	Rationale	Cohort design initially rated as moderate.	Two high RoB, the single moderate RoB is a null finding.	High heterogeneity (I^2 = 81%), due to magnitude, not direction.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	Little evidence of a plausible shape of ERF (Naess 2007).	Confounding in both directions possible.	Too few studies to assess consistency across populations.	
$PM_{2.5}$	Cohort	+++ (N = 6)	0	0	0	0	+	0	0	++++ (High)
	Rationale	Cohort design initially rated as moderate.	Two studies high RoB, RR similar in low/moderate RoB group compared to full group.	Moderate heterogeneity (I^2 = 61%), due primarily to magnitude, not direction.	Sample size met and estimate consistent with an association.	No formal evaluation possible.	Some evidence of a plausible shape of ERF (Cesaroni 2013; Naess 2007).	Confounding in both directions possible.	Too few studies to assess consistency across populations.	

ERF = exposure–response function; RoB = risk of bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

Table 11.10. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and IHD Mortality[a]

	High ++++ Moderate +++ Low ++ Very low +		Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ ($N = 6$)	0	0	0	0	+	0	0	++++ (High)
	Rationale	Cohort design initially rated as moderate.	One study high RoB for confounding, RR similar in low/moderate RoB group compared to full group.	Moderate heterogeneity (I^2 = 57%), explained by high RoB in selection bias. Primarily in magnitude, not direction.	Sample size met, and confidence interval does not include unity.	No formal evaluation possible.	Some evidence of a plausible shape of ERF (Cesaroni 2013; Crouse 2015).	Confounding in both directions possible.	Too few studies to assess consistency across populations.	
NO_x	Cohort	+++ ($N = 4$)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	One study high RoB confounding study, with low weight in meta-analysis. Low/moderate RoB group larger RR than full group.	Moderate heterogeneity (I^2 = 73%), explained by subgroup analysis on smoking adjustment.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	Little evidence of a plausible shape of ERF (Stockfelt 2015).	Confounding in both directions possible.	Too few studies to assess consistency across populations.	
EC	Cohort	+++ ($N = 6$)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	One study high RoB on confounding, same RR as the combined RR of other five studies.	High heterogeneity (I^2 = 76%), explained by region. Primarily in magnitude, not direction.	Sample size met and estimate consistent with an association.	No formal evaluation possible.	No evidence of a plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency across populations.	

Continues next page

Table 11.10 (*Continued*). Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and IHD Mortality[a]

	High ++++ Moderate +++ Low ++ Very low +		Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
$PM_{2.5}$	Cohort	+++ (N = 7)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	One study high RoB for confounding, RR similar in low/moderate RoB group compared to full group.	Low heterogeneity (I^2 = 33%).	Sample size met, and confidence interval does not include unity.	No formal evaluation possible.	No evidence of a plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency across populations.	

ERF = exposure–response function; RoB = risk of bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

Table 11.11. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and Stroke Mortality[a]

	High ++++ Moderate +++ Low ++ Very low +		Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ (N = 6)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	One study high RoB, RR similar in low/moderate RoB group compared to full group.	Low heterogeneity (I^2 = 49%).	Sample size met and confidence interval includes unity, but precise.	No formal evaluation possible.	Little evidence of a plausible shape of ERF (Cesaroni 2013).	Confounding in both directions possible.	Too few studies to assess consistency across populations.	
NO_X	Cohort	+++ (N = 3)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	No high RoB.	Low heterogeneity (I^2 = 0%).	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of a plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency across populations.	
$PM_{2.5}$	Cohort	+++ (N = 3)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	The study with 89% of the weight in the meta-analysis rated high RoB for confounding, but RRs of the two other studies consistent and precise.	Low heterogeneity (I^2 = 0%).	Sample size met, and confidence interval does not include unity.	No formal evaluation possible.	Little evidence of a plausible shape of ERF (Cesaroni 2013).	Confounding in both directions possible.	Too few studies to assess consistency across populations.	

ERF = exposure–response function; RoB = risk of bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

Table 11.12. Confidence Rating in the Quality of the Body of Evidence for Traffic-Related Air Pollutants and COPD Mortality[a]

	High Moderate Low Very low	++++ +++ ++ +	Factors Decreasing Confidence (0 if no concern; – if serious concern to downgrade confidence)				Factors Increasing Confidence (0 if not present; + if sufficient to upgrade confidence)			
Pollutant	Study Design	Initial Confidence Rating (# studies)	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response	Consideration of Residual Confounding	Consistency Across Populations	Final Confidence Rating
NO_2	Cohort	+++ (N = 3)	–	0	0	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	The high RoB on confounding study carries 80% of the weight and without this study there is no evidence of an association.	Low heterogeneity (I^2 = 0%).	Sample size met and estimate consistent with an association.	No formal evaluation possible.	Little evidence of a plausible shape of ERF (Naess 2007).	Confounding in both directions possible.	Too few studies to assess consistency across populations.	

ERF = exposure–response function; RoB = risk of bias.

[a] The downgrading factor *indirectness* and the upgrading factor *large magnitude of effect* were not considered further.

irrespective of the source. The assignment of high confidence in the evidence to most long-term $PM_{2.5}$ exposure and mortality associations agrees well with recent assessments made by the U.S. Environmental Protection Agency (U.S. EPA) using a different methodology (U.S. EPA 2019). Our narrative evaluation was similar in method to the assessment of epidemiological evidence within the Integrated Science Assessment (ISA) by the U.S. EPA. The ISA included toxicological studies in addition to epidemiological studies. The ISA included substantially more studies than the current review, primarily because the Panel did not include $PM_{2.5}$ studies based on monitoring alone and most nationwide studies. The Panel judged these studies to be insufficiently specific for evaluating health effects of TRAP. In the 2019 ISA, the association between $PM_{2.5}$ and all-cause mortality was rated as causal, based on assessment of different scientific disciplines beyond the epidemiological mortality studies. For PM_{10}, our assessment resulted in lower confidence compared with $PM_{2.5}$, consistent with the ISA assessments for coarse particles. The 2019 PM ISA evaluated evidence from studies of PM_{coarse} and all-cause mortality as suggestive. The assessment for PM_{coarse} is not directly comparable to PM_{10}, as PM_{10} is the sum of $PM_{2.5}$ and PM_{coarse}. In the 2016 ISA for NO_2, associations with total mortality and cardiovascular effects including mortality was judged as suggestive (U.S. EPA 2016). Respiratory effects were judged as likely causal but based primarily on asthma morbidity and not respiratory mortality. The assessment was based on inconsistency in significant findings across studies, concerns about the independent effect of NO_2 and limited support from studies on cardiovascular and respiratory morbidity. Health Canada judged the evidence for a causal association between NO_2 and total mortality as suggestive, with a very similar rationale as provided by the U.S. EPA (Health Canada 2016). In our review, the issue of independent effects is less of an issue as we assess evidence for TRAP as a mixture, which is an important difference. Finally, the Panel's conclusions are also supported by the large number of short-term health effect studies on all-cause mortality and TRAP, particularly for NO_2, EC, and carbon monoxide (Chapter 4).

The high confidence assessment for lung cancer mortality agrees well with the assessment in 2013 by the International Agency for Research on Cancer (IARC), which designated outdoor air pollution and particulate air pollution specifically as a Group 1 human carcinogen, the highest level of certainty in the IARC system, based on both human and animal studies (IARC 2016). In another assessment, IARC judged there was sufficient evidence, both from human and animal studies, for diesel engine exhaust to be considered a Group 1 human carcinogen (IARC 2014). Gasoline exhaust was judged to be a possible human carcinogen (Group 2b). Health Canada also judged that there was sufficient evidence that diesel exhaust was carcinogenic to humans (Health Canada 2016). Evidence for cardiovascular effects of diesel exhaust related to long-term exposure were judged as suggestive. In the 2016 NO_2 ISA, associations with cancer were judged as suggestive only, based on some inconsistencies across epidemiological studies, lack of control for other (traffic-related) pollutants, and lack of evidence from mechanistic studies (U.S. EPA 2016).

In the context of the 2021 WHO Air Quality Guidelines, the systematic reviews of the association between long-term exposure to $PM_{2.5}$ and NO_2 and mortality found strong evidence of an association (Chen and Hoek 2020; Huangfu and Atkinson 2020). In the WHO review, the confidence assessment was based on the GRADE methods (Chen and Hoek 2020). The tools differ from the approach used by the Panel, although the risk of bias tool was similar. In both systematic reviews a substantially larger number of studies was included: $N = 71$ for $PM_{2.5}$ (90% from North America and Europe) and $N = 41$ for NO_2, as studies were included irrespective of the air pollution source. Application of the adapted GRADE tool resulted in an assessment of *high certainty of evidence* for $PM_{2.5}$ with all assessed health outcomes except for respiratory mortality (moderate) (Chen and Hoek 2020). Associations for NO_2 and mortality were significantly above unity for all-cause (24 cohorts), respiratory (15 cohorts), COPD (9 cohorts), and ALRI (5 cohorts), mortality, respectively (Huangfu and Atkinson 2020). Circulatory mortality was not assessed. Certainty in the evidence for associations with mortality was rated moderate for all-cause, respiratory, and ALRI mortality and high for COPD mortality (Huangfu and Atkinson 2020). In another recent systematic review, significant associations between NO_2 and multiple causes of death were found (Stieb et al. 2021). Using a different risk of bias tool, the evidence for all causes of death was rated as moderate, except for stroke, for which the evidence was rated as low. In a systematic review by Huang and colleagues, robust epidemiological evidence was found for an association of NO_2 with all-cause, cardiovascular, and respiratory mortality (Huang et al. 2021). Associations with NO_2 remained in multipollutant models (Huang et al. 2021).

The Panel noted the consistency between stroke mortality and stroke morbidity results (Chapter 10) in terms of the pollutant with the strongest associations ($PM_{2.5}$). As the assessments for the two health outcomes were derived from different studies, this strengthens the confidence in an association with $PM_{2.5}$. As there was little evidence for an association in the meta-analysis with the more specific traffic-related pollutant NO_2, the judgment of a low to moderate confidence in an association with TRAP remains appropriate for stroke mortality, consistent with the recent review by Stieb and colleagues (2021).

The Panel noted the consistency between the evaluations of COPD mortality and COPD incidence (Chapter 9). Both for mortality and morbidity, the confidence assessment was low. In the morbidity evaluation more studies were included than in the mortality evaluation. For mortality it was not possible to make an evaluation for ALRI mortality because of too few

studies. In Chapter 9, the evaluation for ALRI in children resulted in high confidence of an association. The Panel notes that the effect estimates for the two ALRI mortality studies were above unity, suggesting there may be an association. In the systematic review on NO_2, consistent associations with ALRI mortality were found (Huangfu and Atkinson 2020).

Some large new studies have been identified after the completion of the search for this review. The ELAPSE study documented consistent associations between $PM_{2.5}$, NO_2, BC, and all-cause, circulatory, and respiratory mortality in a large pooled European cohort with detailed lifestyle covariates (Brunekreef et al. 2021). The study was based on fine resolution (100 m × 100 m) Europewide hybrid LUR models, using statistical procedures as in the included ESCAPE studies, exploiting only within-cohort exposure contrasts (Beelen et al. 2014). Within ELAPSE, consistent associations for these pollutants were also found in large administrative cohorts, but six of them would likely not have been selected as they were national cohorts. Analyses within the Rome Longitudinal cohort confirmed associations included in the current review (Badaloni et al. 2017; Cesaroni et al. 2013). In a large Dutch national cohort, PM from traffic sources—assessed with a dispersion model assessing specific sources—was associated with all-cause mortality, adjusting for particles from other sources (Fischer et al. 2020).

The lung cancer mortality assessment is further supported by studies documenting associations between outdoor air pollution and lung cancer incidence, a body of evidence not systematically included in this review. Most systematic reviews on air pollution and lung cancer include incidence and mortality studies in a single meta-analysis because of the high fatality of lung cancer (Hamra et al. 2014, 2015; Turner et al. 2020). In the review on NO_2, the number of incidence studies was similar to the number of mortality studies; in the $PM_{2.5}$ review, the number of incidence studies was about half the number of studies based on mortality (Hamra et al. 2014, 2015). Inspection of the reviews shows evidence of associations of $PM_{2.5}$ and NO_2 with lung cancer incidence as well as mortality. The recent ELAPSE study reported significant associations between $PM_{2.5}$ and lung cancer incidence in a large European cohort (Hvidtfeldt et al. 2021). The large administrative cohort studies are typically based on lung cancer mortality, because linkage with cancer registries has not often been made. In the Ontario Population Health and Environment cohort of about 5 million adults, NO_2 and $PM_{2.5}$ were significantly associated with lung cancer incidence (Bai et al. 2020).

11.4.3 STRENGTHS AND LIMITATIONS

The main strength of the review is the systematic approach in identifying, selecting, and evaluating studies using explicit evaluation frameworks for exposure and confidence assessment. The application of both a narrative assessment and a modified OHAT assessment is another strength, given the ongoing discussions about limitations in evidence synthesis and risk of bias assessment (e.g., Savitz et al. 2019). A large number of studies were available to assess the evidence; although for some specific causes the information was more limited.

The main limitations in the assessment were generic limitations applying to all health outcomes, including: (a) difficulties in the judgment of which studies can be interpreted as studies in which the contrast in exposure is primarily related to traffic; (b) a limited number of studies for performing a full confidence assessment; (c) difficulties in applying the formal risk of bias and confidence-assessment methods. In the exposure framework, the Panel excluded studies at the urban and regional scale because of difficulties in separating exposure contrasts related to traffic sources from other sources. The implication is that the Panel did not assess the full impact of traffic sources, as traffic emissions affect urban and regional background as well. Within the Panel, there was debate about the need to downgrade confidence based on unexplained heterogeneity due to magnitude. Following the study protocol, the Panel primarily downgraded the evidence if there was heterogeneity due to difference in direction, but also discussed the degree of unexplained heterogeneity extensively in the evaluation. The Panel furthermore noted that if the degree of heterogeneity was so large that the meta-analytical CIs clearly included unity and was wide, a downgrade was applied for imprecision. In the mortality analyses, the meta-analytical summary CIs generally were wider than those of some individual studies, which reflected heterogeneity. The Panel judged this to be a better approach than downgrading due to heterogeneity based on statistics that are difficult to interpret, such as the I^2 statistic or the statistical significance of the heterogeneity test. The I^2 statistic is expressed on a relative scale and may be interpreted as high, even if all effect estimates can be considered as small (e.g., for NO_2 all RRs were between 1.00 and 1.12 with an I^2 of 83%). Despite the difficulties of applying the modified OHAT assessment, the Panel noted that the conclusions from the narrative evaluation and the OHAT assessment broadly agreed.

Despite the relatively small number of studies that have evaluated potential confounding by traffic noise, the Panel judged that it is unlikely that traffic noise has substantially affected TRAP associations with all-cause and circulatory mortality (more discussion in Sections 11.2.5 and 11.3.4). Recent analyses within the ELAPSE study have also found very mild attenuations of associations—between $PM_{2.5}$, NO_2, and BC and all-cause and circulatory mortality, and between $PM_{2.5}$, NO_2, and BC and stroke and IHD morbidity—upon adjustment for traffic noise in a large pooled European cohort and several large administrative cohorts (Brunekreef et al. 2021).

11.4.4 BIOLOGICAL PLAUSIBILITY

Toxicological studies have reported plausible mechanisms relating TRAP to fatal respiratory and circulatory disease (e.g., Brook and Rajagopalan 2010; Newby et al. 2015). These mechanisms include oxidative stress and respiratory and systemic inflammation. In the 2010 HEI Traffic Review, and in Chapter 3 in the current report, an overview of the evidence from toxicology is presented. A more in-depth discussion is provided in the overall discussion of the current report (Chapter 14).

11.4.5 UNANSWERED QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

There is already a large body of literature on TRAP and mortality. The Panel's assessment of high confidence in an association between TRAP and mortality implies that new studies addressing the generic question of associations may not add significantly to the evidence base. More research on some specific questions may, however, be useful in increasing the policy relevance of the current assessment:

1. The Panel considered pollutants to be indicators of TRAP and did not address the question of which components of TRAP may be most toxic. The distinction between tailpipe and nontailpipe pollutants would be especially useful to address in future studies. More long-term studies on UFPs are also needed as few studies were available; there are reasons to suspect that UFPs might be health relevant beyond what is already known.
2. The evidence for some specific causes of death was weaker than for all-cause mortality; however, the number of available studies was small. Some new studies would be useful, particularly those on stroke, COPD, and ALRI mortality.
3. More studies in areas outside Europe and North America are needed. The small number of studies outside these areas was due to fewer air pollution studies in general and fewer sufficiently traffic-specific studies. The development and application of more traffic-specific studies outside Europe and North America would be useful.
4. More traffic-specific studies are needed, including those with adjustment for pollution from nontraffic sources. Most studies were set up to study pollutants rather than specific sources because air quality standards and limit values are expressed per pollutant.
5. More studies on the joint health effects of air pollution, traffic noise, green space, and other built environment exposures would be useful.

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MATERIALS AVAILABLE ON THE HEI WEBSITE

Appendices A to C and Additional Materials 11.1 to 11.8 contain supplemental material not included in the main report. They are available on the HEI website at *www.healtheffects.org/publications.*

Appendices

11A All-Cause Mortality

11B Cause-Specific Mortality

11C References for Studies Included in the Systematic Review of Mortality

Additional Materials

11.1 All-Cause Mortality

11.2 Circulatory Mortality

11.3 Respiratory Mortality

11.4 Lung Cancer Mortality

11.5 Ischemic Heart Disease Mortality

11.6 Stroke Mortality

11.7 Chronic Obstructive Pulmonary Disease Mortality

11.8 Risk of Bias Rationales for Studies Included in Meta-analyses

ABBREVIATIONS

ALRI	acute lower respiratory infection
BC	black carbon
BMI	body mass index
BS	black smoke
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CTM	chemical transport model
EC	elemental carbon
ERF	exposure–response function
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IHD	ischemic heart disease
ISA	Integrated Science Assessment
LUR	land use regression
NO	nitric oxide
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
OHAT	Office of Health Assessment and Translation
OR	odds ratio
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 µm in aerodynamic diameter
$PM_{2.5\ abs}$	$PM_{2.5}$ absorbance
PM_{coarse}	PM with aerodynamic diameter between 10 µm and 2.5 µm
PM_{10}	PM ≤10 µm in aerodynamic diameter
RR	relative risk
RoB	risk of bias
SES	socioeconomic status
TRAP	traffic-related air pollution
UFPs	ultrafine particles
U.S. EPA	U.S. Environmental Protection Agency
WHO	World Health Organization

PART D: FINDINGS FROM LITERATURE REVIEWS OF EPIDEMIOLOGICAL STUDIES

Chapter 12

Traffic-Related Air Pollution and Neurodevelopmental Outcomes

CONTENTS

CHAPTER 12

Traffic-Related Air Pollution and Neurodevelopmental Outcomes

12.1 SUMMARY

There has been increased interest in understanding how traffic-related air pollution (TRAP*) affects the developing brain. Gestation and early life are periods of rapid central nervous system development when the brain may be at heightened risk for insult from environmental toxicant exposures; these effects could set the stage for adverse trajectories in neurodevelopment over the life course (Grandjean and Landrigan 2014).

Although the 2010 HEI Traffic Review did not assess TRAP-related effects on neurological outcomes, the Panel observed a growing body of literature investigating these outcomes in the intervening years. A rapidly emerging body of epidemiological studies has reported associations between prenatal and childhood exposure to TRAP and adverse neurodevelopment in children across multiple domains of intellectual and behavioral development. The Panel conducted a literature review of this evidence because the Panel thought these were important emerging areas that should be represented in the Report, even while a larger body of evidence develops. Although the Panel did not conduct meta-analyses, risk of bias assessments, or confidence assessments of the quality in the body of evidence on TRAP and these outcomes at this stage, given the rapidity with which this literature is emerging, there may be enough studies in the near future to conduct this more formal systematic review.

A total of 49 studies of TRAP and neurodevelopment representing 30 different study populations were selected using methods and criteria previously described. The majority of studies were conducted in Europe and North America, with considerably fewer in Asia and South America. Most studies used prospective cohort study designs, although a number also used case–control (particularly studies of autism spectrum disorder [ASD]) and cross-sectional designs. Studies ranged widely in size, from a few hundred to approximately 130,000 participants. Study periods differed across studies and ranged from as early as 1986 to as late as 2017.

Studies primarily estimated exposure with land use regression or dispersion/chemical transport models (CTM), and a number also used traffic-specific source apportionment, residential distance to traffic, or traffic density. The most frequently studied individual pollutant was nitrogen dioxide (NO_2), followed by elemental carbon (EC), particulate matter with an aerodynamic diameter ≤2.5 µm ($PM_{2.5}$), particulate matter with an aerodynamic diameter ≤10 µm (PM_{10}), and nitrogen oxides (NO_x). Few studies examined chemical and source-specific components of PM, PM with aerodynamic diameters generally larger than 2.5 µm and smaller than, or equal to, 10 µm (PM_{coarse}), benzene, polycyclic aromatic hydrocarbon (PAH), and ultrafine particles, which have diameters less than 0.1 µm (UFPs).

Confidence in the presence of an association of TRAP and neurodevelopment in children was mixed. The Panel found moderate confidence in the presence of an association of

Highlights

- There has been a rapid growth in the literature on associations of traffic-related air pollution with neurodevelopment in children. A total of 49 studies were reviewed across three outcome categories: cognitive function, attention deficit hyperactivity disorder and related behaviors, and autism spectrum disorders and related behaviors.
- Confidence in the presence of an association of TRAP and neurodevelopment in children was mixed, ranging from low to moderate-to-high confidence. Studies of traffic-related air pollution and cognitive function (the largest number of studies *n* = 30) showed moderate confidence, studies of traffic-related air pollution and attention deficit hyperactivity disorder and related behaviors (*n* = 8 studies) showed low confidence, and studies of traffic-related air pollution and autism spectrum disorders and related behaviors (*n* = 14 studies) showed moderate to high confidence.
- Although meta-analyses, risk of bias assessment, and a confidence assessment of the quality in the body of evidence were not conducted for this newly emerging literature, continued growth in the number of studies on traffic-related air pollution and neurodevelopment should facilitate a more comprehensive review in the near future.

This document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83234701 to the Health Effects Institute; however, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

TRAP with poorer cognitive function. Studies of TRAP and cognitive function, which had the largest number of studies of pollutants and indirect traffic measures (n = 30 studies), showed that with exposure to individual traffic-related air pollutants—namely, NO_2, EC, and $PM_{2.5}$—a bit less than half the studies found evidence for associations with poorer cognitive function, including general intelligence, attention, and working memory. Associations of these pollutants with poorer cognition were found for both pregnancy and childhood exposure. For NO_x, associations with cognitive outcomes were all null. There was some evidence for adverse associations with chemical and source-specific components of PM, PM_{10}, PM_{coarse}, and UFPs, but literature was scant. Associations with indirect traffic measures were also mixed and slightly stronger for traffic density versus distance to roadway. In general, associations were slightly stronger for attention and executive function, compared with measures of intelligence.

For attention deficit hyperactivity disorder (ADHD) and related behaviors (n = 8 studies), the literature was considerably weaker overall, and the Panel found low confidence for an association of TRAP with ADHD and related behaviors. The majority of studies reported null associations, although a small number of studies found associations with childhood exposure to NO_2, EC, and $PM_{2.5}$.

There was moderate to high confidence in the presence of an association of TRAP with ASD (n = 14 studies), with most studies of NO_2 and $PM_{2.5}$ reporting associations of prenatal or early life exposure with higher ASD risk. Studies of other pollutants, including indirect traffic measures, showed mixed or null findings.

12.2 OVERVIEW OF CHAPTER AND OUTCOMES

The Panel considered domains related to three categories of neurodevelopmental outcomes in children age <18 years at start of follow-up: (1) cognitive function, including poorer performance or slower development along a range of cognitive domains (i.e., general, verbal, and nonverbal IQ, learning, memory, language, visuospatial skills, visual-motor abilities, attention, and dimensions of executive function, including working memory and response inhibition) (n = 30 studies, Appendix Table 12A-1, available on the HEI website); (2) ADHD diagnosis and related behaviors (i.e., inattention, hyperactivity, and impulse control) (n = 8 studies, Appendix Table 12B-1); and (3) ASD diagnosis and related behaviors (i.e., social cognition as well as restricted and repetitive behaviors) (n = 14 studies, Appendix Table 12C-1; available on the HEI website). Although a number of studies measured neurodevelopmental outcomes by assessing participants directly (using neuropsychological testing) or by interviewing parents and teachers (using structured behavioral rating scales), several studies obtained data on clinically diagnosed outcomes from health care administrative records (e.g., Pagalan et al. 2019; Saez et al. 2018), health insurance data (e.g., Raz et al. 2018b), or national registries (e.g., Becerra et al. 2013; e.g., Ritz et al. 2018). Children's ages at assessment ranged from infancy to late adolescence, although most studies assessed outcomes in mid-childhood.

The Panel included studies that considered a range of exposure windows. Thirty studies estimated prenatal TRAP exposure and 31 studies estimated childhood TRAP exposure from as young as the first year of life to age 15 years. Thirteen studies estimated associations with both prenatal and childhood TRAP exposure.

Most studies adjusted for a core set of covariates in multivariable models. Core variables included child age at assessment, child sex, and at least one measure of socioeconomic status (SES), such as parental education, household income, or neighborhood SES/poverty index. Some studies adjusted for other potential confounders, such as marital status, parity, maternal smoking during pregnancy, and quality of the home environment. A few studies also adjusted for noise or early life exposure to other environmental pollutants, such as lead. In addition, some studies also examined differences in TRAP exposure and neurodevelopmental associations by sex, which has been shown to be a modifier of the effect of other environmental exposures on neurodevelopment (Weiss 2011).

Each section of this chapter (12.3–12.5) starts with a general description and characterization of the available literature reporting on associations of TRAP with each respective neurodevelopmental outcome. A review describing results of associations with individual traffic-related air pollutants (primarily NO_2, NO_X, EC, and $PM_{2.5}$) follows, as well an examination of associations with indirect traffic measures (distance to major roadways and traffic density). Many studies report associations with multiple exposure measures related to TRAP (e.g., EC and NO_2).

The chapter concludes with an overall discussion of the confidence in the evidence, including a summary of the main findings for each endpoint, findings in relation to other assessments, strengths and limitations, and finally unanswered questions and future directions for research.

This literature review differs from the systematic review presented in other chapters in some important respects: (1) no meta-analyses were conducted; (2) there was no evaluation of the confidence in the quality of the body of evidence; and (3) there was no formal risk of bias assessment on individual studies. Chapter 5 details the Panel's decision not to include neurodevelopmental outcomes as a primary outcome in this report.

12.3 COGNITIVE FUNCTION

12.3.1 STUDY SELECTION AND DESCRIPTION

Thirty studies examined associations between TRAP, including indirect traffic measures (distance and density),

and measures of cognitive function in children (Appendix Table 12A-1). These 30 studies represented 18 different study populations, although in some cases pooling of studies meant that study populations were not mutually exclusive (e.g., the ESCAPE study). All except one South American study were conducted in Europe and North America and all were published between 2008 and 2019. Of the 18 different study populations, 14 used prospective cohort designs and 5 used cross-sectional designs. Cognitive function was assessed primarily via direct testing across a variety of domains at one point in time (i.e., not longitudinally), including intellectual function (e.g., verbal and nonverbal IQ), memory, learning, language, attention, and executive function.

Sample sizes varied from 174 to 9,482 participants. Larger studies were often a result of pooling across cohorts, such as the ESCAPE study, which spanned multiple European countries (Guxens et al. 2014) and the INMA study of Spanish cities (Guxens et al. 2012). Cognitive function was assessed in children as young as age 8 months (Ha et al. 2019) and up to age 20 years (Wang et al. 2017), although most studies assessed school-age children 6–10 years old.

Exposure estimates were based primarily on land use regression or dispersion models, although several studies used surface monitoring or source apportionment. Many studies reported on multiple traffic-related air pollutants. Ten studies assessed indirect traffic measures, and seven of those also reported on at least one traffic-related air pollutant. Three studies examined indirect measures only (Ha et al. 2019; Khan et al. 2019; Kicinski et al. 2015). Exposure was assessed during pregnancy/at birth based on maternal residence for 16 studies, during childhood (newborn to age 15 years), for 20 studies (also primarily based on residence), and during both periods for 6 studies.

Almost all studies of TRAP and cognitive function adjusted for a core set of covariates, which included child's age at assessment, sex, and some measure of SES; three studies did not adjust for sex (Freire et al. 2010; Ha et al. 2019; Lubczyńska et al. 2017). Most studies (n = 22) also adjusted for maternal smoking or passive smoking during pregnancy. Only seven studies—mostly European cohorts (all included in ESCAPE) (Guxens et al. 2012, 2014, 2018; Lertxundi et al. 2019; Lubczyńska et al. 2017; Porta et al. 2016; Sentís et al. 2017) and one North American study (Loftus et al. 2019)—adjusted for maternal prepregnancy body mass index. Seven studies examined confounding by prenatal or early life blood lead levels (Chiu et al. 2013; Guxens et al. 2012; Harris et al. 2015, 2016; Kicinski et al. 2015; Lertxundi et al. 2015; Suglia et al. 2008) and one study measured airborne lead (Pujol et al. 2016). Lead is a well-recognized neurotoxicant, with considerable literature showing associations with poorer cognitive function in children (Bellinger 2008). A third of the studies (10 of the 30) adjusted for confounding by traffic noise (Basagaña et al. 2016; Clark et al. 2012; Forns et al. 2017; Guxens et al. 2012; Mortamais et al. 2017; Porta et al. 2016; Saenen et al. 2016; Sentís et al. 2017; Sunyer et al. 2015; van Kempen et al. 2012). Thirteen studies examined differences in TRAP and cognitive function associations by sex (Chiu et al. 2013; Cowell et al. 2015; Fuertes et al. 2016; Ha et al. 2019; Harris et al. 2015, 2016; Lertxundi et al. 2019; Loftus et al. 2019; Mortamais et al. 2017; Rivas et al. 2019; Sentís et al. 2017; Sunyer et al. 2015; Wang et al. 2017) and half of the studies (15) examined the shape of the exposure–response function (Basagaña et al. 2016; Chiu et al. 2013; Cowell et al. 2015; Guxens et al. 2012, 2014; Ha et al. 2019; Harris et al. 2015, 2016; Lertxundi et al. 2015, 2019; Lubczyńska et al. 2017; Porta et al. 2016; Sentís et al. 2017; Suglia et al. 2008; Sunyer et al. 2015).

12.3.2 LITERATURE REVIEW

12.3.2.1 Comparing Results Across Different Traffic-Related Air Pollutants

Evidence for associations of TRAP with cognitive function was mixed. The traffic-related air pollutant with the largest number of studies of cognitive function was NO_2, with 14 studies representing nine distinct study populations (Table 12.1). Of these 14 studies, which included nearly all European cohorts, five found associations of NO_2 with at least one measure of cognitive function. Three studies reported associations of prenatal exposure to NO_2 with poorer cognition, including poorer infant cognition in the INMA Gipuzkoa study (Lertxundi et al. 2015), lower verbal IQ in the GASPII study (Porta et al. 2016), and poorer attention in the INMA multicity cohort (Sentís et al. 2017). The BREATHE study in Barcelona, Spain, reported associations of poorer working memory with childhood NO_2 exposure (Forns et al. 2017; Sunyer et al. 2015). The INMA Granada study found suggestive, although imprecise, associations for early childhood NO_2 exposure with poorer general cognitive abilities, including verbal ability, quantitative skills, and memory (Freire et al. 2010). The majority of studies of prenatal and childhood NO_2 reported null or very imprecise associations across all cognitive function endpoints, including general cognition (Gonzalez-Casanova et al. 2018; Guxens et al. 2012, 2014; Lertxundi et al. 2019; Loftus et al. 2019; van Kempen et al. 2012), memory (Clark et al. 2012), parent-reported dyslexia (Fuertes et al. 2016), and attention and working memory (Sunyer et al. 2015). Four of the five studies that reported associations of NO_2 with cognitive function examined exposure–response functions and determined that associations did not meaningfully deviate from linearity (Lertxundi et al. 2015; Porta et al. 2016; Sentís et al. 2017; Sunyer et al. 2015).

For NO_x (Table 12.2), only three studies representing three geographically diverse cohorts all reported null associations with general cognitive function (Gonzalez-Casanova et al. 2018; Guxens et al. 2014; Wang et al. 2017).

Table 12.1. Associations of NO_2 with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuopsychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Clark 2012	RANCH UK	London, United Kingdom	2002	719	42.73	Reading comprehension	Suffolk Reading Scale 2	Annual average at assessment	9 to 10	Reading comprehension (–)	Mean difference	0.00 (–0.01 to 0.01)	1 μg/m^3
						Working memory	Search and Memory Task			Working memory (–)		0.04 (–0.17 to 0.25)	
						Memory	Child Memory Scale			Conceptual recall (–)		–0.00 (–0.02 to 0.01)	
										Recognition memory (–)		–0.01 (–0.04 to 0.03)	
										Information recall (–)		0.01 (–0.04 to 0.06)	
Forns 2017	BREATHE	Barcelona, Spain	2012–2015	1,439	48.7	Working memory	*n*-back test	Average in year of first assessment	8.5 and 11.4	3-back detectability (3.5-year change) (–)	Mean difference	–4.22 (–6.22 to –2.22)	22.3 μg/m^3
Freire 2010	INMA Granada	Granada, Spain	2000–2006	210	24.75	General cognition	McCarthy Scales of Children's Abilities	Annual average at assessment	4	General cognition (–)	Mean difference	–4.19 (–14.02 to 5.64)	>24.8 vs. <15.4
												–1.07 (–9.99 to 7.85)	15.4–24.8 vs. <15.4
						Verbal cognition				Verbal ability (–)		–3.09 (–13.31 to 7.13)	
												–0.25 (–9.53 to 9.03)	
						Perceptual performance				Perceptual-performance cognition (–)		–2.17 (–12.76 to 8.41)	
												0.45 (–9.17 to 10.06)	
						Quantitative cognition				Quantitative skills (–)		–6.71 (–17.91 to 4.49)	
												–4.16 (–14.33 to 6.02)	
						Memory				Memory (–)		–5.52 (–16.18 to 5.13)	
												–2.28 (–11.95 to 7.38)	

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Table 12.1 (*Continued*). Associations of NO_2 with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuopsychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Fuertes 2016	GINIplus, LISAplus	Multiple cities, Germany	1995–2013	4,745	20.6 South, 23.2 North	Dyslexia	Parent questionnaire	Annual average at birth	10 and 15	Dyslexia (+)	OR	1.04 (0.93 to 1.16)	8.1 µg/m³ South, 3.2 µg/m³ North
								10				1.02 (0.86 to 1.22)	
								15				1.00 (0.90 to 1.12)	
Gonzalez-Casanova 2018	POSGRAD	Mexico-City, Mexico	2005–2014	718	16	General cognition	Composite[e]	Entire pregnancy	1, 1.5, 5, and 7	Low vs. positive cognitive development (over 6 years) (+)	OR	1.01 (0.99 to 1.03)	20.4 ppb
										Average vs. positive cognitive development (over 6 years) (+)		1.01 (0.99 to 1.03)	
Guxens 2012	INMA	Multiple cities, Spain	2002–2010	1,854	29.0	Infant cognition	Bayley Scales of Infant Development	Entire pregnancy	14 months	Infant cognition (–)	Mean difference	–0.95 (–3.90 to 1.89)	2-fold increase
Guxens 2014	ESCAPE	Multiple cities, multiple countries	2000–2011	9,482	11.5 to 43.9	General cognition	Composite[f]	Entire pregnancy	1 to 6	General cognition (–)	Mean difference	–0.23 (–0.96 to 0.50)	10 µg/m³
						Verbal cognition				Language development (–)		0.15 (–0.39 to 0.70)	
Lertxundi 2015	INMA Gipuzkoa	Gipuzkoa, Spain	2006–2010	438	20.33	Infant cognition	Bayley Scales of Infant Development	Entire pregnancy	13 to 18 months (mean 15 months)	Infant cognition (–)	Mean difference	–0.25 (90% CI: –0.40 to –0.10)	1 µg/m³

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Table 12.1 (*Continued*). Associations of NO_2 with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuopsychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Lertxundi 2019	INMA	Multiple cities, Spain	2004–2014	1,119	32.3	General cognition	McCarthy Scales of Children's Abilities	Entire pregnancy	4 to 6	General cognition (–)	Mean difference	–0.07 (–0.17 to 0.03)	1 µg/m^3
						Verbal cognition				Verbal cognition (–)		–0.06 (–0.15 to 0.03)	
						Perceptual-performance				Perceptive-Manipulative cognition (–)		–0.04 (–0.15 to 0.08)	
						Quantitative cognition				Numeric cognition (–)		–0.13 (–0.25 to 0.00)	
						Memory				Memory (–)		–0.10 (–0.22 to 0.02)	
Loftus 2019	CANDLE	Shelby County, Tennessee, United States	2006–2017	905	12.06	General cognition	Stanford Binet Intelligence Scales, edition 5	Entire pregnancy	4 to 6	Full Scale IQ (–)	Mean difference	1.15 (–0.95 to 3.25)	5 µg/m^3
						Verbal cognition				Verbal IQ (–)		0.82 (–1.31 to 2.94)	
						Quantitative cognition				Nonverbal IQ (–)		1.10 (–1.04 to 3.23)	
Porta 2016	GASPII	Rome, Italy	2003–2011	474	44.9	General cognition	Wechsler Intelligence Scale for Children–III	Annual average at birth	7	Full scale IQ (–)	Mean difference	–1.1 (–2.3 to 0.10)	10 µg/m^3
						Verbal cognition				Verbal IQ (–)		–1.4 (–2.6 to –0.20)	
						Perceptual-performance cognition				Performance IQ (–)		–0.58 (–1.9 to 0.73)	

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Table 12.1 (*Continued*). Associations of NO_2 with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuopsychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Sentís 2017	INMA	Multiple cities, Spain	2003–2013	1,298	31.1–25.7	Attention	Kiddie-Conners Continuous Performance Test	Entire pregnancy	4 to 5	Hit reaction time (msec) (+)	Mean difference	–1.12 (–9.00 to 6.75)	10 µg/m^3
										Hit reaction time standard error (+)		1.12 (0.22 to 2.02)	
										Detectability (–)		–0.03 (–0.09 to 0.03)	
										Omission errors (+)	RR	1.06 (1.01 to 1.11)	
						Response inhibition				Commission errors (+)		1.04 (0.97 to 1.12)	
						Attention		Birth to 4		Hit reaction time (+)	Mean difference	–4.70 (–13.80 to 4.39)	
										Hit reaction time standard error (+)		0.81 (–0.82 to 2.43)	
										Detectability (–)		–0.03 (–0.09 to 0.03)	
										Omission errors (+)	RR	1.05 (0.99 to 1.11)	
						Response inhibition				Commission errors (+)		1.04 (0.96 to 1.13)	

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Table 12.1 (*Continued*). Associations of NO_2 with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuopsychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Sunyer 2015	BREATHE	Barcelona, Spain	2012–2013	2,715	48.5	Attention	Attentional Network Task	Annual average at assessment	9	Hit reaction standard error (1-year change) (+)	Mean difference	3.8 (–0.10 to 7.6)	23.3 µg/m^3
						Working memory	*n*-back test			2-back detectability (1-year change) (–)		–6.6 (–12 to –1.2)	
										3-back detectability (1-year change) (–)		–6.7 (–11 to –2.3)	
van Kempen 2012	RANCH Netherlands	Amsterdam, the Netherlands	2002	485	31.0	Attention	Neurobehavioral Evaluation System	Annual average at assessment	10	Simple Reaction Time Test: Reaction time (+)	Mean difference	–2.01 (–11.55 to 7.53)	10 µg/m^3
										Switching Attention Test: Block test errors (+) reaction time (+)		–0.01 (–0.20 to 0.17) 7.33 (–6.48 to 21.14)	
										Switching Attention Test: Arrow test errors (+) reaction time (+)		–0.14 (–0.45 to 0.16) 0.11 (–19.92 to 20.15)	
										Switching Attention Test: Switch test errors (+) reaction time (+)		–0.53 (–1.63 to 0.57), –13.40 (–41.29 to 14.49)	

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Table 12.1 (*Continued*). Associations of NO_2 with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuopsychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)[d]	Increment
						Working memory				Symbol Digit Substitution Test: latency (+)		0.00 (–0.11 to 0.10)	
						Memory				Digit Memory Span Test: span length (–)		0.09 (–0.03 to 0.21)	

OR = odds ratio; RR = relative risk.

[a] All study designs are cohort except Clark 2012, Freire 2010, and van Kempen 2012 (cross-sectional).

[b] Unit in the increment column. Exposure assessment for all studies is LUR, except for Forns 2016, and Sunyer 2015 (surface monitoring).

[c] A negative direction (–) means that a lower score indicates poorer cognitive function or greater cognitive difficulty; a positive direction (+) means that a higher score indicates poorer cognitive function or greater cognitive difficulty. Ratio measures >1.0 indicate higher risk for the outcome.

[d] Dark orange = evidence of association with poorer cognition; light orange = suggestive evidence of association with poorer cognition.

[e] Composite of Bayley Scales of Infant Development II, McCarthy Scales of Children's Abilities, Wechsler Abbreviated Scale of Intelligence.

[f] Composite of Bayley Scales of Infant Development I, II & III, McArthur Communicative Development Inventory, Denver Developmental Screening Test II, McCarthy Scales of Children's Abilities.

Table 12.2. Associations of NO_X with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuro-psychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)	Increment
Gonzalez-Casanova 2018	POSGRAD	Mexico City, Mexico	2005–2014	718	21.2	General cognition	Composite[d]	Entire pregnancy	1, 1.5, 5, and 7	Low vs. positive cognitive development (+)	OR	1.00 (0.96 to 1.03)	14.4 ppb
										Average vs. positive cognitive development (+)		1.01 (0.98 to 1.04)	
Guxens 2014	ESCAPE	Multiple cities, multiple countries	2000–2011	9,482	42 to 70	Verbal cognition	Composite[e]	Entire pregnancy	1 to 6	Language development (–)	Mean difference	0.18 (–0.18 to 0.53)	20 μg/m^3
						General cognition				General cognition (–)		–0.16 (–0.71 to 0.39)	
Wang 2017	RFAB	Los Angeles, California, United States	1990–2015	1,042	18	General cognition	Wechsler Abbreviated Scale of Intelligence	Year before assessment	9 to 11 and 18 to 20	Full-scale IQ (–)	Mean difference	0.26 (–0.76 to 1.28)	7.73 μg/m^3
						Verbal cognition			9 to 11 and 18 to 20	Verbal IQ (–)		0.43 (–0.67 to 1.53)	
						Perceptual-performance			9 to 11 and 18 to 20	Performance IQ (–)		0.09 (–0.97 to 1.15)	

OR = odds ratio.

[a] Study design is cohort for all studies.

[b] Unit in the increment column. Exposure assessment for all studies is LUR except Wang 2017 (dispersion/chemical transport modeling).

[c] A negative direction (–) means that a lower score indicates poorer cognitive function or greater cognitive difficulty; a positive direction (+) means that a higher score indicates poorer cognitive function or greater cognitive difficulty. Ratio measures >1.0 indicate higher risk for the outcome.

[d] Composite of Bayley Scales of Infant Development II, McCarthy Scales of Children's Abilities, Wechsler Abbreviated Scale of Intelligence.

[e] Composite of Bayley Scales of Infant Development I, II & III, McArthur Communicative Development Inventory, Denver Developmental Screening Test II, McCarthy Scales of Children's Abilities.

There were 11 studies that investigated associations of EC, which includes black carbon, black smoke, and PM absorbance) with cognitive function (Table 12.3), representing eight cohorts (although in some cases a study was part of a set of pooled studies, e.g., the Generation R study [Guxens et al. 2018] was also included in ESCAPE [Guxens et al. 2014]). Five of the 11 studies found associations, primarily for childhood EC exposure, with poorer function for a range of cognitive endpoints, including general cognition and visual memory in the Boston MISSEB study (Suglia et al. 2008), attention in the MISSEB and BREATHE study (Chiu et al. 2013; Sunyer et al. 2015), working memory in the BREATHE cohorts (Forns et al. 2017; Sunyer et al. 2015), and behavioral regulation in Project Viva (Harris et al. 2016). Project Viva, which found many null associations, also reported that higher childhood EC exposure was associated with better cognition, particularly nonverbal IQ (Harris et al. 2015), and that higher prenatal EC exposure was associated with fewer teacher-reported behavior problems (Harris et al. 2016). Five studies reported null associations of prenatal and childhood EC across all tests of cognition, including tests of general cognition (Guxens et al. 2014), memory and learning (Cowell et al. 2015; Guxens et al. 2018), attention and working memory (Saenen et al. 2016), and parent-reported dyslexia (Fuertes et al. 2016). Of the five studies that found associations of EC with poorer cognitive function, three examined exposure–response functions (Harris et al. 2016; Suglia et al. 2008; Sunyer et al. 2015). Two of the studies found that associations did not deviate from linearity (Suglia et al. 2008; Sunyer et al. 2015), and one found a potential threshold effect for EC (at 0.5 $\mu g/m^3$) with executive function (Harris et al. 2016).

Eight studies (representing seven cohorts) examined $PM_{2.5}$ in relation with cognitive function (Appendix Table 12A-2). Only the BREATHE cohort reported consistent associations for prenatal and childhood $PM_{2.5}$ with cognition and, more specifically, attention and working memory (Rivas et al. 2019). The COGNAC study also found associations of childhood $PM_{2.5}$ with poorer attention and working memory but not short-term memory or processing speed (Saenen et al. 2016). In the Generation R study, prenatal $PM_{2.5}$ was associated with poorer response inhibition but was not associated with attention (Guxens et al. 2018). Paradoxically, $PM_{2.5}$ was associated with better verbal IQ and visual motor abilities in Project Viva, although associations were null across other general cognition outcomes (Harris et al. 2015). Four studies reported null associations of $PM_{2.5}$ with all cognition tests administered in domains of parent-reported dyslexia (Fuertes et al. 2016), general cognition (Guxens et al. 2014; Lertxundi et al. 2019), and executive function (Harris et al. 2016). None of the studies that reported associations of $PM_{2.5}$ with poorer cognitive function examined the shape of the exposure–response function.

Two of four studies found associations of PM_{10} with poorer cognition (Appendix Table 12A-3), including the CANDLE study, which reported poorer general cognition (Loftus et al. 2019) with prenatal PM_{10} exposure, and the COGNAC study, which reported worse attention (Saenen et al. 2016) with childhood PM_{10} exposure. Associations with PM_{coarse} were all null (Guxens et al. 2014, 2018). For the four studies of chemical and source-specific components of PM (Appendix Table 12A-4), only the BREATHE study reported associations of PM components, in particular $PM_{2.5}$ from traffic and $PM_{2.5}$ copper, with attention and working memory (Basagaña et al. 2016; Pujol et al. 2016), whereas the ESCAPE study reported null associations of $PM_{2.5}$, copper, iron, and zinc and traffic from principal component analysis with general cognition (Lubczyńska et al. 2017). Finally, only two studies that examined UFPs—both BREATHE studies—(Appendix Table 12A-5) found associations of childhood UFP exposure with greater difficulty in attention and working memory (Forns et al. 2017; Sunyer et al. 2015). Only the BREATHE studies examined exposure–response functions and found no evidence for nonlinearity in studies reporting associations with chemical and source-specific components of PM and UFPs (Basagaña et al. 2016; Sunyer et al. 2015).

Three studies examined benzene exposure (Appendix Table 12A-6) and one study examined PAH exposure (Appendix Table 12A-7) in relation to cognitive function. Studies of prenatal benzene exposure in the POSGRAD and INMA Gipuzkoa cohorts (Gonzalez-Casanova et al. 2018; Lertxundi et al. 2015), and childhood PAH (measured as benzo[a]pyrene) exposure in the BREATHE study (Mortamais et al. 2017), all report null associations with general cognition and attention. The INMA cohort reported suggestive associations of benzene with poorer infant mental development (Guxens et al. 2012).

There were 10 studies reporting indirect traffic measures, representing eight different cohorts (Appendix Table 12A-8). Of the six studies that examined distance to roadway in relation to cognitive function, only Project Viva found that shorter distance to roadway at birth was associated with lower verbal and nonverbal IQ (Harris et al. 2015). There were also suggestive associations for shorter distance to roadway and poorer executive function in Project Viva (Harris et al. 2016), and slightly higher risk for failure to meet developmental milestones by age 3 years in the Upstate KIDS study (Ha et al. 2019). The evidence for traffic density was a bit stronger, with three of the six studies reporting associations of higher childhood exposure to traffic density with poorer cognitive function (Harris et al. 2016; Porta et al. 2016; Sunyer et al. 2015). Project Viva reported associations with poorer executive function (Harris et al. 2016), the GASPII study with poorer verbal IQ (Porta et al. 2016), and the BREATHE study with poorer attention and working memory (Sunyer et al. 2015). Two studies reported null associations of traffic density with language (Guxens et al. 2014) and attention and memory (Kicinski et al. 2015), and Project Viva reported associations of prenatal exposure to higher traffic density with slightly higher nonverbal IQ (Harris et al. 2015).

Table 12.3. Associations of EC with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Pollutant	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuro-psychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Chiu 2013	MISSEB	Boston, Massachusetts, United States	1986–1998	174	BC	0.63	Attention	Conner's Continuous Performance Test	Birth to assessment	9 to 11	Omission errors (+)	Mean difference	0.62 (–8.57 to 9.81)	0.70–0.99 vs. 0.28–0.53 μg/m³
													4.89 (–4.71 to 14.49)	0.63–0.69 vs. 0.28–0.53 μg/m³
													2.66 (–6.34 to 11.66)	0.54–0.62 vs. 0.28–0.53 μg/m³
							Response inhibition				Commission errors (+)		3.32 (–0.87 to 7.51)	
													4.75 (0.36 to 9.14)	
													6.15 (2.03 to 10.27)	
							Attention				Hit reaction time (+)		1.75 (–4.44 to 7.94)	
													6.14 (–0.35 to 12.63)	
													6.51 (0.43 to 12.59)	
Cowell 2015	ACCESS	Boston, Massachusetts, United States	2002–2015	258	BC	0.4	Memory	Wide Range Assessment of Memory and Learning	Entire pregnancy	6	General memory index (–)	Mean difference	–0.55 (SE: 1.0, $P = 0.58$)	0.21 μg/m³
Forns 2017	BREATHE	Barcelona, Spain	2012–2015	1,439	EC	1.5	Working memory	n-back test	8.5	8.5 and 11.4	3-back detectability (3.5-year change) (–)	Mean difference	–2.13 (–3.26 to –0.99)	0.6 μg/m³

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Table 12.3 (*Continued*). Associations of EC with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Pollutant	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuro-psychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Fuertes 2016	GINIplus, LISAplus	Multiple cities, Germany	1995–2013	4,745	$PM_{2.5}$ abs	1.7 South, 1.2 North	Dyslexia	Parent questionnaire	Annual average at birth	10 and 15	Dyslexia (+)	OR	1.08 (0.98 to 1.19)	0.2 1×10^{-5}/m South, 0.2 1×10^{-5}/m North
									10				1.06 (0.86 to 1.31)	
									15				0.99 (0.90 to 1.10)	
Guxens 2014	ESCAPE	Multiple cities, multiple countries	2000–2011	9,482	$PM_{2.5}$ abs	7 to 20	General cognition	Composite[e]	Entire pregnancy	1 to 6	General cognition (–)	Mean difference	0.55 (–2.16 to 3.25)	1 1×10^{-5}/m
							Verbal cognition				Language development (–)		0.06 (–0.87 to 0.99)	
Guxens 2018	Generation R	Rotterdam, the Netherlands	2002–2012	783	$PM_{2.5}$ abs	1.9	Memory	Developmental Neuropsychological Assessment	Entire pregnancy	6 to 10	Memory for faces (–)	Mean difference	0.22 (–0.24 to 0.69)	1 1×10^{-5}/m
											Memory for faces delayed (–)		0.29 (–0.23 to 0.81)	
Harris 2015	Project Viva	Boston, Massachusetts, United States	1999–2010	1,095	BC	0.69	Verbal cognition	Kaufman Brief Intelligence Test	Third trimester	8.0	Verbal IQ (–)	Mean difference	0.2 (–0.9 to 1.4)	0.32 μg/m³
							Nonverbal cognition				Nonverbal IQ (–)		1.2 (–0.2 to 2.7)	
							Verbal cognition		Birth to 6		Verbal IQ (–)		0.9 (–0.4 to 2.2)	0.22 μg/m³
							Nonverbal cognition				Nonverbal IQ (–)		1.7 (0.1 to 3.4)	
							Verbal cognition		Year before assessment		Verbal IQ (–)		1.1 (–0.2 to 2.4)	0.20 μg/m³

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Table 12.3 (*Continued*). Associations of EC with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Pollutant	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuro-psychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)[d]	Increment
							Nonverbal cognition		Year before assessment		Nonverbal IQ (–)		0.7 (–0.9 to 2.4)	
							Memory	Wide Range Assessment of Memory and Learning	Third trimester		Design memory (–)		–0.1 (–0.3 to 0.2)	0.32 µg/m³
											Picture memory (–)		–0.1 (–0.3 to 0.2)	
									Birth to 6		Design memory (–)		–0.1 (–0.4 to 0.2)	0.22 µg/m³
											Picture memory (–)		–0.1 (–0.4 to 0.2)	
									Year before assessment		Design memory (–)		–0.1 (–0.4 to 0.2)	0.20 µg/m³
											Picture memory (–)		0.0 (–0.3 to 0.3)	
Harris 2016	Project Viva	Boston, Massa-chusetts, United States	1999–2010	1,212	BC	0.47	Executive function	Behavior Rating Inventory of Executive Function (Teacher rated)	Third trimester	6.6 to 10.9, median 7.7	Global Executive Function (+)	Mean difference	–1.0 (–1.9 to 0.0)	0.33 µg/m³
											Behavioral Regulation Index (+)		–0.2 (–1.1 to 0.8)	
											Metacogni-tion Index (+)		–1.2 (–2.2 to –0.2)	
									Birth to 3		Global Executive Function (+)		0.0 (–1.0 to 1.0)	0.23 µg/m³
											Behavioral Regulation Index (+)		0.6 (–0.4 to 1.5)	
											Metacogni-tion Index (+)		–0.3 (–1.4 to 0.7)	

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Table 12.3 (*Continued*). Associations of EC with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Pollutant	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuro-psychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)[d]	Increment
									Birth to 6		Global Executive Function (+)		0.4 (–0.7 to 1.5)	0.22 μg/m³
											Behavioral Regulation Index (+)		1.0 (0.0 to 2.1)	
											Metacogni-tion Index (+)		0.0 (–1.1 to 1.2)	
									Year before assessment		Global Executive Function (+)		1.0 (–0.1 to 2.1)	0.20 μg/m³
											Behavioral Regulation Index (+)		1.7 (0.6 to 2.8)	
											Metacogni-tion Index (+)		0.5 (–0.6 to 1.6)	
							Behavior problems	Strengths and Difficul-ties Question-naire (teacher report)	Third trimester		Total difficulties (+)		–0.9 (–1.4 to –0.4)	0.33 μg/m³
									Birth to 3				–0.3 (–0.9 to 0.2)	0.23 μg/m³
									Birth to 6				–0.1 (–0.7 to 0.5)	0.22 μg/m³
									Year before assessment				0.1 (–0.5 to 0.8)	0.20 μg/m³
								Strengths and Difficul-ties Question-naire (parent report)	Third trimester		Total difficul-ties (+)		–0.2 (–0.6 to 0.2)	0.33 μg/m³
									Birth to 3				–0.1 (–0.5 to 0.3)	0.23 μg/m³
									Birth to 6				0.0 (–0.5 to 0.4)	0.22 μg/m³
									Year before assessment				0.1 (–0.4 to 0.5)	0.20 μg/m³

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Table 12.3 (*Continued*). Associations of EC with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Pollutant	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuro-psychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Saenen 2016	COGNAC	Flanders, Belgium	2011–2014	310	BC	1.54	Executive function	Stroop Test	Year before assessment	10	Selective attention (+)	Mean difference	6.7 (–38.4 to 51.9)	0.20 μg/m³
							Attention	NES3: Continuous Performance Test			Reaction time (+)		5.72 (–0.34 to 11.8)	
							Working memory	NES3: Digit Span Test			Digit span backward (+)		0.10 (–0.01 to 0.20)	
								NES3: Pattern Comparison Test			Pattern comparison latency (+)		0.07 (–0.06 to 0.19)	
								NES3: Digit Symbol Test			Digit symbol latency (+)		0.50 (–1.99 to 2.99)	
							Memory	NES3: Digit Span Test			Digit span forward (+)		0.03 (–0.09 to 0.14)	
Suglia 2008	MISSEB	Boston, Massachusetts, United States	1986–2001	218	BC	0.56	General cognition	Kaufman Brief Intelligence Test	Birth to assessment	8 to 11, mean 9.7	Composite intelligence (–)	Mean difference	–3.3 (–6.4 to –0.1)	0.4 μg/m³
							Verbal cognition				Verbal intelligence (–)		–2.0 (–5.3 to 1.4)	
							Nonverbal cognition				Nonverbal intelligence (–)		–4.0 (–7.6 to –0.4)	
							Memory	Wide Range Assessment of Memory and Learning			General memory (–)		–3.7 (–7.3 to –0.1)	
											Verbal memory (–)		–1.2 (–4.7 to 2.3)	
											Visual memory (–)		–5.3 (–8.8 to –1.8)	
											Learning (–)		–2.6 (–6.5 to 1.2)	

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Table 12.3 (*Continued*). Associations of EC with Cognitive Function

Reference	Study Name[a]	Location	Study Period	Sample Size	Pollutant	Mean or Median Exposure[b]	Cognitive Domain(s)	Neuro-psychological Test(s)	Exposure Window	Age at Outcome (yr)	Outcome (Direction[c])	Effect Measure	Effect Estimate (95% CI)[d]	Increment
Sunyer 2015	BREATHE	Barcelona, Spain	2012–2013	2,715	EC	1.32	Attention	Attentional Network Task	Annual average at assessment	9	Hit reaction time standard error (1-year change) (+)	Mean difference	3.8 (1.0 to 6.6)	0.7 μg/m^3
							Working memory	n-back test			2-back detect-ability (1-year change) (–)		–4.1 (–8.0 to –0.2)	
											3-back detect-ability (1-year change) (–)		–4.4 (–7.6 to –1.3)	

NES3 = Neurobehavioral Evaluation System 3; OR = odds ratio.

[a] Study design is cohort for all studies.

[b] Unit in the increment column. Exposure assessment for all studies is LUR except Forns 2016 and Sunyer 2015 (surface monitoring).

[c] A negative direction (–) means that a lower score indicates poorer cognitive function or greater cognitive difficulty; a positive direction (+) means that a higher score indicates poorer cognitive function or greater cognitive difficulty. Ratio measures >1.0 indicate higher risk for the outcome.

[d] Dark orange = evidence of association with poorer cognition; light orange = suggestive evidence of association with poorer cognition; dark blue = evidence of association with better cognition; light blue = suggestive evidence of association with better cognition.

[e] Composite of Bayley Scales of Infant Development I, II & III, McArthur Communicative Development Inventory, Denver Developmental Screening Test II, McCarthy Scales of Children's Abilities

Of the eight studies that adjusted for early life lead exposure and the 10 that adjusted for noise, none reported confounding by these variables. For the 13 studies that examined sex differences, six reported stronger exposure–outcome associations among boys (Chiu et al. 2013; Cowell et al. 2015; Lertxundi et al. 2019; Rivas et al. 2019; Sunyer et al. 2015; Wang et al. 2017) and only one study showed slightly stronger associations for girls (Sentís et al. 2017); the rest found no evidence for sex differences (Fuertes et al. 2016; Ha et al. 2019; Harris et al. 2016, 2015; Loftus et al. 2019; Mortamais et al. 2017; Sunyer et al. 2015).

12.3.2.2 Comparing Results Across Cognitive Function Domains

Patterns of associations of TRAP exposure with cognitive function were also mixed when examined by cognitive domain. Tables of TRAP and cognitive function by domain are not included in the report, as all results can be found in tables organized by traffic-related air pollutant. Of the 9 studies of general cognition (e.g., Full Scale IQ), only two studies showed associations with poorer general cognitive function, including associations with prenatal PM_{10} exposure (Loftus et al. 2019) and childhood black carbon exposure (Suglia et al. 2008). When broken down into verbal and nonverbal intelligence, there were 11 studies of verbal intelligence, three of which showed associations with prenatal TRAP, including NO_2 (Porta et al. 2016), PM_{10} (Loftus et al. 2019), distance to roadway (Harris et al. 2015), and traffic density (Porta et al. 2016). Of the four studies of nonverbal intelligence, only two found associations with prenatal TRAP, including EC (Suglia et al. 2008) and distance to roadway (Harris et al. 2015). Associations of TRAP with quantitative intelligence and perceptual performance reported in three and four studies, respectively, were all null. In addition, of the 10 studies that examined TRAP in relation to memory, only one study reported associations of childhood EC with visual and general memory (Suglia et al. 2008).

Studies of TRAP and attention and executive functions, including working memory and response inhibition, were slightly more suggestive, but also mixed. There were 12 studies of TRAP and attention, the most of any neurodevelopmental domain. Of the six studies that reported associations with attention, four were from the BREATHE cohort, which used an Attentional Network Task and reported associations of childhood $PM_{2.5}$ traffic (Basagaña et al. 2016); $PM_{2.5}$ copper (Pujol et al. 2016); $PM_{2.5}$ (Rivas et al. 2019); and EC, traffic density, and UFPs (Sunyer et al. 2015). In addition, a BREATHE study reported suggestive associations between NO_2 with hit reaction time and variability (Sunyer et al. 2015). Two other studies reported associations of prenatal exposure to NO_2 (Sentís et al. 2017) and childhood exposure to PM_{10} and $PM_{2.5}$ (Saenen et al. 2016) with poorer attention measured with continuous performance tests. Studies reporting associations of TRAP with working memory were also heavily dominated by results from BREATHE (four of the eight studies were from BREATHE). The BREATHE study reported associations of childhood $PM_{2.5}$ traffic (Basagaña et al. 2016), EC, NO_2, UFPs, and traffic density (Forns et al. 2017; Sunyer et al. 2015), and suggestively $PM_{2.5}$ (Rivas et al. 2019), with an *n*-back test. In the *n*-back test, participants are asked to respond to whether a stimulus matched the one presented in a trial that appeared *n* items ago (in BREATHE this was two or three trials ago, referred to as 2-back and 3-back, respectively). Associations of TRAP with working memory for the other four studies, all conducted in populations other than BREATHE, were null. For the three studies of response inhibition, one study found associations of childhood EC with commission errors (Chiu et al. 2013), and one study reported associations of prenatal $PM_{2.5}$ with inhibition errors (Guxens et al. 2018). However, Chiu et al. (2013) documented no clear exposure–response function, and Guxens et al. (2018) reported null associations for the other three measures of response inhibition. Finally, there were only two studies of other measures of executive function, including cognitive flexibility, metacognition, and behavioral regulation. One study found that childhood EC and traffic density were associated with poorer teacher-rated executive function (behavioral regulation, in particular) but also reported associations in the opposite direction, with better metacognition with prenatal exposure to black carbon (Harris et al. 2016). The other study found associations of childhood $PM_{2.5}$ and PM_{coarse} with selective attention on a cognitive flexibility test (Saenen et al. 2016).

12.3.2.3 Summary

The Panel found moderate confidence in the presence of an association of TRAP with poorer cognitive function, based on fairly robust literature (30 studies), representing 18 different cohorts ranging in study size and depth of data collection, predominantly based in Europe and North America. Studies examined a variety of traffic-related air pollutants and found suggestive associations for NO_2, EC, and $PM_{2.5}$ with prenatal and childhood exposure. However, studies found somewhat inconsistent associations across cognitive domains, with the most suggestive associations found for attention and executive function. Associations with indirect traffic measures were also mixed and slightly stronger for traffic density versus distance to roadway.

12.4 ATTENTION DEFICIT HYPERACTIVITY DISORDER AND RELATED BEHAVIORS

12.4.1 STUDY SELECTION AND DESCRIPTION

There were considerably fewer studies of TRAP and ADHD and related behaviors (inattention, hyperactivity, and impulsivity) compared with cognitive function, with only eight studies representing seven different study populations,

all based in Europe and North America (Appendix Table 12B-1). Sample sizes varied from a few hundred participants to approximately 29,000 in ESCAPE, a multicohort study of several European studies (Forns et al. 2018). Study populations were primarily drawn from prospective population-based cohorts (Forns et al. 2018; Fuertes et al. 2016; Gong et al. 2014; Newman et al. 2013; Roberts et al. 2019; Mortamais et al. 2017), but also included a cross-sectional analysis of the BREATHE cohort (Forns et al. 2016), and one case–control study (Saez et al. 2018).

All of the studies examined childhood TRAP exposure in association with ADHD, except for the ESCAPE study (Forns et al. 2018), which assessed prenatal exposure only. Two other studies additionally examined TRAP exposure during pregnancy or birth (Fuertes et al. 2016; Gong et al. 2014). Age at childhood exposure assessment ranged from infancy to 15 years. Most studies reported multiple traffic-related air pollutants. Only two studies also included indirect traffic measures (distance or density).

Studies assessed ADHD and related behaviors primarily using parent or teacher rating scales (and in one case self-report) of symptomatology related to ADHD, including inattention, hyperactivity, and impulsivity. One study examined ADHD diagnosis as reported by the primary physician (Saez et al. 2018). In addition, there were several studies in the cognitive function section (Section 12.3) that examined attention and response inhibition (Chiu et al. 2013; Mortamais et al. 2017; Pujol et al. 2016; Saenen et al. 2016; Sentís et al. 2017; van Kempen et al. 2012). Although these were not specific to ADHD per se, they do reflect behaviors (attention and response inhibition) that, when impaired at the extreme, are consistent with an ADHD diagnosis and could be considered as further supporting evidence. Age of ADHD assessment ranged from 4 to 18 years, and two studies assessed outcomes longitudinally (Fuertes et al. 2016; Roberts et al. 2019).

Seven of the eight studies reported associations adjusted for a core set of covariates, including age at assessment, sex, prenatal/postnatal tobacco smoke exposure, and some measure of SES; only one study did not adjust for SES or prenatal smoke exposure (Saez et al. 2018). Only one study adjusted for maternal prepregnancy body mass index (Forns et al. 2018), and one study adjusted for age of the home as a surrogate for lead exposure (Newman et al. 2013). The BREATHE studies adjusted for exposure to traffic noise (Forns et al. 2016; Mortamais et al. 2017) and three studies examined differences of associations of TRAP and ADHD by sex (Forns et al. 2018; Fuertes et al. 2016; Mortamais et al. 2017).

12.4.2 LITERATURE REVIEW

The confidence in an association of TRAP with ADHD and related behaviors was low. Of the four studies of NO_2 (Table 12.4)—all based in Europe—only the BREATHE study reported associations of cross-sectionally assessed NO_2 with higher risk for parent-reported inattentive/hyperactive behaviors on the Strength and Difficulties Questionnaire. The same study, however, reported null associations of NO_2 with teacher-reported ADHD symptomatology derived from ADHD diagnostic criteria as described in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (Forns et al. 2016). NO_2 and ADHD associations for the other three studies were all null (Forns et al. 2018; Fuertes et al. 2016; Roberts et al. 2019). There were only two studies of NO_x and ADHD (Table 12.5), and both showed null associations (Forns et al. 2018; Gong et al. 2014).

The evidence was slightly stronger, but still weak, for EC (Table 12.6). Of the four studies, representing four different cohorts, two found associations with ADHD, including the BREATHE study, which reported associations of childhood EC exposure with higher risk for parent-reported inattentive/hyperactive behaviors but null associations with teacher-reported ADHD symptomatology (Forns et al. 2016). In addition, a pooled analysis of the GINIplus and LISAplus study found associations of childhood EC exposure with higher risk for borderline/abnormal versus normal Strength and Difficulties Questionnaire hyperactivity and inattention scores, longitudinally measured at age 10 (parent report) and 15 years (self-report) (Fuertes et al. 2016). The U.S. CCAAPS study found suggestive associations of EC exposure from birth to 1 year with risk for hyperactivity on the Behavioral Assessment System for Children, Second Edition, but not inattention (Newman et al. 2013). Associations of EC with ADHD were null—and even slightly protective—for the ESCAPE study (Forns et al. 2018).

For $PM_{2.5}$, only one study found evidence for an association with ADHD (Appendix Table 12B-2). The German GINIplus and LISAplus study reported associations of childhood exposure to $PM_{2.5}$ with higher risk for borderline/abnormal vs. normal Strength and Difficulties Questionnaire hyperactivity and inattention scores (Fuertes et al. 2016). The results of the remaining two studies were null (Forns et al. 2018; Roberts et al. 2019). Associations were also null for the three studies of PM_{10} mass and PM_{coarse} mass with ADHD (Appendix Table 12B-3) (Forns et al. 2018; Fuertes et al. 2016; Gong et al. 2014), and the one study of PAH reported suggestive associations with teacher report of ADHD traits (Appendix Table 12B-4) (Mortamais et al. 2017).

Finally, evidence from two studies of indirect traffic measures and ADHD (Appendix Table 12B-5) showed null associations across all outcomes (Forns et al. 2018; Saez et al. 2018).

None of the studies that adjusted for lead or noise reported confounding of TRAP–ADHD associations by these variables (Forns et al. 2018; Mortamais et al. 2017; Newman et al. 2013). Of the three studies that examined differences of associations of TRAP and ADHD by sex, none reported evidence of modification by sex (Forns et al. 2018; Fuertes et al. 2016; Mortamais et al. 2017). Only one study considered the exposure–response

Table 12.4. Associations of NO_2 with ADHD and Related Behaviors

Reference	Study Name	Location	Study Design	Study Period	Sample Size	Exposure Window	Age at Outcome (yr)	Exposure Assessment	Mean or Median Exposure[a]	Neuro-psychological Test(s)	Outcome	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Forns 2016	BREATHE	Barcelona, Spain	Cross-sectional	2012–2013	2,805	At assessment	7 to 11	Surface monitoring	48.46	ADHD-DSM-IV criteria (teacher)	ADHD symptomatology	Adjusted means ratio	1.03 (0.94 to 1.13)	22.26 µg/m³
										Strengths and Difficulties Questionnaire (parent)	Hyperactivity/inattention		1.07 (1.01 to 1.14)	
Forns 2018	ESCAPE	Multiple cities, multiple countries	Cohort	1992–2012	29,127	Entire pregnancy	3 to 10	LUR	15–45	Multiple tests[d]	ADHD traits within borderline or clinical range	OR	0.95 (0.89 to 1.01)	10 µg/m³
Fuertes 2016	GINIplus, LISAplus	Multiple cities, Germany	Cohort	1995–2013	4,745	Annual average at birth	10 and 15	LUR	20.6 South, 23.2 North	Strengths and Difficulties Questionnaire (parent at 10, self-report at 15)	Hyperactivity/inattention problems: Borderline/abnormal vs. normal	OR	1.03 (0.94 to 1.12)	8.1 µg/m³ South, 3.2 µg/m³ North
						10							1.04 (0.93 to 1.17)	
						15							1.02 (0.93 to 1.11)	
Roberts 2019	E-Risk Longitudinal Twin Study	London, United Kingdom	Cohort	1994–2013	284	At assessment	12	Dispersion/CTM	37.9	DSM-IV criteria, Rutter Child Scales (parent and teacher)	ADHD traits: inattention, hyperactivity-impulsivity	Mean difference	0.04 (–0.10 to 0.19)	1 µg/m³
							18			DSM-IV, DSM-V criteria (parent and co-informant)	ADHD traits		0.04 (–0.13 to 0.21)	
										Diagnostic Interview Schedule, using DSM-IV, DSM-V criteria	ADHD psychiatric diagnosis	OR	1.20 (0.69 to 2.09)	

OR = odds ratio.

[a] Unit in the increment column.

[b] A higher score indicates more ADHD traits. Ratio measures >1.0 indicate higher risk for ADHD.

[c] Light orange = suggestive evidence of association with ADHD or more ADHD traits.

[d] Autism-tics, Attention Deficit and Hyperactivity and Other Co-Morbidities (parent report); Child Behavior Checklist for Toddlers, attention deficit/hyperactivity problems (parent report); Strengths and Difficulties Questionnaire, hyperactivity/inattention (parent report); ADHD-DSM-IV list criteria (teacher-report).

Table 12.5. Associations of NO_x with ADHD and Related Behaviors

Reference	Study Name	Location	Study Design	Study Period	Sample Size	Exposure Window	Age at Outcome (yr)	Exposure Assessment	Mean or Median Exposure[a]	Neuro-psycho-logical Test(s)	Outcome	Effect Measure	Effect Estimate (95% CI)	Increment
Forns 2018	ESCAPE	Multiple cities, multiple countries	Cohort	1992–2012	29,127	Entire pregnancy	3 to 10	LUR	25–80	Multiple tests[c]	ADHD traits within borderline or clinical range	OR	0.97 (0.92 to 1.01)	20 µg/m^3
Gong 2014	CATSS	Stockholm, Sweden	Cohort	1992–2012	3,426	Entire pregnancy	9 or 12	Dispersion/ CTM	9.5	Autism-Tics, ADHD, and Other Comorbidities inventory (parent)	Probable ADHD diagnosis based on DSM-IV criteria	OR	0.64 (0.33 to 1.24)	95th to 5th percentile difference
						First year							0.88 (0.48 to 1.60)	
						Year before assessment							1.15 (0.62 to 2.15)	

OR = odds ratio.

[a] Unit in the increment column.

[b] A higher score indicates more ADHD traits. Ratio measures >1.0 indicate higher risk for ADHD.

[c]Autism-tics, Attention Deficit and Hyperactivity and Other Co-Morbidities (parent report); Child Behavior Checklist for Toddlers, attention deficit/hyperactivity problems (parent report); Strengths and Difficulties Questionnaire, hyperactivity/inattention (parent report); ADHD-DSM-IV list criteria (teacher-report).

Table 12.6. Associations of EC with ADHD and Related Behaviors

Reference	Study Name	Location	Study Design	Study Period	Sample Size	Exposure Window	Age at Outcome (yr)	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	Neuro-psychological Test(s)	Outcome	Effect Measure	Effect Estimate (95% CI)[c]	Increment
Forns 2016	BREATHE	Barcelona, Spain	Cross-sectional	2012–2013	2,714	At assessment	7–11	Surface monitoring	EC	1.33	Strengths and Difficulties Questionnaire (parent)	Hyper-activity/ inattention	Adjusted means ratio	1.07 (1.03 to 1.12)	0.86 µg/m^3
											ADHD-DSM-IV crite-ria (teacher)	ADHD symp-tomatology		0.99 (0.93 to 1.07)	
Forns 2018	ESCAPE	Multi-ple cities, multiple countries	Cohort	1992–2012	29,127	Entire pregnancy	3 to 10	LUR	$PM_{2.5}$ abs	1.3–2.6	Multiple tests[d]	ADHD traits within bor-derline or clinical range	OR	0.89 (0.75 to 1.07)	1 1×10^{-5}/m
Fuertes 2016	GINIplus, LISAplus	Multi-ple cities, Germany	Cohort	1995–2013	4,745	Annual average at birth	10 and 15	LUR	$PM_{2.5}$ abs	1.7 South, 1.2 North	Strengths and Difficulties Questionnaire (parent at 10, self-report at 15)	Hyperac-tivity/ inat-tention: borderline/ abnormal vs. normal	OR	1.07 (0.99 to 1.16)	0.2 1×10^{-5}/m south, 0.2 1×10^{-5}/m north
						10								1.14 (1.05 to 1.25)	
						15								1.13 (1.04 to 1.23)	
Newman 2013	CCAAPS	Cincin-nati, Ohio, United States	Cohort	2001–2010	576	First year	7	LUR	EC	0.4	Behavioral Assessment System for Children, 2nd ed. (parent)	At risk for hyperactiv-ity (T score ≥mean + 1 SD)	OR	1.7 (1.0 to 2.7)	≥0.40 vs. <0.40 µg/m^3
												At risk for attention problems (T score≥ mean+1 SD)		1.1 (0.6 to 1.7)	

OR = odds ratio.

[a] Unit in the increment column.

[b] A higher score indicates more ADHD traits. Ratio measures >1.0 indicate higher risk for ADHD.

[c] Dark orange = evidence of association with ADHD or more ADHD traits; light orange = suggestive evidence of association with ADHD or more ADHD traits.

[d] Autism-tics, Attention Deficit and Hyperactivity and Other Co-Morbidities (parent report); Child Behavior Checklist for Toddlers, attention deficit/hyperactivity problems (parent report); Strengths and Difficulties Questionnaire, hyperactivity/inattention (parent report); ADHD-DSM-IV list criteria (teacher-report).

function between TRAP and risk for ADHD and reported null findings (Forns et al. 2018).

In summary, the Panel found low confidence in the presence of an association of TRAP with ADHD and related behaviors. There was a small amount of literature of TRAP and ADHD and related behaviors, with only eight studies representing seven cohorts in Europe and North America. Most studies reported null associations of pollutants with ADHD and related behaviors. The small number of studies that did find associations tended to find them with childhood exposure to EC and less so with NO_2 and $PM_{2.5}$.

12.5 AUTISM SPECTRUM DISORDERS AND RELATED BEHAVIORS

12.5.1 STUDY SELECTION AND DESCRIPTION

There were 14 studies that reported associations of TRAP with ASD and related behaviors, representing 11 different study populations (Appendix Table 12C-1). Most studies were based in North America and Europe, and there was one study based in China and another in Israel. Sample sizes ranged from a few hundred participants to almost 130,000. The majority of the study populations (n = 7) used a case–control design, and the rest (n = 4) used a cohort study design. All but one study (Chen et al. 2018) examined prenatal TRAP exposure, and approximately half of the studies also looked at exposure during the first few years of life.

Children were assessed for/diagnosed with ASD at ages as young as 2 years and as old as 13 years. With the exception of two studies, studies defined ASD based on a clinical diagnosis by a physician, psychologist, or related practitioner. The two studies that did not use clinical diagnosis used validated instruments for assessing ASD traits, including the Autism-Tics, ADHD, and other Comorbidities inventory (Gong et al. 2014; Guxens et al. 2016); the Pervasive Developmental Problems of the Child Behavior Checklist for Toddlers (Guxens et al. 2016); the Social Responsiveness Scale (Guxens et al. 2016); and the Childhood Autism Spectrum Test (Guxens et al. 2016).

Thirteen of the 14 studies reported associations adjusted for a core set of covariates, including sex, parental (primarily maternal) age at birth, and some measure of SES. Most studies (n = 9) adjusted for maternal or early life tobacco smoke exposure (Chen et al. 2018; Gong et al. 2014, 2017; Guxens et al. 2016; Ritz et al. 2018; Talbott et al. 2015a, 2015b; Volk et al. 2011, 2013). Only one study adjusted for maternal prepregnancy body mass index (Guxens et al. 2016), and no studies adjusted for traffic noise exposure. About half of the studies (n = 6) looked at whether the sex of the child modified TRAP–ASD associations (Gong et al. 2017; Guxens et al. 2016; Pagalan et al. 2019; Raz et al. 2018b; Ritz et al. 2018; von Ehrenstein et al. 2014).

12.5.2 LITERATURE REVIEW

There was moderate to high confidence in the presence of associations of TRAP with ASD and related behaviors. Four of the five studies of NO_2, representing five different cohorts in North America, Europe, and Israel reported associations with increased risk for ASD (Table 12.7). Both an Israeli and Danish study reported associations of NO_2 exposure in the first 9 months of life with approximately 8% to 9% higher risk for ASD diagnosis, as reported in national data sources (Raz et al. 2018b; Ritz et al. 2018). The Israeli study found similar associations of NO_2 during pregnancy with ASD (Raz et al. 2018b). Two North American studies also found suggestive associations of prenatal NO_2 exposure with ASD diagnosis (Becerra et al. 2013; Pagalan et al. 2019). Only the ESCAPE study, which pooled several European studies using cut points in the borderline-to-clinical range on various assessments of ASD traits, found null or even slightly protective associations for prenatal NO_2 exposure (Guxens et al. 2016).

For the five studies of NO_x, representing four different cohorts, only the CHARGE study in the state of California in the United States found associations with ASD (Table 12.8). Associations in the CHARGE study were strongest with NO_x exposure during the third trimester of pregnancy (Goodrich et al. 2018; Volk et al. 2013) and the first year of life (Volk et al. 2013). Associations of prenatal NO_x with ASD were null for the remaining cohorts, which were all European cohorts (Gong et al. 2014, 2017; Guxens et al. 2016). There were similarly mixed findings for NO (Appendix Table 12C-2) in two North American studies, with one reporting higher risk for ASD with pregnancy NO exposure in a Canadian cohort study (Pagalan et al. 2019) and another reporting null associations in a Los Angeles case–control study (Becerra et al. 2013). Only the ESCAPE study examined associations of EC and ASD traits (Table 12.9) and reported null, or even slightly protective, associations (Guxens et al. 2016).

For the four studies representing four cohorts of $PM_{2.5}$, only early childhood exposure was associated with higher risk for ASD (Appendix Table 12C-3). Three of the four studies, located in Asia, Europe, and North America, reported associations of $PM_{2.5}$ exposure during the first, second, and third year of life and higher risk of ASD diagnosis (Chen et al. 2018; Ritz et al. 2018; Talbott et al. 2015a). Both studies of prenatal exposure reported null associations (Guxens et al. 2016; Ritz et al. 2018).

Similarly, for the five studies of PM_{10} and PM_{coarse} (Appendix Table 12C-4), representing five cohorts, only two studies reported associations of childhood PM_{10} exposure with ASD (Chen et al. 2018; Ritz et al. 2018). Associations were null across the four studies of prenatal exposure (Gong et al. 2014, 2017; Guxens et al. 2016; Ritz et al. 2018). Of the two U.S. studies that reported associations with chemical and source-specific components of PM, including diesel PM and $PM_{2.5}$ copper, (Appendix Table 12C-5) (Talbott et al. 2015b;

Table 12.7. Associations of NO_2 with ASD and Related Behaviors

Reference	Study Name	Location	Study Design	Study Period	Sample Size	Exposure Window	Age at Outcome (yr)	Exposure Assessment	Mean or Median Exposure[a]	ASD Diagnosis or Neuropsychological Test(s)	Odds Ratio (95% CI)[b]	Increment
Becerra 2013	Los Angeles County DDS	Los Angeles County, California, United States	Case–control	1998–2009	58,423	Entire pregnancy	3 to 5	LUR	28.0	Autistic disorder diagnosis identified using California Department of Developmental Services database	1.05 (0.98 to 1.12)	9.70 ppb
Guxens 2016	ESCAPE	Multiple cities, multiple countries	Cohort	1992–2012	8,079	Entire pregnancy	4 to 10	LUR	17.9–42.2	Borderline/clinical range of autistic traits using validated cutoffs for 4 tests.[d]	0.95 (0.81 to 1.10)	10 µg/m^3
										Clinical range for 4 tests.[d]	0.87 (0.67 to 1.14)	
Pagalan 2019	Vancouver 2004–2009 birth	Vancouver, British Columbia, Canada	Cohort	2004–2014	129,436	Entire pregnancy	Up to 5	LUR	14.3	ASD diagnosis by physician on standardized health service criteria using Autism Diagnostic Observation Schedule and Autism Diagnostic Interview Revised	1.06 (0.99 to 1.12)	4.8 ppb
Raz 2018	NII Israel	Multiple cities, Israel	Case-control	2005–2014	56,290	Entire pregnancy	4 to 9	Dispersion/ CTM	16.7	ASD disability determined by physician-led team, on DSM-IV criteria, from national insurance data	1.08 (1.01 to 1.15)	5.85 ppb
						9 months					1.09 (1.02 to 1.18)	

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Table 12.7 (*Continued*). Associations of NO_2 with ASD and Related Behaviors

Reference	Study Name	Location	Study Design	Study Period	Sample Size	Exposure Window	Age at Outcome (yr)	Exposure Assessment	Mean or Median Exposure[a]	ASD Diagnosis or Neuropsychological Test(s)	Odds Ratio (95% CI)[b]	Increment
Ritz 2018	Danish ASD	Denmark	Case-control	1995–2016	83,526	Entire pregnancy	Below 5 to not reported	Dispersion/ CTM	19.57	ASD as reported in Danish National Patient Register, based on admissions and outpatient/emergency room consultations, and the Danish Psychiatric Central Register based on psychiatric admissions to hospitals and outpatient clinics	1.00 (0.93 to 1.08)	11.41 µg/m^3
						9 months					1.08 (1.01 to 1.15)	

[a] Unit in the increment column.

[b] OR >1.0 indicate higher risk for ASD.

[c] Dark orange = evidence of association with ASD or more ASD traits; light orange = suggestive evidence of association with ASD or more ASD traits.

[d] Depending on the cohort: Autism-tics, ADHD, and Other Co-morbidities inventory, Pervasive Developmental Problems of the Child Behavior Checklist for Toddlers, Social Responsiveness Scale, Childhood Autism Spectrum Test.

Table 12.8. Associations of NO_x with ASD and Related Behaviors

Reference	Study Name	Location	Study Design	Study Period	Sample Size	Exposure Window	Age at Outcome (yr)	Exposure Assessment	Mean or Median Exposure[a]	ASD Diagnosis or Neuropsychological Test(s)	Odds Ratio (95% CI)[b,c]	Increment
Gong 2014	CATSS	Stockholm, Sweden	Cohort	1992–2012	3,426	Entire pregnancy	9 or 12	Dispersion/ CTM	9.5	Autism-Tics, ADHD, and other Comorbidities inventory, used a cutoff consistent with ASD diagnosis based on DSM-IV criteria	0.76 (0.27 to 2.12)	95th to 5th percentile difference
						First year					0.78 (0.33 to 1.85)	
						Year before assessment					1.23 (0.38 to 3.97)	
Gong 2017	Stockholm Youth Cohort	Stockholm, Sweden	Case–control	2001–2011	23,373	Entire pregnancy	Up to13	Dispersion/ CTM	11.0	ASD diagnosis from national registries, based on ICD9/10 and DSM-IV criteria, with and without intellectual disability	1.02 (0.94 to 1.10)	20 µg/m^3
						First year					1.05 (0.95 to 1.14)	
Goodrich 2018	CHARGE	California, United States	Case–control	2002–2011	606	Entire pregnancy	2 to 5	Dispersion/ CTM	19.15	ASD diagnosis identified using California Department of Developmental Services (uses Autism Diagnostic Observation Schedule-Generic Autism Diagnostic Interview-Revised)	1.31 (0.94 to 1.82)	27.66 ppb
						First trimester					1.27 (0.91 to 1.76)	29.40 ppb
						Second trimester					1.23 (0.88 to 1.70)	29.64 ppb
						Third trimester					1.47 (1.05 to 2.06)	29.54 ppb

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Table 12.8 (*Continued*). Associations of NO_x with ASD and Related Behaviors

Reference	Study Name	Location	Study Design	Study Period	Sample Size	Exposure Window	Age at Outcome (yr)	Exposure Assessment	Mean or Median Exposure[a]	ASD Diagnosis or Neuropsychological Test(s)	Odds Ratio (95% CI)[b,c]	Increment
Guxens 2016	ESCAPE	Multiple cities, multiple countries	Cohort	1992–2012	8,079	Entire pregnancy	4 to 10	LUR	36–75	Borderline/clinical range using validated cutoffs for 4 tests[d]	0.98 (0.88 to 1.09)	20 µg/m^3
										Clinical range[d]	0.93 (0.78 to 1.11)	
Volk 2013	CHARGE	California, United States	Case-control	2003–2009	524	Entire pregnancy	2 to 5	Dispersion/CTM	16.9	ASD diagnosis identified using California Department of Developmental Services criteria (uses Autism Diagnostic Observation Schedule-Generic Autism Diagnostic Interview-Revised)	1.98 (1.20 to 3.31)	>31.8 vs. <9.7 ppb
											1.09 (0.67 to 1.78)	16.9–31.8 vs. <9.7 ppb
											1.26 (0.77 to 2.06)	9.7–16.9 vs. <9.7 ppb
						First trimester					1.85 (1.11 to 3.08)	
											1.28 (0.79 to 2.08)	
											1.28 (0.77 to 2.15)	
						Second trimester					1.65 (1.00 to 2.74)	
											1.13 (0.69 to 1.84)	
											0.90 (0.54 to 1.49)	

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Table 12.8 (*Continued*). Associations of NO_x with ASD and Related Behaviors

Reference	Study Name	Location	Study Design	Study Period	Sample Size	Exposure Window	Age at Outcome (yr)	Exposure Assessment	Mean or Median Exposure[a]	ASD Diagnosis or Neuropsychological Test(s)	Odds Ratio (95% CI)[b,c]	Increment
						Third trimester					2.10 (1.27 to 3.51)	>31.8 vs. <9.7 ppb
											0.91 (0.56 to 1.46)	16.9–31.8 vs. <9.7 ppb
											1.17 (0.71 to 1.93)	9.7–16.9 vs. <9.7 ppb
						First year					3.10 (1.76 to 5.57)	
											1.00 (0.62 to 1.62)	
											0.91 (0.56 to 1.47)	

[a] Unit in the increment column.

[b] Odds ratio >1.0 indicates higher risk for ASD.

[c] Dark orange = evidence of association with ASD or more ASD traits; light orange = suggestive evidence of association with ASD or more ASD traits.

[d] Depending on the cohort: Autism-tics, ADHD, and Other Co-morbidities inventory, Pervasive Developmental Problems of the Child Behavior Checklist for Toddlers, Social Responsiveness Scale, Childhood Autism Spectrum Test.

Table 12.9. Associations of EC with ASD and Related Behaviors

Reference	Study Name	Location	Study Design	Study Period	Sample Size	Exposure Window	Age at Outcome Assessment (yr)	Exposure Assessment	Pollutant	Mean or Median Exposure[a]	ASD Diagnosis or Neuropsychological Test(s)	Odds Ratio (95% CI)[b]	Increment
Guxens 2016	ESCAPE	Multiple cities, multiple countries	Cohort	1992–2012	8,079	Entire pregnancy	4 to 10	LUR	$PM_{2.5}$ abs	1.3–2.3	Borderline/clinical range for autistic traits using validated cutoffs for 4 tests[c]	0.82 (0.57 to 1.18)	1 1×10^{-5}/m
											Clinical range[c]	0.70 (0.44 to 1.12)	

[a] Unit in the increment column.

[b] Odds ratio >1.0 indicate higher risk for ASD.

[c] Depending on the cohort: Autism-tics, ADHD, and Other Co-morbidities inventory, Pervasive Developmental Problems of the Child Behavior Checklist for Toddlers, Social Responsiveness Scale, Childhood Autism Spectrum Test.

von Ehrenstein et al. 2014), only the California study found high risk for ASD with pregnancy $PM_{2.5}$ copper exposure (von Ehrenstein et al. 2014). The same study was the only one to examine associations of PAHs and benzene with ASD (Appendix Tables 12C-6 and 12C-7) and reported a null association with PAHs and an association of benzene with higher risk for ASD (von Ehrenstein et al. 2014).

Only two cohorts, a European and U.S. cohort, examined associations of indirect traffic measures with ASD (Appendix Table 12C-8). Associations for the ESCAPE cohort were null (Guxens et al. 2016) and the California CHARGE case–control study found that living in close proximity to a freeway was associated with higher risk of an ASD diagnosis; associations with distance to the nearest major road were null (Volk et al. 2011).

Of the six studies that looked at differences in TRAP–ASD associations by sex, two saw no differences (Gong et al. 2017; Guxens et al. 2016). The other four saw slightly stronger associations (mostly not statistically significant) for boys with exposure to NO_2 (Pagalan et al. 2019; Raz et al. 2018b), NO (Pagalan et al. 2019), $PM_{2.5}$ (Ritz et al. 2018), PM_{10} (Ritz et al. 2018), and PAH (von Ehrenstein et al. 2014). One study found slightly stronger NO_2–ASD associations for girls (Ritz et al. 2018).

Five studies considered exposure–response functions for TRAP with ASD (Gong et al. 2017; Guxens et al. 2016; Raz et al. 2018b; Volk et al. 2011, 2013), three of which detected associations of TRAP with ASD (Raz et al. 2018b; Volk et al. 2011, 2013). One study found no evidence for nonlinearity of associations (Raz et al. 2018b). An analysis of data from the CHARGE case–control study reported potential threshold associations for those in the closest distance-to-freeway category and not the middle categories (Volk et al. 2011). Another analysis of the CHARGE study also reported similar trends across quartiles or as indicated by smoothing splines of NO_x (Volk et al. 2013).

There appeared to be some geographical heterogeneity in associations of TRAP and ASD, with associations found for North American studies but not for European studies. However, this may be explained by study design, where nearly all of the North American studies used the case–control design, including two case–control studies in state of California in the United States: the Los Angeles County DDS study in the United States (Becerra et al. 2013) and the CHARGE study (Goodrich et al. 2018; Volk et al. 2011, 2013); and a study based in the state of Pennsylvania in the United States (Talbott et al. 2015a, 2015b). These studies all showed associations of TRAP with ASD. The European studies, many of which were cohort studies pooled in the ESCAPE study (Gong et al. 2014, 2017; Guxens et al. 2016), all found null associations of TRAP with ASD.

In summary, there was moderate to high confidence in the presence of associations of TRAP with ASD. The strongest associations were with NO_2, with the majority of studies (four of five) reporting higher risk for ASD with both gestation and early infancy exposure. Associations were also strong for $PM_{2.5}$, where the majority of studies (three of four) reported higher risk for ASD with exposure in the first few years of life. The results of studies of other pollutants—NO_x, EC, and other pollutants—were mixed or null. Evidence for associations with indirect traffic measures was scant, with only one of two studies reporting higher risk with distance measures.

12.6 OVERALL DISCUSSION

12.6.1 SUMMARY OF MAIN FINDINGS

The literature on TRAP and neurodevelopment has seen rapid growth since the 2010 HEI Traffic Review. There were 49 studies, representing 30 different study populations, that met criteria for inclusion in this review. All of the studies were published after 2008, and the majority were published in the past several years (since 2015). This increase reflects a growing recognition of the potential vulnerability of the developing brain to TRAP and the serious consequences of disruptions in neurodevelopment, which include long-lasting impacts on academic success, job attainment, and social connections (Bellinger 2009).

Based on the results of these 49 studies, the confidence in the presence of an association of TRAP and neurodevelopment in children was mixed. There was moderate confidence in the presence of associations of TRAP with cognitive function, based on associations with NO_2, EC, and $PM_{2.5}$ exposure during both gestation and childhood. The confidence in an association of TRAP exposure and ADHD and related behaviors was low, with most studies reporting null associations. And there was moderate-to-high confidence in the presence of an association for TRAP exposure and ASD, with most studies of prenatal and early life exposure to NO_2 and $PM_{2.5}$ reporting an increased risk for ASD and related behaviors.

Inconsistency of the strength of the evidence within and across the three outcome categories was observed and could be due to a number of different reasons. First, not all outcomes were assessed the same way and included a variety of different tests, reporters (i.e., parents and teachers), and assessment methods (i.e., direct observation, neuropsychological assessment, rating scales, and clinical diagnosis). In addition, age at outcome assessment can impact whether an association is detected given that the brain is continuing to develop and mature into early adulthood (White et al. 2009). The impact of TRAP on neurodevelopmental outcomes is likely to be subtle, and less sensitive outcome assessment methods typically available for these studies could explain null associations.

Second, there may be differences in how TRAP impacts the developing brain. For example, different TRAP components

may target specific brain regions, which could lead to more localized effects, as has been shown for other neurotoxicants, such as lead and methylmercury exposure (Costa et al. 2004). This could explain the variable evidence found across the different outcome categories. More research on the mechanisms by which TRAP impacts the developing brain could help illuminate which regions of the brain are most sensitive to insult.

Third, effects on the brain may depend on when during gestation and early life exposure occurs as different developmental windows may be more sensitive to TRAP exposure than others. The prenatal period is well recognized as a time of rapid brain development and as a very sensitive window to exogenous insult (Grandjean and Landrigan 2014). However, important brain development continues during childhood and into early adulthood and thus neurocognitive functions that develop and mature during these windows may also be susceptible to TRAP exposure (Landrigan et al. 2004). In this review, we included a number of studies that reported stronger associations with poorer cognitive and behavioral outcomes with childhood versus prenatal TRAP exposure.

Finally, most individual studies adjusted for a core set of confounders (age, sex, and at least one measure of SES). However, studies varied widely with respect to inclusion of a range of other potential confounders, including measures of environmental tobacco smoke exposure, parental support/home enrichment, environmental lead exposure, parental psychopathology, and traffic noise exposure. Appendix Figure 12C-1 shows a directed acyclic graph representing the array of confounders considered across studies. Many of the variables considered were measures of SES. Closer consideration of which of these variables should be considered critical confounders of TRAP and neurodevelopment would help determine which studies were deficient and suffered from residual confounding. In addition, contextual features may play a role in different associations across cohorts. Animal studies have shown that environmental enrichment can temper the effects of toxicant exposures such as lead (Guilarte et al. 2003) and alcohol (Klintsova et al. 1998). These studies also imply that vulnerability may arise from adverse contextual-level factors, such as poverty, a poorer caregiving environment, and social stressors. Finally, variability in associations could be explained by differences in underlying susceptibility to TRAP due to genetic variability (Eichler et al. 2010). For example, a study of airborne copper exposure in the BREATHE study showed that genetic variation modified the associations with inattentiveness in school-aged children (Alemany et al. 2017).

A little fewer than half of studies examined differences in TRAP and neurodevelopmental associations by sex (21 studies), and among those that did, study power may have limited the ability to detect subtle differences. Eight studies reported slightly stronger associations among boys versus girls, but only for cognitive function and ASD. Only two studies reported stronger associations among girls, also for cognitive function and ASD, and the remaining 12 studies saw no sex differences. Sex differences in air pollution may have mechanistic underpinnings (Torres-Rojas and Jones 2018). For example, a study comparing male and female mice showed that neurons from male mice were more sensitive to oxidative stress–induced toxicity than the same cells from female mice (Giordano et al. 2013). These sex differences may be an important area for further research.

12.6.2 POTENTIAL MECHANISMS

There are several suspected mechanisms for associations of TRAP with neurodevelopment. With respect to prenatal TRAP exposure, studies have shown that pollutants such as PAHs and UFPs cross the placenta (Bongaerts et al. 2020; Peterson et al. 2015) reaching the developing fetus. These same pollutants may also potentially lead to suboptimal placental growth and function (van den Hooven et al. 2012), which could in turn adversely affect fetal brain development (Rosenfeld 2021). Prenatal PM exposure has also been shown to lead to higher levels of biomarkers of oxidative stress in maternal peripheral blood and cord blood (Grevendonk et al. 2016), another potential pathway for adverse effects on neurodevelopment (Costa et al. 2017). Childhood exposure to PM—particularly UFPs—can translocate to the brain via the circulatory system (Genc et al. 2012; Hahad et al. 2020) and can also directly access the brain via the olfactory system (Lucchini et al. 2012; Oberdörster et al. 2004). In addition, studies have shown evidence for neuroinflammation in children in response to air pollution exposure (Brockmeyer and D'Angiulli 2016; Calderón-Garcidueñas et al. 2008). Neuroimaging studies have also shown that air pollution may impact brain structure and function (Guxens et al. 2018; Peterson et al. 2015) and should be a focus for further study.

12.6.3 FINDINGS IN COMPARISON WITH OTHER ASSESSMENTS AND STUDIES

The U.S. Environmental Protection Agency (U.S. EPA) Integrated Science Assessment for Particulate Matter (U.S. EPA 2019) has considered $PM_{2.5}$, PM_{coarse}, and UFPs, irrespective of the source. The evidence was considered sufficient to conclude a *likely to be causal* relationship between $PM_{2.5}$ exposure and nervous system effects, and suggestive for a causal relationship for PM_{coarse} and UFPs and nervous system effects. Nervous system outcomes considered include brain inflammation and oxidative stress, morphological changes in the brain, cognitive and behavioral effects, neurodegenerative diseases, and neurodevelopmental effects. It is worth noting that the evidence from studies of neurodevelopmental effects did not substantially contribute to the causality determination for nervous system effects (U.S. EPA 2019). A determination of

inadequate was reached in the integrated science assessment of NO_2 in 2016 for postnatal development (U.S. EPA 2016).

Several review papers have been published on the evidence for associations of TRAP with neurodevelopment, most of which were published in the past 5 years. An early review published in 2015 that covered studies published between 2012 and 2015 concluded that there was sufficient evidence for associations of prenatal and childhood exposure to PAHs with poorer cognitive function (IQ) and associations of NO_2, NO_x, and $PM_{2.5}$ with ASD (Suades-González et al. 2015). Studies included in that review overlapped with many studies included in the current review, particularly the earlier studies.

Another review that focused on cognitive function across the life course found evidence suggesting a relationship of prenatal and childhood exposure to air pollution from traffic as well as other sources with poorer cognitive development, including intelligence and memory (Clifford et al. 2016). Like the current review, the review by Clifford and colleagues also reported evidence that boys may be more adversely affected by air pollution than girls.

A systematic review that focused on NO_2 and neurodevelopment, and included studies published up until 2019, conducted meta-analyses based on 10 cohorts (Shang et al. 2020). This review reported that a 10-μg/m^3 increase in prenatal NO_2 exposure was associated with poorer mental and psychomotor function (–0.62 [95% CI: –1.34 to –0.18] and –0.76 [–1.34 to –0.18], respectively). However, studies included in this meta-analysis included evidence from mostly one study, the ESCAPE study (also included in the current review), which pooled results from several European cohorts that administered tests of cognitive and psychomotor function (Guxens et al. 2014). This review also reported null associations with other cognitive endpoints (e.g., general cognition and language) from meta-analysis. Finally, the review included qualitative evidence for NO_2 with poorer attention and other problem behaviors, although there was insufficient evidence to conduct meta-analyses or conclude that there were associations with these outcomes with any certainty.

Three reviews were conducted that were specific to PM and developmental disorders, including ADHD and ASD (Fordyce et al. 2018; Lam et al. 2016; Myhre et al. 2018). The two reviews that examined PM ($PM_{2.5}$ and PM_{10}) in relation to ADHD (Fordyce et al. 2018; Myhre et al. 2018) reported weak evidence for associations across the studies they reviewed, similar to the current review. The two studies that examined PM in relation to ASD (Fordyce et al. 2018; Lam et al. 2016) came to different conclusions, however. The review by Fordyce and colleagues (2018) reported that associations with $PM_{2.5}$ and PM_{10} with ASD were weak and inconsistent, citing exposure assessment—specifically a lack of individual-level exposure measurement—as the main problem with this body of evidence. The systematic review by Lam and colleagues (2016) of ASD reported OR = 1.07 (95% CI: 1.06–1.08) per 10-μg/m^3 increase in PM_{10} exposure across six studies and OR = 2.32 (2.15–2.51) per 10-μg/m^3 increase in $PM_{2.5}$ exposure across three studies. The more suggestive evidence for TRAP and ASD from the Lam et al. review (2016) more closely matches what the Panel concluded in the current literature review; however, it should be noted that the Lam et al. review was not specific to TRAP and included other air pollution sources. Another systematic review and meta-analysis of TRAP and ASD (Flores-Pajot et al. 2016) also reported summary estimates that suggest higher risk for ASD with prenatal exposure to NO_2 (OR = 1.05; 0.99–1.11 per 10-ppb increase) and $PM_{2.5}$ (OR = 1.34; 0.83–2.17 per 10-μg/m^3 increase).

A very recent review published by researchers involved in the U.S. Environmental influences on Child Health Outcomes (ECHO) program, which is actively harmonizing data from ECHO cohorts to answer this question, reviewed studies of air pollution, including TRAP, in relation to cognitive function, ADHD, and ASD (Volk et al. 2020). This review reported that TRAP (NO_2, black carbon, $PM_{2.5}$, PM_{10}, and distance to roadway/traffic density) was associated with mental and psychomotor development in early childhood and, much like the Shang et al. 2020 review, this was primarily based on the ESCAPE study (Guxens et al. 2012, 2014; Lertxundi et al. 2015). The review also reported that associations of TRAP with cognitive function and ADHD and related behaviors were mixed, while associations with ASD were stronger, similar to what the Panel concluded in the current review.

Given the fast pace of research on TRAP and neurodevelopment, a number of additional studies are likely to have been published since this review. These more current findings should be considered alongside the evidence included in this review.

12.6.4 STRENGTHS AND LIMITATIONS

A strength of this review is that it facilitated a systematic approach to identifying, selecting, and evaluating studies of TRAP and neurodevelopment. Although meta-analyses were not conducted on this relatively new body of evidence, this review takes account of a rapidly evolving literature, inclusive of a diverse set of study designs and outcomes, across a large number of cohorts worldwide. The rapidly growing body of evidence on TRAP and neurodevelopment will enable a more comprehensive review, including meta-analyses and a formal confidence assessment, in future evaluations.

Because it comes during a rapid growth of studies of TRAP and neurodevelopment, this review has likely missed a number of studies that were published following the cutoff for study inclusion.

The Panel noted several limitations in the literature review. First, heterogeneity of outcome assessment, particularly for cognitive function, made synthesizing and harmonizing associations across studies challenging. The most consistent outcome across studies of cognitive function was IQ, which is a fairly nonspecific outcome because it is a composite of a number of different skills (verbal, memory, working memory, visuospatial, etc.). Studies that did focus on specific domains used a diverse array of tests, making direct comparison difficult. This issue is certainly not unique to studies of TRAP and has been identified as a limitation of the neurodevelopmental literature across different environmental exposures (Youngstrom et al. 2011). In addition, clinically diagnosed outcomes (ADHD and ASD) also have their limitations in epidemiological studies (Sagiv et al. 2015). Studies often rely on presentation at a clinic/health care center for diagnosis. These outcomes are also vulnerable to changes in diagnostic criteria. Finally, they may be less sensitive, making it harder to detect more subtle associations with environmental exposures. Future studies that will use a common set of instruments assessing quantitative, dimensional traits may be able to overcome some of these limitations.

Second, a consistent critical window of susceptibility to TRAP exposure was not identified for any of the outcome categories. Associations were found with TRAP exposure during gestation, although most studies did not examine or identify a specific period during gestation, and with exposure during a fairly large age range during childhood. Because the biological mechanism for associations of TRAP with neurodevelopment remains speculative, it is possible that some studies did not examine the most sensitive period during neurodevelopment, which could have masked associations.

Third, limited sample size for a number of the studies of TRAP and neurodevelopment resulted in imprecise effect estimates for a number of the studies included in the review. Given the time and expense of assembling and following a cohort prospectively, many of the birth cohort studies were limited in size. For clinically diagnosed outcomes (ADHD and ASD), case–control studies were more efficient, but some still produced imprecise estimates. Given that the effects of TRAP are likely to be subtle, and that the high prevalence of exposure makes these subtle associations important from a public health perspective (Bellinger 2007), estimating precise associations in studies with large sample sizes is a priority for studies of TRAP and neurodevelopment.

Finally, studies of TRAP and neurodevelopment are vulnerable to live birth bias, a type of selection bias where a fetus needs to survive until birth to be available for analysis (Liew et al. 2015; Raz et al. 2018a). This could remove the most susceptible fetuses from the population, resulting in attenuation of associations of TRAP with neurodevelopment.

12.6.5 UNANSWERED QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

Growth in the literature on TRAP and neurodevelopment will soon make possible a more formal systematic review of this literature, providing a more comprehensive picture of the strength of the evidence, including which outcomes are most strongly associated with TRAP and, ideally, which windows of exposure are most vulnerable to TRAP exposure. Specific future directions for research on TRAP and neurodevelopment include the following:

1. The literature on the critical window for TRAP exposure, e.g., prenatal vs. childhood, and specifically when during these periods, has had limited consideration. Although some studies have looked at more than one window of exposure, the evidence so far is mixed. Future studies looking at the sensitivity of critical windows of development to TRAP exposure are needed to guide public health recommendations.
2. A more common set of endpoints across studies would help for making comparisons across the literature. The diversity in endpoints and age at outcome assessment may explain disparate findings across studies.
3. Studies of clinical diagnosis (i.e., ASD and, for small number of studies, ADHD) have limitations (detailed in the previous section). Future studies of quantitative, dimensional traits may offset some of these limitations.
4. Expanding the range of outcomes to include other neurodevelopmental endpoints, such as internalizing behaviors (e.g., anxiety and depression), will be important as more data become available for these outcomes.
5. Neuroimaging may provide clues about mechanisms as well as indicate what parts of the brain are affected by TRAP and should be explored further (Rauh and Margolis 2016).

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MATERIALS AVAILABLE ON THE HEI WEBSITE

Appendices 12A to 12D contain supplemental material not included in the main report. They are available on the HEI website at *www.healtheffects.org/publications*.

Appendices

12A Cognitive Function

12B Attention Deficit Hyperactivity Disorder (ADHD) Diagnosis and Related Behaviors

12C Autism Spectrum Disorder (ASD) Diagnosis and Related Behaviors

12D References for Studies Included in the Literature Review of Neurodevelopmental Outcomes

ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
ASD	autism spectrum disorder
CTM	chemical transport model
EC	elemental carbon
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
PAH	polycyclic aromatic hydrocarbon
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
$PM_{2.5}$ abs	$PM_{2.5}$ absorbance
PM_{10}	particulate matter ≤10 μm in aerodynamic diameter
PM_{coarse}	particulate matter between 2.5 and 10 μm in aerodynamic diameter
PNC	particle number concentration
SES	socioeconomic status
TRAP	traffic-related air pollution
UFPs	ultrafine particles
U.S. EPA	U.S. Environmental Protection Agency

PART D: FINDINGS FROM LITERATURE REVIEWS OF EPIDEMIOLOGICAL STUDIES

Chapter 13

Traffic-Related Air Pollution and Neurodegenerative Outcomes

CONTENTS

CHAPTER 13

Traffic-Related Air Pollution and Neurodegenerative Outcomes

13.1 SUMMARY

The 2010 HEI Traffic Review did not evaluate the association between traffic-related air pollution (TRAP*) and neurological outcomes. The intervening years saw an expansion in the body of literature investigating dementia-related outcomes and Parkinson disease. To represent these important emerging areas in the Report while a larger body of evidence develops, the Panel conducted a narrative review of this literature. The dementia-related outcomes encompassed cognitive performance, longitudinal decline in performance, and incident dementia or mild cognitive impairment. The epidemiological evidence on Parkinson disease included studies of Parkinson disease and parkinsonism.

A total of 15 studies of TRAP and dementia-related outcomes—representing 10 individual cohorts—met the predefined inclusion criteria for this review. All studies were conducted in Europe and North America. Most used cohort study designs, though a few used cross-sectional designs. Studies ranged widely in size, from a few hundred to more than 2 million participants. Study periods varied from as early as 1988 to as late as 2013. The studies estimated exposure primarily with land use regression (LUR) or dispersion/chemical transport models (CTM), and a few used residential distance to traffic, or traffic density. The most frequently studied individual pollutants were elemental carbon (EC) and NO_2 (each appeared in seven studies), followed by $PM_{2.5}$ and NO_x (each appeared in six studies), and PM_{10} (which appeared in five studies). Three studies examined PM_{coarse}.

Associations of TRAP with dementia-related outcomes were mixed. Associations were most suggestive for NO_2 and NO_x. Less consistent was the evidence from studies on $PM_{2.5}$ and EC, and even less so and far sparser was the evidence on PM_{10} and PM_{coarse}. Associations with indirect traffic measures were also mixed. Evaluating the consistency of evidence across specific pollutant–outcome pairs was challenging because of scant literature for any given exposure–outcome pair. Studies of TRAP in relation to both cognition and incident dementia generally found adverse associations. Findings on TRAP in relation to cognitive decline were all null.

Some common features of the research investigating TRAP and dementia-related outcomes limited its usefulness. First, most studies of dementia relied on diagnostic codes and claims in health care databases, none of which were validated against uniformly conducted criterion-standard evaluations. Because of the likely association of TRAP exposure with health care use and referral patterns (where residential proximity to busy roads is often associated with socio-economic position and consequently with health care access and use), this evidence may have been subject to differential misclassification. Second, the potential for selection bias is common in studies of TRAP and dementia-related outcomes in older adults, because attrition from illness-related drop-out and death is common, and some illnesses associated with attrition may also be associated with both TRAP exposure and adverse

Highlights

- There has been rapid growth in the literature on associations of TRAP with dementia and outcomes related to it. A total of 15 studies were reviewed with respect to the following dementia-related outcomes: cognitive function, rate of change in cognitive function (cognitive decline), and incident dementia or mild cognitive impairment.
- Confidence in the presence of an association of TRAP and dementia-related outcomes was mixed, with consistency depending on the pollutant and potential for bias depending on the outcome. The Panel judged confidence in the presence of an association of TRAP with dementia-related outcomes as low to moderate.
- A total of six studies were reviewed with respect to Parkinson disease. Overall evidence for an association of TRAP with Parkinson disease was inconsistent, with some of it potentially influenced by systematic bias. The Panel judged confidence in the presence of an association of TRAP with Parkinson disease as low.
- Although meta-analyses, risk of bias assessment, and confidence assessment of the quality in the body of evidence were not conducted, the continued growth in this literature should facilitate a more comprehensive review in the near future.

This document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83234701 to the Health Effects Institute; however, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

cognitive outcomes. Although such differential attrition bias is unlikely to explain adverse associations of TRAP with dementia risk, it may have contributed to the null associations with cognitive decline. Third, some statistical adjustments for confounding did not align with plausible underlying causal (and noncausal) pathways between TRAP and dementia: some studies lacked adjustments for education, an important source of confounding in many settings, or adjusted for factors, such as late-life body mass index, that are influenced by incipient disease. Finally, it is unclear to what extent the findings reflect these or other biases, the role TRAP plays in the etiology of dementia, or both.

Thus, based largely on the suggestive findings on NO_2 and NO_x overall and the findings on the specific outcome of cognitive function, along with the previously enumerated limitations, the Panel judged the confidence in the presence of an association of TRAP with dementia-related outcomes as low to moderate.

Regarding Parkinson disease, a total of six studies of TRAP and this outcome, representing five cohorts, met the predefined inclusion criteria for this review. All studies were conducted in Europe and North America. Three studies used cohort study designs; the other three studies followed case–control designs. Study populations ranged from about a thousand to more than 2 million participants. Study periods differed across studies and ranged from the early 1990s to the early 2010s. Five studies estimated exposure with LUR models or dispersion/chemical transport models; two used distance to roadway measures. The most frequently studied individual pollutant was NO_2 (N = 5 studies). EC, NO_x, PM_{10}, $PM_{2.5}$, and PM_{coarse} were each evaluated by two studies.

Associations of TRAP with Parkinson disease were inconsistent, marked by imprecision and several null or inverse estimates. The evidence corresponding to EC, NO_x, PM_{10}, $PM_{2.5}$, PM_{coarse}, and distance to traffic was further limited by a small number of studies. Several other limitations of this body of research were noted. First, all studies relied to varying degrees on health care administrative data to identify Parkinson disease cases, subjecting their associations to bias from possible outcome misclassification. Some also included parkinsonism in their case definitions; the influence of using this composite outcome on findings is not known. Second, as Parkinson disease is a condition of older age, there is potential for selection bias in these studies, following mechanisms similar to those in TRAP and dementia-related outcomes. This bias may have contributed to the null and inverse associations of TRAP with Parkinson disease. Third, statistical adjustments for confounding often excluded refined adjustment for smoking history, which is strongly and inversely associated with Parkinson disease and, in some settings, is also associated with higher TRAP exposure. Information on the association of TRAP with dimensions of smoking history and other potential sources of confounding was lacking. Finally, without further information, it is difficult to firmly determine the existence, direction and magnitude of these potential biases. Thus, based on the inconsistent findings, small number of studies, and enumerated limitations, the Panel judged the confidence in the presence of an association of TRAP with Parkinson disease to be low.

13.2 OVERVIEW OF CHAPTER AND OUTCOMES

The Panel evaluated published studies of TRAP exposure in relation to two major neurological outcomes among adults: dementia (and related cognitive outcomes) and Parkinson disease. The Panel considered three outcomes related to dementia in older adults: cognitive function (Appendix Table 13A-1; available on the HEI website), rate of decline in cognitive function (Appendix Table 13A-1), and mild cognitive impairment or clinically diagnosed dementia itself (Appendix Table 13B-1). Lower and worsening cognitive performance are both precursors to (Amieva et al. 2005; Elias et al. 2000; Irwin et al. 2018; Karr et al. 2018; Li et al. 2017; Rajan et al. 2017) and manifestations of dementia (Karr et al. 2018; Leoutsakos et al. 2015; Rajan et al. 2017). Most persons who develop dementia pass through a precursor phase of mild cognitive impairment, when cognitive symptoms are perceptible but not severe enough to interfere with the activities of daily living. Those who have mild cognitive impairment are at higher risk of subsequently developing dementia, but mild cognitive impairment does not always lead to dementia, and in some individuals mild cognitive impairment reverts to normal cognition or remains stable (Petersen et al. 2018; Ward et al. 2013).

In all studies of cognitive function and decline, participants were assessed directly with neuropsychological tests. Studies of dementia mainly relied on records from the administration of health care in the community, such as outpatient or inpatient diagnostic codes or insurance claims (Carey et al. 2018; Cerza et al. 2019; Chen et al. 2017a, 2017b; Ilango et al. 2019). Use of direct assessment was less common (Oudin et al. 2016; Tzivian et al. 2016b). Most participants were in their 60s or older at the time of first assessment, although some studies included participants as young as 45 years old.

The Panel collectively considered studies of Parkinson disease and parkinsonism (Appendix Table 13C-1). Parkinsonism encompasses the movement symptoms of Parkinson disease; it is often caused by Parkinson disease itself but can result from other conditions including but not limited to essential tremor, dementia with Lewy bodies, and some strokes. Throughout this chapter, references to the body of research on Parkinson disease include studies of parkinsonism as well, unless specified otherwise. All studies of Parkinson disease used health care records and claims to identify

persons who had developed this outcome. Most participants were in their 60s or older at the first assessment for Parkinson disease, although some were in their 20s.

Both outcome-specific sections (13.3 and 13.4) start with a general characterization of the published literature reporting on associations of TRAP with the respective outcome. The review describes estimated associations with individual traffic-related air pollutants followed by associations with indirect measures of traffic (distance to major roadway and traffic density). Because of the interrelated nature of the dementia-related outcomes, findings on those outcomes were reviewed collectively, although challenges specific to individual outcomes were identified. In addition, when TRAP is deleteriously associated with dementia-related outcomes, those associations are inverse (cognition and cognitive change) or positive (dementia and mild cognitive impairment risk). For clarity and simplicity, such inverse and positive associations are described as adverse.

The chapter concludes with an overall discussion of the evidence, including a summary of the main findings for each endpoint, findings in relation to other reviews, strengths and limitations, and finally unanswered questions and future directions for research.

This literature review differs from the systematic literature review presented in other chapters in some important respects: (1) no meta-analyses were conducted, (2) there was no evaluation of the confidence in the quality of the body of evidence, and (3) there is no formal risk of bias assessment on individual studies. Chapter 5 details the Panel's decision not to include neurodegenerative outcomes as a primary outcome in this report.

13.3 COGNITIVE FUNCTION, COGNITIVE DECLINE, AND DEMENTIA

13.3.1 STUDY SELECTION AND DESCRIPTION

13.3.1.1 Cognitive Function

Six studies, using data from five different populations, reported on associations between TRAP, including indirect traffic measures (e.g., distance to major roadway), and cognitive function among adults (Appendix Table 13A-1). All studies were based in Europe or North America, and they ranged in size from 396 to 3,085 participants. The mean testing age of participants varied from 54 to 78 years. These studies were published between 2009 and 2016. No qualifying papers were published in the period spanning January 2017 to the July 2019 cutoff. The studies covered exposures that participants experienced mainly in the 2000s, occasionally extending as far back as the 1980s. Most studies evaluated exposure during a period prior to cognitive testing, typically 1 to 5 years. The Panel classified as cross-sectional the studies using exposures that were contemporaneous with the cognitive assessment and the studies using a single cognitive assessment—as opposed to repeated, longitudinal assessments.

Five studies used exposures that were estimated using LUR models or dispersion/chemical transport models. Four studies used indirect measures, and for one of these, indirect measures comprised the sole TRAP measure. EC, the most commonly assessed traffic-related pollutant, was evaluated in relation to cognitive performance in four different populations. Other pollutants evaluated included NO_2, NO_x, PM_{10}, $PM_{2.5}$, and PM_{coarse}.

All studies assessed cognitive function via direct testing. Overarching domains represented in this research included memory, executive function, and visuospatial ability. Some tests were specific to subdomains (e.g., episodic memory); others assessed two or more domains, but not in a way that performance in each domain could be optimally disentangled (e.g., tests that involved both semantic memory and executive function); still other tests were designed as global measures of function. Most studies used at least one such global measure, reflected in performance on a single test (e.g., the Mini-Mental State Examination) or via a composite score computed from scores on multiple tests. Comparisons were typically in the form of differences in mean cognitive test score per increment in TRAP exposure, but a few comparisons involved odds ratios where "cases" were defined as scoring below a set threshold on a test. Each study generated separate TRAP–cognition associations for 1 to 12 cognitive tests.

Five of the six studies of cognitive function adjusted for age, education, and sex—a set of covariates likely to represent much of the confounding bias in these analyses. Three of these also included other measures of individual and/or area-based socioeconomic status (SES) (Power et al. 2011; Tonne et al. 2014; Wellenius et al. 2012). One study set in the SALIA cohort lacked adjustment for participant-specific education, a strong determinant of test performance, but adjusted for the higher of the participant's or the participant's husband's formal education level (Schikowski et al. 2015). Except for this study, all studies adjusted for measures of physical activity. All studies adjusted for some combination of race/ethnicity, smoking status, or alcohol intake. The study set in the HNR cohort explored adjustment for noise (Tzivian et al. 2016a). Three studies adjusted for body mass index (BMI), which could be influenced by incipient dementia (Ranft et al 2009; Schikowski et al. 2015; Wellenius et al. 2012), and three studies adjusted for history of conditions, such as respiratory disease, cardiovascular disease, stroke, and diabetes, which could have been influenced by TRAP exposure (Power et al. 2011; Ranft et al. 2009; Wellenius et al. 2012).

13.3.1.2 Cognitive Decline

Three studies representing three study populations reported on associations between TRAP or indirect traffic measures and rate of decline in cognitive function among adults (Appendix Table 13A-1). Published between 2014 and 2017, these studies were based in Europe or North America, and ranged in size from 387 to 2,791 participants. Mean baseline age of participants varied from 61 to 72 years. After baseline cognitive testing, study participants underwent one to four subsequent waves of testing every 3 to 5 years. The temporal aspects of exposure and cognitive decline measurement varied. In the VA Normative Aging Study, investigators estimated each participant's exposure over the year prior to baseline cognitive testing (Colicino et al. 2014). The other two studies estimated exposures during the interval during which decline was measured—a single 5-year interval in the Whitehall II study (Tonne et al. 2014) and up to four sequential 5-year intervals in the Betula study (Oudin et al. 2017). All studies estimated exposures using LUR models or dispersion/chemical transport models. The pollutants evaluated were EC, NO_x, and PM_{10} and $PM_{2.5}$ from traffic; each of these was evaluated by a single study.

As with the studies of cognitive function, all studies of cognitive decline directly measured participants' performance. With fewer studies, the domains represented were constrained, but were broadly similar to those in the research on cognitive function. Comparisons of rate of change in cognitive test performance took the form of differences in mean change in cognitive test score per set time interval. The studies estimated separate TRAP–cognitive decline associations for one to four cognitive tests.

All three studies adjusted for a core set of covariates—including time since the baseline assessment, age at baseline assessment, education, and sex—through conditioning or restriction. These studies also adjusted for measures of physical activity and considered smoking history as a source of confounding. Two studies adjusted for hypertension (Colicino et al. 2014) and BMI (Colicino et al. 2014; Oudin et al. 2017). None of the studies adjusted for noise.

13.3.1.3 Dementia and Mild Cognitive Impairment

Six studies, representing five different populations, reported on associations between TRAP or indirect traffic measures (e.g., traffic density or distance to major roadway) and dementia among older adults (Appendix Table 13B-1). A seventh study evaluated mild cognitive impairment (Tzivian et al. 2016b). All seven studies were set in Europe or North America and ranged in size from about 1,800 to more than 2 million participants. Mean baseline age vary from 59 to 75, although some studies did only report an age range (up to 85 years). These studies, published between 2016 and 2019, covered exposures in the 1990s through early 2010s. Almost all studies followed a cohort design, though there was considerable variation in the timing of measured exposures in relation to the outcomes. Several studies evaluated average exposures over an interval of 1–5 years in relation to events that occurred after a lag of 1 or more years (Carey et al. 2018; Chen et al. 2017a, 2017b; Ilango et al. 2019; Tzivian et al. 2016b). Others evaluated annual average exposures over a set year in relation to events that occurred over an interval starting before that exposure year (Cerza et al. 2019; Oudin et al. 2016).

Six studies used exposures that were estimated using LUR models or dispersion/chemical transport models. Four studies used indirect traffic measures, and in one of these studies, the indirect measure, distance to roadway, was the only measure of TRAP (Chen et al. 2017b). NO_2 was the most commonly evaluated traffic-related air pollutant in relation to dementia or mild cognitive impairment ($N = 5$). $PM_{2.5}$ and indirect traffic measures were each assessed in four studies. Other pollutants evaluated included EC, NO_x, PM_{10}, and PM_{coarse}.

The studies used three major approaches to ascertain dementia or mild cognitive impairment "events." The study of mild cognitive impairment, in the HNR cohort, directly assessed all participants using a standardized uniform procedure. This procedure, which hewed to mild cognitive impairment diagnostic criteria (Petersen 2004), involved cognitive testing and soliciting each participant's self-perceived cognitive decline (Tzivian et al. 2016b). To ascertain incident cases of dementia, investigators for the Betula study deployed both direct clinical evaluations for dementia and ongoing medical record review (Oudin et al. 2016). Medical records are part of a class of health administrative data derived from the provision of and billing for health care in the community. Administrative data, such as diagnosis codes and prescription claims, were the sole source of dementia data in the five other dementia studies. Four of these defined incident cases using combinations of diagnosis codes from primary care, hospitalizations, prescriptions, and death certificates. The fifth defined cases as a first hospitalization for dementia (Cerza et al. 2019), a definition that likely included both new-onset cases and exacerbation of established dementia or comorbid conditions.

Dementia and mild cognitive impairment outcomes were compared across levels of TRAP exposure using relative measures of cumulative incidence or incidence rates. Four of the seven dementia or mild cognitive impairment studies adjusted for a core set of covariates likely to account for a substantial amount of confounding in these analyses, including age, education, and sex (Cerza et al. 2019; Ilango et al. 2019; Oudin et al. 2016; Tzivian et al. 2016b); three of these also included other measures of individual and/or area-based SES (Cerza et al. 2019; Ilango et al. 2019; Tzivian et al. 2016b). Three studies lacking adjustment for education did adjust for various area-based measures of SES (Carey et al. 2018; Chen et al. 2017a, 2017b). Some studies adjusted for measures of smoking status, physical activity, or alcohol intake (Carey et al. 2018; Ilango et al. 2019; Oudin et al. 2016;

Tzivian et al. 2016b). Adjustment for noise was explored in two studies (Carey et al. 2018; Tzivian et al. 2016b) A third study in (Oudin et al. 2016) did not adjust for noise, but the same population was investigated with adjustment for noise by Andersson and colleagues (2018). Four studies adjusted for BMI, which could have been influenced by incipient dementia (Carey et al. 2018; Ilango et al. 2019; Oudin et al. 2016; Tzivian et al. 2016b), and one study adjusted for conditions, such as hypertension and diabetes, which could have been influenced by TRAP exposure (Chen et al. 2017b).

13.3.2 RESULTS

13.3.2.1 Comparing Results Across Different Traffic-Related Air Pollutants

The traffic-related air pollutant with the largest number of studies of dementia-related outcomes was NO_2, with seven studies set in six study populations (Table 13.1). The findings indicated an adverse association with dementia-related outcomes. Specifically, the two studies of cognition and four of the five studies of dementia or mild cognitive impairment reported generally adverse associations. In the CPRD cohort, the exposure–response function was adverse with respect to dementia incidence (Carey et al. 2018). Two of these studies lacked adjustment for educational attainment (Carey et al. 2018; Chen et al. 2017a). In addition, there were no reported estimates of NO_2 in relation to cognitive decline, an outcome that reflects, more directly than cognitive performance, the dynamic and protracted process of neuro degeneration.

Findings for PM with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), with six studies representing five distinct populations (Appendix Table 13A-2 and Appendix Table 13B-2), were less consistent. The two studies of cognition yielded inconsistent findings: the study set in the HNR cohort reported that higher exposure corresponded to worse performance on most of its cognitive tests (Tzivian et al. 2016a), whereas the other study reported a mixture of mainly small associations between exposure and performance on a suite of tests (Schikowski et al. 2015). By contrast, three of the four studies of dementia or mild cognitive impairment reported adverse associations with $PM_{2.5}$ exposure (Appendix Table 13B-2). One of these was the study of mild cognitive impairment set in the HNR (Tzivian et al. 2016b) in which adverse associations were also identified with cognitive performance (Tzivian et al. 2016a). Investigators for the CPRD study also characterized the exposure–response function for $PM_{2.5}$ and dementia as adverse and roughly monotonic over quintiles of exposure (Carey et al. 2018).

Six studies of four different study populations reported on associations of NO_x with dementia-related outcomes (Table 13.2). The two studies of NO_x and cognition were set in the same two cohorts as those of NO_2 and cognition, and the corresponding associations were similarly adverse. Two of the three studies on dementia or mild cognitive impairment reported adverse associations. In the Betula cohort, the exposure–response function was adverse with respect to dementia incidence (Oudin et al. 2016). In contrast to this adverse association, a study of NO_x and cognitive decline in the same cohort found no evidence of an association (Oudin et al. 2017).

There were five studies, set in four populations that evaluated EC, with mixed findings (Appendix Table 13A-3). Two studies of cognition reported associations that were generally small in magnitude and/or mixed in direction across several tests (Schikowski et al. 2015; Wellenius et al. 2012). These findings stood in contrast to those from the two other cognition studies, set in the HNR cohort using PM absorbance ($PM_{2.5abs}$) and the VA Normative Aging Study using black carbon (BC), which documented clear adverse associations (Power et al. 2011; Tzivian et al. 2016a). In a companion study in the HNR cohort, investigators reported an adverse association of $PM_{2.5abs}$ with mild cognitive impairment (Tzivian et al. 2016b), consistent with the adverse association pertaining to cognition in this cohort (Appendix Table 13B-3). However, a companion study of BC and cognitive decline in the VA Normative Aging Study found no association between the two (Colicino et al. 2014).

Findings from the five studies (representing four populations) that evaluated PM with aerodynamic diameter ≤10 μm (PM_{10}) were equivocal (Appendix Tables 13A-4 and 13B-4). Adverse associations were prominent only with respect to cognition and mild cognitive impairment in the HNR cohort (Tzivian et al. 2016a, 2016b). Three studies, using data from two study populations evaluated PM_{coarse} in relation to cognitive function, mild cognitive impairment, or dementia with findings that conflicted across population. (Appendix Tables 13A-4 and 13B-4). There were no studies reporting on cognitive decline.

Indirect traffic measures were used in eight studies, conducted in six different populations, and their results were inconsistent (Appendix Tables 13A-5 and 13B-5). Of the four studies of cognition, two reported overall adverse associations, but the earlier adverse associations with road proximity in the SALIA cohort (Ranft et al. 2009) were countered by small and mixed associations with traffic density that were generated by a later investigation using a larger sample of this cohort (Schikowski et al. 2015). Two of the four studies of dementia or mild cognitive impairment reported adverse associations, although one of these associations was small and imprecise. Investigators for two of the cognition studies characterized exposure–response function in their cohorts, finding generally monotonic and adverse patterns (Ranft et al. 2009; Wellenius et al. 2012). Exposure–response functions characterized in studies of dementia were adverse to varying degrees (Carey et al. 2018; Chen et al. 2017b) or absent (Cerza et al. 2019). There were no studies reporting on indirect traffic measures in relation to cognitive decline.

Analyses in some studies—the HNR, CPRD, and Betula cohorts—were conducted with further adjustment for measures

Table 13.1. Associations of NO_2 with Dementia-Related Outcomes

Reference	Study Name	Location	Study Design	Study Period	Sample Size[a]	Mean Age Baseline (years)	Exposure Assessment	Mean or Median Exposure[b]	Outcome	Neuropsychological Tests and Outcome Details (direction[c])	Effect Measure	Effect Estimate (95% CI)	Increment
Carey 2018	CPRD	London, England	Cohort	2005–2013	130,978	50–79	Dispersion/ CTM	37.1	Dementia	Incident diagnosis of dementia from medical records	HR	1.16 (1.05 to 1.28)	7.47 µg/m^3
Cerza 2019	Rome Longitudinal Study	Rome, Italy	Cohort	2001–2013	350,844	74.5	LUR	43.9	Dementia	First hospitalization for dementia from medical records	HR	0.97 (0.96 to 0.99)	10 µg/m^3
Chen 2017a	ONPHEC	Ontario, Canada	Cohort	2001–2013	2,066,639	50–85	LUR	16.2	Dementia	Dementia defined by hospital admission, physician claims or prescriptions	HR	1.11 (1.09 to 1.13)	14.2 ppb
Ilango 2019	CCHS	Ontario, Canada	Cohort	1996–2013	34,391	59	LUR	10.4	Dementia	Hospital admission with diagnosis of dementia, 3 physician claims in 2 years, or prescription claim related to dementia	HR	1.10 (0.99 to 1.19)	5 ppb
Schikowski 2015	SALIA	Ruhr Areas, Germany	Cross-sectional	2007–2009	789	55	LUR	25.9	Cognitive function	Global cognition; CERAD (–)	Mean difference	–1.10 (–2.37 to 0.18)	9.6 µg/m^3
										Global cognition: MMSE (–)		0.00 (–0.16 to 0.16)	
										Semantic memory: Semantic fluency (–)		–0.00 (–0.12 to 0.12)	
										Semantic memory: Boston naming test (–)		–0.14 (–0.29 to 0.01)	
										Semantic memory: phonetic fluency (–)		–0.08 (–0.22 to 0.06)	
										Episodic memory: word list learning (–)		–0.01 (–0.16 to 0.14)	
										Episodic memory: word list recall (–)		0.03 (–0.12 to 0.18)	
										Constructional praxis: figure copying (–)		–0.27 (–0.45 to –0.10)	
										Constructional praxis: figure recall (–)		–0.04 (–0.18 to 0.11)	
										Executive function: trail-making A (–)		–0.06 (–0.19 to 0.06)	

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Table 13.1 (*Continued*). Associations of NO_2 with Dementia-Related Outcomes

Reference	Study Name	Location	Study Design	Study Period	Sample Size[a]	Mean Age Baseline (years)	Exposure Assessment	Mean or Median Exposure[b]	Outcome	Neuropsychological Tests and Outcome Details (direction[c])	Effect Measure	Effect Estimate (95% CI)	Increment
										Executive function: trail-making B (–)		–0.07 (–0.20 to 0.06)	
										Executive function: trail-making B/A (–)		–0.01 (–0.14 to 0.12)	
Tzivian 2016a	HNR	Ruhr areas, Germany	Cross-sectional	2006–2008	3,085	64	LUR	30.1	Cognitive function	Global cognitive score (–)	Mean difference	–0.17 (–0.29 to –0.04)	6.11 µg/m^3
										Verbal fluency (–)		–0.06 (–0.10 to –0.02)	
										Labyrinth test (problem solving/ processing speed) (–)		–0.03 (–0.07 to 0.01)	
										Immediate recall (verbal memory) (–)		–0.04 (–0.08 to 0.01)	
										Delayed recall (verbal memory) (–)		–0.04 (–0.07 to 0.01)	
										Clock drawing test (dichotomous, abstraction/ visual-spatial organization)	OR	1.01 (0.92 to 1.12)	
Tzivian 2016b	HNR	Ruhr areas, Germany	Cross-sectional/ cohort	2006–2008	2,050	45–75	LUR	30.1	Mild cognitive impair-ment	Low score on one of five HNR tests (immediate and delayed memory, abstraction, problem-solving speed, visual-spatial organiza-tion, verbal fluency) or self-reported cognitive decline in past 2 years	OR	1.10 (0.97 to 1.25)	6.11 µg/m^3

HR = hazard ratio; OR = odds ratio.

[a] Sex is "both" in all studies except Schikowski 2015 (female).

[b] Unit in the increment column.

[c] A negative direction (–) means that a lower score indicates poorer cognitive function. Ratio measures (HRs, ORs) >1.0 indicate higher risk for the outcome.

Table 13.2. Associations of NO_x with Dementia-Related Outcomes

Reference	Study Name	Location	Study Design	Study Period	Sample Size[a]	Mean Age Baseline (yr)	Exposure Assessment	Mean or Median Exposure[b]	Outcome	Neuropsychological Tests and Outcome Details (direction[c])	Effect Measure	Effect Estimate (95% CI)	Increment
Cerza 2019	Rome Longitudinal Study	Rome, Italy	Cohort	2001–2013	350,844	74.5	LUR	87.4	Dementia	First hospitalization for dementia from medical records	HR	1.01 (1.00 to 1.02)	20 μg/m³
Oudin 2016	Betula	Umea, Sweden	Cohort	1993–2010	1,806	55–85	LUR	17	Dementia	Diagnosis of dementia using medical records and assessed from cognitive test battery, MMSE and questionnaire	HR	1.43 (1.00 to 2.05)	>26 vs. 4.8–9 μg/m³
												1.48 (1.03 to 2.11)	17–26 vs. 4.8–9 μg/m³
												1.11 (0.76 to 1.63)	9–17 vs. 4.8–9 μg/m³
Oudin 2017	Betula	Umea, Sweden	Cohort	1988–2010	1,469	69	LUR	20.9	Cognitive decline	5–year change in Episodic Memory Measure (EMM) based on 5 subtests of immediate and delayed recall (–)	Mean difference	0.00 (–0.02 to 0.03)	1 μg/m³
Schikowski 2015	SALIA	Ruhr areas, Germany	Cross-sectional	2007–2009	789	55	LUR	39.5	Cognitive function	Global cognition; CERAD (–)	Mean difference	–1.35 (–2.59 to –0.10)	23.4 μg/m³
										Global cognition: MMSE (–)		–0.04 (–0.19 to 0.12)	
										Semantic memory: Semantic fluency (–)		0.01 (–0.10 to 0.13)	
										Semantic memory: Boston naming test (–)		–0.16 (–0.30 to –0.01)	
										Semantic memory: phonetic fluency (–)		–0.09 (–0.23 to 0.05)	
										Episodic memory: word list learning (–)		–0.04 (–0.19 to 0.10)	
										Episodic memory: word list recall (–)		–0.01 (–0.16 to 0.13)	
										Constructional praxis: figure copying (–)		–0.25 (–0.42 to –0.08)	

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Table 13.2 (*Continued*). Associations of NO_x with Dementia-Related Outcomes

Reference	Study Name	Location	Study Design	Study Period	Sample Size[a]	Mean Age Baseline (yr)	Exposure Assessment	Mean or Median Exposure[b]	Outcome	Neuropsychological Tests and Outcome Details (direction[c])	Effect Measure	Effect Estimate (95% CI)	Increment
										Constructional praxis: figure recall (–)		–0.04 (–0.19 to 0.10)	
										Executive function: trail-making A (–)		–0.07 (–0.19 to 0.06)	
										Executive function: trail-making B (–)		–0.09 (–0.21 to 0.04)	
										Executive function: trail-making B/A (–)		–0.02 (–0.15 to 0.10)	
Tzivian 2016a	HNR	Ruhr areas, Germany	Cross-sectional	2006–2008	3,085	64	LUR	50.47	Cognitive function	Global cognitive score (–)	Mean difference	–0.23 (–0.36 to –0.10)	15.70 µg/m^3
										Verbal fluency (–)		–0.08 (–0.12 to –0.03)	
										Labyrinth test (problem-solving/ processing speed) (–)		–0.06 (–0.10 to –0.02)	
										Immediate recall (verbal memory) (–)		–0.04 (–0.08 to –0.01)	
										Delayed recall (verbal memory) (–)		–0.04 (–0.08 to –0.01)	
										Clock drawing test (dichotomous, abstraction/visual-spatial organization)	OR	1.00 (0.90 to 1.07)	
Tzivian 2016b	HNR	Ruhr areas, Germany	Cross-sectional/ cohort	2006–2008	2,050	45–75	LUR	50.5	Mild cognitive impairment	Low score on one of five HNR tests (immediate and delayed memory, abstraction, problem-solving speed, visual-spatial organization, verbal fluency) or self-reported cognitive decline in past 2 years	OR	1.10 (0.96–1.26)	15.70 µg/m^3

HR = hazard ratio; OR = odds ratio.

[a] Sex is "both" in all studies except Schikowski 2015 (female).

[b] Unit in the increment column.

[c] A negative direction (–) means that a lower score indicates poorer cognitive function. Ratio measures (HRs, ORs) >1.0 indicate higher risk for the outcome.

of traffic noise (Carey et al. 2018; Oudin et al. 2016; Tzivian et al. 2016a, 2016b). These adjustments yielded estimates that were attenuated to varying degrees but remained adverse.

13.3.2.2 Comparing Results Across Dementia and Related Cognitive Outcomes

Overall, findings from the six studies of TRAP and cognition provided suggestive evidence of an adverse association. In most studies, there was at least one adverse association between a traffic-related air pollutant and a cognitive outcome. Performance on cognitive tests can be influenced by noncognitive characteristics that may be sources of confounding, although many of the studies of TRAP and cognition featured designs and/or analyses that likely reduced the influence of systematic error on their associations.

Associations from the seven studies of TRAP and dementia or mild cognitive impairment were consistently adverse, with only one study reporting no evidence of such an association (Cerza et al. 2019). Most studies included multiple exposures and outcomes, and findings were generally consistent across pollutants. In spite of the consistency of these results, there were concerns about the potential for differential misclassification of dementia status in most of these studies.

None of the three studies of TRAP in relation to cognitive decline found an adverse association. Each of the three cohorts in these cognitive decline studies was represented in studies of other dementia-related outcomes. In the Whitehall cohort, the null associations of traffic pollutants with cognitive decline concorded with the null associations of these pollutants with performance at one wave of testing (Tonne et al. 2014). By contrast, in the Betula cohort, the null association of NO_x with cognitive decline was at odds with the adverse association of NO_x with dementia risk (Oudin et al. 2016). Similarly, in the VA Normative Aging Study, the null association of BC with cognitive decline was inconsistent with the adverse association of this pollutant with cognitive function at any given wave (Power et al. 2011). Although studies of cognitive decline are instrumental to understanding the associations of TRAP on the pathological process of cognitive degeneration, such studies often involve methodological challenges of their own. Please see Section 13.5.3 for additional discussion.

13.3.2.3 Summary

The Panel found low-to-moderate confidence in the presence of an adverse association of TRAP with dementia-related outcomes. Associations were most suggestive for NO_2 and NO_x. This assessment was based on the moderate number of studies overall, the reasonable possibility that confounding or other systematic biases (such as outcome misclassification) could explain some findings, and the consistency of associations in both European and U.S. studies. Embedded in this assessment were the findings from studies of cognitive function, which were generally suggestive of an adverse association and consistent (although sparsely distributed) across regions. Detracting from a higher confidence rating was the small number of studies on cognitive decline—all of which yielded null findings, plausible but unexamined differential outcome misclassification in studies of dementia that relied on administrative data, and lack of data from settings outside of Europe and North America.

13.4 PARKINSON DISEASE

13.4.1 STUDY SELECTION AND DESCRIPTION

Six studies, using data from five populations, reported on associations between TRAP or indirect traffic measures (e.g., distance to major roadway) and Parkinson disease among adults (Appendix Table 13C-1). Three studies used a cohort study design; the three other studies were case–control studies, with two evaluating exposure in prospective relation to incident Parkinson disease events, and the other evaluating exposure during the same period during which both prevalent and incident Parkinson disease cases were ascertained (Finkelstein and Jerrett 2007). All studies were based in Europe or North America, and they ranged in size from 1,290 to more than 2 million participants. Participants' baseline age ranged from 14 to 92 years in one study (Finkelstein and Jerrett 2007) and from 53 to 67 years in the other five studies. These studies, published between 2007 and 2019, covered TRAP exposures that participants experienced mainly in the 1990s, with some exposures extending as far back as the 1970s and other extending into the 2010s. Most studies estimated each participant's TRAP exposures over years to decades prior to the occurrence (or evaluation) of the Parkinson disease outcome. In others, the exposure and outcome assessment periods overlapped (Cerza et al. 2018; Finkelstein and Jerrett 2007).

Five studies used exposures that were estimated using LUR or dispersion/chemical transport models. Two studies used indirect traffic measures, and for one of these, an indirect measure was the sole TRAP measure. NO_2, the most commonly assessed TRAP, was evaluated in relation to Parkinson disease in five independent populations (with overlap between the two studies based in Ontario [Finkelstein and Jerrett 2007; Shin et al. 2018] that was likely to be minor). Other pollutants evaluated included EC, NO_x, PM_{10}, $PM_{2.5}$, and PM between 2.5 and 10 μm in aerodynamic diameter (PM_{coarse}).

All studies ascertained Parkinson disease events via data sources connected to receipt of medical care. Two studies identified cases from diagnostic codes and conducted additional in-depth review of medical records to confirm the diagnosis and its timing (Ritz et al. 2016; Toro et al. 2019). The other studies identified Parkinson disease events using insurance claims or other diagnostic and prescription records, or an algorithmic procedure based on these data. Two studies restricted their case definition to Parkinson disease (Cerza

et al. 2018; Ritz et al. 2016), whereas the remaining studies defined cases, explicitly or implicitly, as persons with Parkinson disease or other conditions that result in parkinsonism.

All studies adjusted for age and sex, and many adjusted for pesticide exposure or surrogates (e.g., urbanicity). Adjustments for smoking history were less consistent, ranging from the absence of smoking adjustment (Cerza et al. 2018; Finkelstein and Jerrett 2007) to indirect adjustments (Chen et al. 2017a, 2017b; Shin et al. 2018) to adjustment for baseline smoking status in categories of current, past, or never (Toro et al. 2019), to adjustment for detailed smoking history (Ritz et al. 2016). Smoking is consistently and strongly inversely associated with Parkinson disease risk (Chen and Ritz 2018; Gallo et al. 2019; Ritz et al. 2007).

13.4.2 RESULTS

The traffic-related air pollutant with the largest number of studies of Parkinson disease was NO_2, with five studies (Table 13.3). These studies yielded inconsistent findings. The PASIDA case–control study set in Denmark reported a large adverse association of NO_2 with Parkinson disease, which was most pronounced among persons living in the Copenhagen metropolitan area (OR = 1.21 per 2.97 μg/m^3 NO^2) (Ritz et al. 2016). The exposure–response function in this study was adverse and monotonic as assessed via spline and over the lowest quartile, middle two quartiles, and highest quartile of NO_2 exposure. Small and less precise adverse associations were reported by a case–control study (Finkelstein and Jerrett 2007) and a cohort study (Shin et al. 2018), both set in Ontario, Canada but in different periods. By contrast, a cohort study set in the Rome Longitudinal Study (Cerza et al. 2018) and a case–control study set in the Netherlands (Toro et al. 2019) both reported inverse associations of varying magnitude and precision. This latter pair of studies, the studies in Rome and the Netherlands, were the only two studies in the review to evaluate exposure to EC, PM_{10}, $PM_{2.5}$, and PM_{coarse} in relation to Parkinson disease risk (Appendix Table 13C-2 and Appendix Table 13C-3).

Indirect traffic measures were used in two studies, a case–control study (Finkelstein and Jerrett 2007) and a cohort study (Chen et al. 2017b), both based in Ontario, Canada (Appendix Tables 13C-4). Both found little distinction in Parkinson disease risk between persons living close to a major road (<50 m) and those living farther away.

There are several plausible and common limitations of this body of research, which are further discussed in Section 13.5.3. Examples of these limitations are confounding by exposure to tobacco (e.g., cigarette smoking is associated with markedly lower Parkinson disease risk [e.g., Gallo et al. 2019]), misclassification of Parkinson disease status, differential survival, and misspecified etiological window of exposure. Most of the studies in this review were likely affected by at least one of these phenomena, although the magnitude of the ensuing bias is unclear. In general, however, we would expect the resulting bias to be downward (via confounding by smoking, if smoking is associated with higher TRAP exposure, and via differential survival) or toward the null (via misclassification of Parkinson disease status, assuming it is nondifferential with respect to TRAP exposure, and misspecified exposure, assuming it is unrelated to Parkinson disease status). The study from which the largest adverse association was reported (Ritz et al. 2016) had some strong design features; it adjusted for smoking status and pack-years of smoking prior to diagnosis or cardinal Parkinson disease symptoms, probed medical records in-depth to confirm participants' diagnostic status, and assessed TRAP exposure over periods of at least 25 years prior to Parkinson disease onset.

The Panel judged that there was low confidence in the evidence of an adverse association between TRAP and Parkinson disease, based on the limited number of studies and the small number of studies evaluating exposures other than NO_2. The Panel also considered the largely unaddressed potential for selection bias, potential confounding by smoking, and potential misclassification of the disease, as possibly explaining largely inconsistent findings.

13.5 OVERALL DISCUSSION

13.5.1 SUMMARY OF MAIN FINDINGS

Based on the available literature, the number of well-designed studies accounting for important biases, and consistency of findings across geographical areas, the Panel judged that there was low-to-moderate confidence in the presence of an adverse association between TRAP and dementia and related cognitive outcomes in adults. Precluding a higher confidence rating were the limited and null findings on cognitive decline, all of which were observed in cohorts in which adverse associations were found with cognition or dementia; the unaddressed potential for selection bias to explain some of these inconsistencies, particularly the null findings on cognitive decline; and the potential but unstudied influence of differential misclassification of dementia cases ascertained from administrative sources. These challenges also made it difficult to evaluate the most etiologically pertinent periods of life or durations exposure. In addition, the literature base on TRAP and dementia-related outcomes has been steadily expanding, and it is likely that conclusions from the comparably small number of studies in this review may change as more research is published. For example, since the cutoff date for this review (July 2019), the number of studies evaluating TRAP in relation to dementia-related outcomes has continued to burgeon. For example, at least six new papers on at least seven new cohorts have published estimates on NO_2 in relation to cognition; results on NO_2 and cognitive change were reported for at least three cohorts (Weuve et al. 2021).

Table 13.3. Associations of NO_2 and NO_x with Parkinson Disease

Reference	Study Name	Location	Study Design	Study Period	Sample Size[a]	Mean Age Baseline (yr)	Exposure Assessment	Pollutant	Mean or Median Exposure[b]	Incidence or Prevalence	Effect Measure	Effect Estimate (95% CI)	Increment
Cerza 2018	Rome Longitudinal Study	Rome, Italy	Cohort	2008–2013	1,008,253	63	LUR	NO_2	42.7	Incidence	HR	0.97 (0.96 to 0.99)	10 μg/m³
								NO_x	84.6			0.97 (0.96 to 0.98)	20 μg/m³
Finkelstein 2007	THUA OHIP	Ontario, Canada	Case–control	1992–1999	52,986	14–92	LUR	NO_2	31.0	Prevalence	OR	1.02 (0.96 to 1.08)	1 ppb
Ritz 2016	PASIDA	Multiple cities, Denmark	Case–control	1996–2009	3,496	62	Dispersion/ CTM	NO_2	12.11–16.83	Incidence	OR	1.21 (1.11 to 1.31) (Copenhagen and suburbs) 1.10 (0.97 to 1.26) (Provincial cities) 0.93 (0.68 to 1.27) (Rural)	2.97 μg/m³
Shin 2018	ONPHEC	Ontario, Canada	Cohort	1996–2013	2,194,519	67	LUR	NO_2	14.7	Incidence	HR	1.04 (1.00 to 1.07)	12.9 μg/m³
Toro 2019	Netherlands Five Hospitals	Multiple cities, the Netherlands	Case–control	2006–2011	1,290	53	LUR	NO_2	26.4	Incidence	OR	0.86 (0.62 to 1.19)	10 μg/m³
								NO_x	43.2			0.91 (0.65 to 1.28)	20 μg/m³

HR = hazard ratio; OR = odds ratio.

[a] Sex is "both" in all studies.

[b] Unit in the increment column.

The Panel judged that there was low confidence in the presence of an adverse association between TRAP and Parkinson disease, based on the limited number of studies. Precluding a higher confidence rating were the largely unaddressed potential for selection bias; lack of adjustment for smoking; and unexamined misclassification of Parkinson disease; the small number of studies evaluating TRAP components other than NO_2; and lack of data from settings outside of Europe and North America.

13.5.2 FINDINGS IN COMPARISON WITH OTHER ASSESSMENTS AND STUDIES

The key findings of this review on TRAP and dementia-related outcomes were (1) generally inconsistent associations of any given pollutant with the collectively considered outcomes of cognition, cognitive decline, and dementia or mild cognitive impairment; (2) suggestive evidence of an adverse association of TRAP with cognitive function and limited and null evidence on cognitive decline (though based on few studies); and (3) evidence on dementia that may have been influenced by misclassification.

The risk of dementia is substantially elevated with stroke. Thus findings on TRAP and dementia and its related outcomes might be expected to correspond with those on TRAP and stroke. As presented in this report (Chapter 10), the confidence in the evidence linking TRAP with stroke risk, though suggestive with respect to EC, PM_{10}, and $PM_{2.5}$, was considered to be only low to moderate, as well.

In its most recent Integrated Science Assessment for PM, published in 2019, the U.S. Environmental Protection Agency (EPA) judged that "animal toxicological and epidemiological evidence supports a likely to be causal relationship between long-term $PM_{2.5}$ exposure and nervous system effects" (U.S. EPA 2019). The report also considered PM_{coarse} and ultrafine particulate matter, irrespective of the source. Nervous system effects were defined broadly and included outcomes in children and adults, as well as subclinical (e.g., cognitive, motor, and psychological function) and clinical endpoints. Epidemiological studies on dementia-related outcomes, including neuroimaging outcomes, were new to this integrated science assessment, reflecting the recent emergence of published research on dementia-related outcomes. It was this literature, more than the companion literature among children, that compelled the U.S. EPA to arrive at its judgment. Evidence on the nervous system effects of long-term exposure to both PM_{coarse} and ultrafine particles was "suggestive." The U.S. EPA's most recent Integrated Science Assessment on NO_2, published in 2016, did not include any epidemiological evidence on neurological outcomes in adults (U.S. EPA 2016).

Among other systematic reviews on air pollution (not restricted to TRAP) and dementia-related outcomes, two of the more recent reviews included papers up through September 2018 (Peters et al. 2019) and December 2020 (Weuve et al. 2021) and conducted study quality assessments. Peters and colleagues (2019) restricted their review to studies on cognitive decline and dementia, for a total of 13 papers. They concluded that the evidence from these studies supported adverse relations of $PM_{2.5}$ and NO_x/NO_2 exposure with dementia risk, with less compelling evidence for a relation with cognitive decline, and limited evidence overall pertaining to other pollutants. The review of Weuve and colleagues (2021) extended to studies of cognition and neuroimaging, for a total of 66 papers. They restricted their interpretation of the findings to 35 higher-quality studies and concluded that that evidence provided support for an adverse association of $PM_{2.5}$ with cognitive decline. Both reviews raised concern about the use by several studies of administrative data to ascertain dementia status. Peters and colleagues (2019) hedged their conclusions with this concern, and Weuve and colleagues (2021) included about one-third of the dementia studies in their findings assessment, mostly those that conducted uniformly administered evaluations of their participants. Neither team conducted meta-analyses, citing insufficiently comparable features across studies.

In the U.S. EPA's Integrated Science Assessment for PM (U.S. EPA 2019), evidence on Parkinson disease contributed to its judgment that the collective evidence was suggestive of a causal effect of short-term $PM_{2.5}$ exposure on diseases of the nervous system. The strongest evidence for this assessment was from experimental animal studies, yet the U.S. EPA cited a large U.S. study of Medicare enrollees (Zanobetti et al. 2014) that indicated a potential association between short-term $PM_{2.5}$ and exacerbation of existing Parkinson disease, although they considered the use of hospital admission records for case identification to be a limitation. By contrast, in assessing evidence on long-term $PM_{2.5}$ exposure and Parkinson disease, they cited collectively inconclusive results from four studies (Kioumourtzoglou et al. 2016; Kirrane et al. 2015; Liu et al. 2016; Palacios et al. 2014). None of those studies were included in the current review because the exposure measurement methods used did not yield estimates of TRAP that were consistent with this review's exposure framework.

Among other more recent systematic reviews on air pollution (thus not specifically TRAP) and Parkinson disease, two included papers up through 2018 (Han et al. 2020) and November 2018 (Kasdagli et al. 2018) and involved again study quality assessments. The two reviews included 13 and 14 long-term exposure studies in meta-analysis, with most studies on $PM_{2.5}$, followed by NO_2. Han et al. 2020 reported a summary estimate of 1.08 (95% CI: 0.98, 1.19) per 10-μg/m^3 increase in $PM_{2.5}$ (N = 9 studies) and 1.03 (0.99, 1.07) per 10-μg/m^3 increase in NO_2 (N = 8 studies). Kasdagli et al. 2018 reported a summary estimate of 1.06 (0.99, 1.14) per 10-μg/m^3 increase in $PM_{2.5}$ (N = 11 studies) and 1.01 (0.98, 1.03) per 10-μg/m^3 in NO_2 (N = 8 studies). Both reviews observed that meta-analysis was constrained by the small number of studies, potential for exposure measurement error and unmeasured confounding, and that studies were limited to high income countries. Kasdagli and colleagues (2018) further noted the lack of relevant

confounder data in administrative cohorts and the need to investigate multipollutant exposures and effect modification, while Han and colleagues (2020) noted the need for more longitudinal cohort studies.

13.5.3 STRENGTHS AND LIMITATIONS

This review offered a systematic approach to identifying, selecting, and evaluating epidemiological studies of TRAP in relation to both dementia-related outcomes and Parkinson disease. In accordance with a protocol established before identifying any papers, meta-analyses were not conducted on this evidence. It is not clear that such analyses would have been useful, given the variety of outcome assessment methods, exposure periods and other differences across studies. This review directs focus to the particulars of this heterogeneous literature and—given the rapid pace at which this literature is growing—to the likelihood that conclusions may evolve as more evidence accrues. The continued growth in this literature should facilitate a more comprehesive review in the near future.

On the whole, the studies identified for this review featured large sample sizes and high-quality exposure assessments. Consideration of co-exposure to noise has emerged in more recent papers on dementia-related outcomes (2015 onward). Nonetheless, some common features of the research limited its usefulness, which are briefly described below, separately for dementia-related outcomes and Parkinson disease. Additional discussion can be found in Appendix 13D.

13.5.3.1 Limitations of Evidence on TRAP and Dementia-Related Outcomes

Overall, adverse associations of TRAP exposure with level of cognitive performance and risk of dementia (or mild cognitive impairment) were more common than adverse associations of TRAP exposure with cognitive decline, though there were only few studies available for the latter. If long-term exposure to TRAP during adulthood contributes to dementia etiology, we would expect exposure to be adversely associated with all three outcomes. The reasons for deviations from this pattern fall largely into two classes. First, TRAP exposure could be involved in specific stages of dementia development and progression. For example, suppose TRAP influences cognitive abilities achieved by mid-life, thereby increasing later susceptibility to dementia (by positioning cognitive level closer to the dementia threshold), but also suppose TRAP does not influence progression. In this situation, adverse associations of TRAP would be more common with cognition and dementia than with cognitive decline—similar to a pattern observed with some early life or time-invariant exposures. Or, second, if TRAP exposure during a particular etiological window promotes progression but not susceptibility, adverse associations of TRAP would be more common with cognitive decline and dementia than with baseline cognitive performance assessed among at-risk persons.

The findings from this review are most consistent with the first scenario in which TRAP influences susceptibility but not decline. Of course, these explanations presume uniformity in the patterning and pace at which dementia unfolds, and the average pattern characterized from numerous populations (Irwin et al. 2018; Karr et al. 2018; Rajan et al. 2017) may mask sources of heterogeneity that make it challenging to definitively interpret and synthesize the results from studies of TRAP and dementia-related outcomes. Moreover, mechanisms specific to disease stage may be another reason that TRAP might be adversely associated with some dementia-related outcomes but not all.

In addition to etiological mechanisms, there may be biases common in studies of specific outcomes (Weuve et al. 2015). First, most studies of dementia relied on diagnostic codes and claims records from health care administrative databases, none of which were validated against uniformly conducted criterion-standard evaluations. Because conditions associated with TRAP exposure such as rural residence, low SES, and TRAP-induced illness may be correlated with health care use and referral patterns, this evidence may have been subject to differential misclassification. Misclassification of dementia status in diagnosis codes and claims is common, and the accuracy of using these data for ascertaining dementia cases is generally much poorer than for ascertaining cases of severe acute conditions (Lang et al. 2017; Taylor et al. 2009). Indirect evidence suggests this misclassification could result in exaggerating adverse associations. Rates of dementia underdiagnosis vary by health status, as well as race/ethnicity and other sociodemographic characteristics (Gianattasio et al. 2019; Power et al. 2020). In many settings, it is plausible that the same factors that predict the accuracy of dementia diagnosis also correlate with TRAP exposure (Hajat et al. 2015; Miranda et al. 2011; Tessum et al. 2021). Note that this particular source of bias is not present in studies of cognitive function and decline. Still, use of cognitive tests that have score ceilings or floors can result in biased effect estimates on decline, but the magnitude and direction of that bias depend on the proportion of participants whose true performance level lies outside of the measured range.

Second, potential for selection bias is common in studies of TRAP and dementia-related outcomes in older adults. Because participation depends on surviving and, in studies involving evaluations, being well enough to participate in the study protocol, and because TRAP exposure and cognitive status are both related to mortality and morbidity risks, differential selection is a potential challenge to studies of all three outcomes. Although such differential attrition bias is unlikely to explain adverse associations of TRAP with dementia risk, it may have contributed to the null associations with cognitive decline. It is worth noting that two of the three cognitive decline studies followed participants for lengthy periods starting from advanced mean ages: up to 12 years from a mean age of 72 in the VA Normative Aging Study (Colicino et al.

2014) and up to 22 years from a mean age of about 69 in the Betula study (Oudin et al. 2017).

Third, statistical adjustments for confounding sometimes did not align with plausible underlying causal (and noncausal) pathways between TRAP and dementia-related outcomes. For example, some dementia studies lacked adjustments for education, or adjusted for factors, such as late-life BMI, that are influenced by incipient disease. Moreover, some studies also adjusted for putative mediators of the effect of TRAP on dementia risk (e.g., cardiovascular conditions, diabetes, and depressive symptoms), distorting the results when treating them as covariates in analyses of TRAP effects.

In summary, the pattern of associations of TRAP with cognitive function, cognitive decline, and dementia risk could involve etiological mechanisms, biases common in studies of specific outcomes, or most likely a combination.

13.5.3.2 Limitations of Evidence on TRAP and Parkinson Disease

First, all studies relied to varying degrees on health care data to identify Parkinson disease cases, potentially subjecting their associations to bias from outcome misclassification. In community health care settings (i.e., in the course of regular medical care outside of investigative settings), misdiagnosis and delays in diagnosis are not uncommon (Breen et al. 2013; Rizzo et al. 2016; Schrag et al. 2018; Wan et al. 2019; Wermuth et al. 2012). Increasing availability of electronic claims, outpatient and hospital diagnosis codes, and prescription records has fueled the use of these data to identify persons with Parkinson disease in epidemiological studies. The accuracy of these records, measured against the full medical record, varies, with a review finding wide-ranging positive predictive values (36%–89%) of individual sources (e.g., hospital discharge only) that improved in magnitude and consistency when sources were used in algorithmic combination (>82%) (Harding et al. 2019). The "gold standard" in these validation studies was the medical record, which is as accurate as the medical system it records. Moreover, except for the PASIDA study and Rome Longitudinal Study (Cerza et al. 2018; Ritz et al. 2016), all other studies used case definitions that explicitly or implicitly included persons with parkinsonism but not necessarily Parkinson disease. The influence of using this composite outcome on the findings is not known.

Little is known about the determinants of misclassification of Parkinson disease in health care data; some reports have noted differences by gender, rural versus urban residence, presenting symptoms, and training of the diagnosing physician (Breen et al. 2013; Rizzo et al. 2016; Schrag et al. 2018). Unlike misclassification of dementia in health care data, which could be linked to TRAP through correlates of misclassification (e.g., presence of other conditions induced by exposure) and therefore plausibly could be differential with respect to TRAP, these mechanisms may operate differently for Parkinson disease. Clearly, misclassification of Parkinson disease is not trivial in many studies. At minimum, it is nondifferential with respect to TRAP exposure, resulting in bias of the association toward the null in many analyses. Even if rural residence, lower SES, or the absence of other diagnosed TRAP-related conditions correspond to more Parkinson disease misclassification, any ensuing differential misclassification probably would not explain the numerous inverse associations reported by these studies.

Second, as Parkinson disease is a condition of older age, and individuals have to survive to the age of onset to participate or continue participating after study entry, there is potential for selection bias in these studies, following mechanisms similar to those in TRAP and dementia-related outcomes. This bias may have contributed to the null and inverse associations of TRAP with Parkinson disease.

Third, an important source of residual confounding in studies of TRAP and Parkinson disease may be smoking history, which is strongly and inversely associated with Parkinson disease, and this information was only available in one study (Ritz et al. 2016). As described previously in this chapter, smoking is consistently and strongly inversely associated with Parkinson disease risk (Chen and Ritz 2018; Gallo et al. 2019; Ritz et al. 2007). The reasons for this association remain unresolved (Chen and Ritz 2018). The direction of bias in the association caused by confounding by smoking hinges on how smoking and TRAP are jointly distributed in the study population, which is not reported in the studies. Parkinson disease risk does not consistently appear to decrease along a gradient of increasing SES (e.g., Caslake et al. 2013; Yang et al. 2016), although this could reflect complex interplay of SES with key Parkinson disease risk factors such as smoking and physical activity.

Finally, without further information, it is difficult to firmly determine the existence, direction, and magnitude to which these potential biases were present in the pattern of associations of TRAP with Parkinson disease.

13.5.4 UNANSWERED QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

If exposure to TRAP affects dementia or Parkinson disease risk, it would offer a novel opportunity for intervention, using regulatory strategies to reduce risk in whole populations. Although the precise mechanisms of such an association need not be known prior to such intervention, whether such an association exists remains a primary question.

To home in on the answer to this question, future research should address the key methodological limitations described in Section 13.5.3. Specifically, with respect to dementia, more studies are needed that use regularly occurring, uniform, standard criterion-based methods to evaluate all study participants (or a strategic stratified random sample) for dementia.

Administrative data will continue to be of interest to many researchers, with the principal caveat that such data can impressively reduce random error to such an extent that the implied certainty of findings (i.e., via precision) is mistaken for lack of systematic error (Lash 2007). Before accepting these data at face value for TRAP research, more understanding is required of the processes that generate these data (from the emergence of symptoms to diagnosis to documentation), as well as how accurate they are and how and whether their inaccuracy might influence associations with TRAP.

In addition to this dementia research, more studies of cognitive change would be helpful. As these studies become more common in TRAP research, more attention should be paid to the potential influence and mitigation of selection bias. This attention should extend to emerging studies of pathology-centered outcomes (e.g., via imaging and histopathology), in which the contours of participation include perceived personal dementia risks and logistical burdens.

Finally, several dimensions of exposure windows and time-related factors merit attention. Most dementias have a long prodromal period that covers decades, and it is possible that TRAP promotes early pathogenic events along with their progression. As of yet, studies are too sparse and too heterogeneous in design to determine whether there are critical windows of susceptibility to exposure and/or a critical duration of exposure. Many studies used exposures in the 1–5 years prior to assessment as proxies for long-term exposure. In addition, outcomes such as cognitive function, cognitive decline, and neuroimaging measures—especially among "younger older adults"—permit the evaluation of TRAP during earlier disease stages. However, it is pertinent to persons who are now older adults to establish whether changing their TRAP exposure could influence their cognitive risks—for example, do exposures over the past year or so affect risk, separate from exposures over the past decade or two? Separate from these dimensions of time is secular time as a potential source of confounding. This is because TRAP levels have fallen in some areas; in parallel, dementia incidence in some populations may have also diminished somewhat (Satizabal et al. 2016; Wolters et al. 2020).

The features that would advance understanding of TRAP and Parkinson disease largely mirror those that would advance understanding of TRAP and dementia. Future research on TRAP and Parkinson disease would benefit from deeper insights on the consequences of Parkinson disease misclassification when using health care data to identify cases and of assessing parkinsonism instead of Parkinson disease. Two studies in this review (Ritz et al. 2016; Toro et al. 2019) measured exposures spanning at least a decade prior to Parkinson disease onset. Future studies likewise should attend to the long prodromal period of Parkinson disease—a period that may span years to decades (Chen and Ritz 2018; Schaeffer et al. 2020). In addition, the potential for confounding by dimensions of smoking history and other strong Parkinson disease risk factors merits further scrutiny. Finally, all studies of TRAP and Parkinson disease in this review were set in Ontario (three studies), Denmark, Italy, and the Netherlands, leaving an opening for informative research set in other regions.

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MATERIALS AVAILABLE ON THE HEI WEBSITE

Appendices 13A to 13E contain supplemental material not included in the main report. They are available on the HEI website at *www.healtheffects.org/publications*.

Appendices

13A Cognitive Function and Cognitive Decline

13B Dementia and Mild Cognitive Impairment

13C Parkinson Disease

13D Further Elaborations on Limitations of Evidence on TRAP and Neurodegenerative Outcomes

13E References for Studies Included in the Narrative Review of Neurodegenerative Outcomes

ABBREVIATIONS

BC	black carbon
BMI	body mass index
CERAD	The Consortium to Establish a Registry for Alzheimer's Disease
CTM	chemical transport model
EC	elemental carbon
LUR	land use regression
MMSE	Mini-Mental State Examination
NO_2	nitrogen dioxide
NO_X	nitrogen oxides
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 µm in aerodynamic diameter
PM_{10}	particulate matter ≤10 µm in aerodynamic diameter
PM_{abs}	particulate matter absorbance
PM_{coarse}	particulate matter between 2.5 and 10 µm in aerodynamic diameter
SES	socioeconomic status
TRAP	traffic-related air pollution
U.S. EPA	U.S. Environmental Protection Agency

PART E: CONCLUSIONS

Chapter 14

Discussion and Conclusions

CONTENTS

CHAPTER 14

Discussion and Conclusions

14.1 INTRODUCTION

The goal of this chapter is to summarize and synthesize the information provided in this Special Report. Here the main conclusions of the systematic review are brought together, and strengths and limitations of the evidence base and the review are discussed. The chapter integrates the four outcome assessments of Chapters 8–11, as well as the mechanistic, technologies and emissions, and exposure-assessment background, throughout the review. Information gathered from individual chapters is used to provide guidance for improving future research on the associations between long-term exposure to traffic-related air pollution (TRAP*) and selected health outcomes.

14.2 MAIN FINDINGS OF THE SYSTEMATIC REVIEW

The overall objective of this Special Report was to systematically evaluate the epidemiological evidence regarding the associations between long-term exposure to TRAP and selected adverse health outcomes. Results were quantitatively combined to evaluate the strength of the evidence, where appropriate. The Panel was charged with drawing conclusions about the confidence in the quality of the body of evidence and with assessing the level of confidence in the presence of an association. The Panel did not assess causality, because they did not conduct separate, independent systematic assessments of the mechanistic, toxicological, and human clinical studies relating TRAP to human health. For these reasons, the descriptors of the overall confidence assessment still mention *association* rather than causal association, causal relationship, or effect.

The Panel used a prespecified rigorous and systematic approach to search the literature, select studies for inclusion in the review, assess study quality, summarize results, and reach conclusions about the confidence in the evidence base, largely based on standards set by Cochrane, World Health Organization (WHO), and the National Institute of Environmental Health Sciences.

In total, 353 studies were included in the review. Respiratory effects in children (*N* = 118 studies, 33%) and birth outcomes

Highlights

- This review is the largest systematic effort to date to evaluate the epidemiological evidence regarding the associations between long-term exposure to traffic-related air pollution and selected adverse health outcomes.
- In total, 353 studies were included in the review. Respiratory effects in children (*N* = 118 studies) and birth outcomes (*N* = 86 studies) were the most common outcomes. Fewer studies investigated cardiometabolic effects (*N* = 57 studies), respiratory effects in adults (*N* = 50 studies), and mortality (*N* = 48 studies).
- Studies have been conducted on populations residing in a wide range of countries, although the majority were done in Europe (*N* = 163 studies), and North America (*N* = 130 studies).
- The findings from the systematic review, meta-analyses, and evaluation of the quality of the studies and potential biases provided an overall high or moderate-to-high level of confidence in an association between long-term exposure to traffic-related air pollution and the adverse health outcomes all-cause, circulatory, ischemic heart disease, and lung cancer mortality, asthma onset in both children and adults, and acute lower respiratory infections in children.
- Experimental data, generated by a substantial body of mechanistic research, provide informative insights into the toxicity of traffic-related air pollution and the biological plausibility underlying the epidemiological associations.
- Although the evidence is already compelling for some of the outcomes investigated, a number of future research opportunities emerged from the results of this review, including research in low- and middle-income countries.
- In light of the large number of people exposed to traffic-related air pollution—both in and beyond the near-road environment—the Panel concluded that the overall high or moderate-to-high level of confidence in the evidence for an association between long-term exposure to traffic-related air pollution and several adverse health outcomes indicates that exposures to traffic-related air pollution remain an important public health concern and deserve greater attention from the public and from policymakers.

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* A list of abbreviations appears at the end of this chapter. For study name abbreviations, please refer to the list of Study Name Abbreviations at the end of the report.

(*N* = 86 studies, 24%) were the most common outcomes. Fewer studies investigated cardiometabolic effects (*N* = 57 studies, 16%), respiratory effects in adults (*N* = 50 studies, 14%), and mortality (*N* = 48 studies, 13%). The studies were conducted in populations residing in a wide range of countries, although the majority were done in Europe (*N* = 163 studies, 46%), and North America (*N* = 130 studies, 37%). Studies in Asia (predominantly China) emerged more recently (*N* = 41 studies, 12%). More TRAP studies in low- and middle-income countries are needed.

Most meta-analyses by outcome involved nitrogen dioxide (NO_2) as the most commonly studied TRAP exposure indicator, followed by elemental carbon (EC) and particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$). Few studies were identified for some pollutants, in particular nontailpipe PM indicators and ultrafine particles (UFPs), and such studies were identified as a future research need.

The results of the meta-analyses of associations between long-term exposure to various traffic-related pollutants and health outcomes are displayed in Table 14.1. We use the term *relative risk* to describe effect estimates, as it is easier to communicate, even if in some of the included studies it would be technically more correct to refer to an odds ratio, or hazard ratio. The following are important considerations while reviewing the results: (1) although the results are presented by pollutant, the individual pollutants are considered indicators of the TRAP mixture; (2) effect estimates cannot be compared directly across traffic-related pollutants because selected increments do not necessarily represent the same contrast in exposure; and (3) studies included in a meta-analysis represent only about half of all studies considered because of various reasons, such as when multiple studies conducted in the same population, less than three studies were available for a particular exposure-outcome pair, or definitions of indirect traffic measures varied across studies. Thus, the Panel did not pursue meta-analyses of indirect traffic measures. Despite not being included in the meta-analyses, the remaining studies added important information to the overall confidence assessment.

Table 14.2 lists the confidence ratings for an association of each health outcome with long-term exposure to TRAP. The narrative assessment evaluates the level of confidence in the presence of an association, considering the meta-analyzed studies as well as other studies not entering the meta-analysis. The modified OHAT assessment evaluates the confidence in the quality of the body of evidence and is heavily geared toward the studies entering a meta-analysis. Detailed descriptors of the level of confidence in the evidence for an association are listed in Sidebar 14.1.

The findings from the systematic review, meta-analyses, and the evaluation of the quality of the studies and potential biases provided an overall high or moderate-to-high level of confidence in an association between long-term exposure to TRAP and the adverse health outcomes all-cause, circulatory, ischemic heart disease (IHD), and lung cancer mortality, asthma onset in both children and adults, and acute lower respiratory infections (ALRI) in children. The main findings for each broad health outcome category are described in the following sections.

14.2.1 BIRTH OUTCOMES

The summary estimates showed that $PM_{2.5}$ exposure over the entire pregnancy is most clearly associated with fetal growth restriction. The summary relative risk was 1.11 (95% confidence interval [CI]: 1.03 to 1.20) for term low birth weight and 1.09 (1.04 to 1.14) for small for gestational age, and a mean difference in term birth weight of −17.3 (−33.2 to −1.5) grams per 5-μg/m^3. The $PM_{2.5}$ associations were supported by consistent associations with PM ≤10 μm in aerodynamic diameter (PM_{10}) as well. Associations for preterm birth were largely null, although a few studies of traffic-PM and indirect traffic measures (distance and density) supported an association. Associations for the other meta-analyzed traffic-related air pollutants—including NO_2, nitrogen oxides (NO_x), and EC—were mostly null for all four birth outcomes, with the exception of an association of NO_x with term low birth weight. Studies that were not included in the meta-analyses broadly agreed with the summary estimates for the various pollutants.

The majority of TRAP studies and birth outcomes were conducted in North America and Europe. Most used a cohort study design and registry data, and therefore lacked potentially important confounder information on lifestyle factors, such as maternal smoking during pregnancy and prepregnancy body mass index (BMI). As a result, those studies were rated high risk of bias for potential confounding, which reduced confidence in quality of the body of evidence, particularly for term birth weight and preterm birth.

The Panel concluded that there was an overall moderate level of confidence in the evidence for an association between TRAP exposure and term low birth weight (categorical outcome) and small for gestational age, and a low level of confidence for term birth weight (continuous outcome) and preterm birth.

14.2.2 RESPIRATORY OUTCOMES

The summary estimates for NO_2 per 10-μg/m^3 were 1.05 (95% CI: 0.99–1.12) for asthma onset in children, 1.10 (1.01–1.21) for asthma onset in adults, and 1.09 (1.03–1.16) for ALRI in children. For these outcomes, positive associations were also reported for other traffic-related air pollutants, either in

Table 14.1. Meta-analytical Summary Estimates of Associations Between Long-Term Exposure to Various Traffic-Related Air Pollutants and Health Outcomes (NOTE: the individual pollutants are considered indicators of TRAP)

Health Outcome	NO_2 per 10-μg/m^3		NO_x per 20-μg/m^3		EC per 1-μg/m^3		PM_{10} per 10-μg/m^3		$PM_{2.5}$ per 5-μg/m^3	
	N	Relative Risk (95% CI)	*N*	Relative Risk (95% CI)	*N*	Relative Risk (95% CI)	*N*	Relative Risk (95% CI)	*N*	Relative Risk (95% CI)
Birth Outcomes										
Term low birth weight	12	1.01 (0.99 to 1.03)	5	1.02 (1.01 to 1.03)	5	1.01 (0.99 to 1.04)	3	1.14 (0.95 to 1.38)	7	1.11 (1.03 to 1.20)
Term birth weight	8	−3.2 (−11.0 to 4.6)[a]	5	−3.4 (−11.7 to 4.8)[a]	4	−2.6 (−6.1 to 0.9)[a]	<3	NA	6	−17.3 (−33.2 to −1.5)[a]
Small for gestational age	11	1.00 (0.98 to 1.02)	<3	NA	3	1.02 (0.92 to 1.14)	4	1.08 (1.01 to 1.14)	4	1.09 (1.04 to 1.14)
Preterm birth	14	1.00 (0.96 to 1.04)	6	1.03 (0.90 to 1.17)	5	1.02 (0.97 to 1.07)	<3	NA	4	0.99 (0.90 to 1.09)
Respiratory Outcomes—Children										
Asthma onset[b]	12	1.05 (0.99 to 1.12)	3	1.25 (0.52 to 3.01)	5	1.11 (0.94 to 1.31)	<3	NA	5	1.33 (0.90 to 1.98)
Asthma ever[c]	21	1.09 (1.01 to 1.18)	6	1.02 (0.99 to 1.05)	3	1.30 (0.56 to 3.04)	5	0.95 (0.64 to 1.40)	3	1.29 (0.58 to 2.87)
Active asthma[c]	12	1.12 (1.02 to 1.23)	3	1.03 (0.97 to 1.09)	3	1.25 (0.98 to 1.59)	4	0.96 (0.70 to 1.31)	<3	NA
ALRI[b]	11	1.09 (1.03 to 1.16)	<3	NA	4	1.30 (0.78 to 2.18)	<3	NA	<3	NA
Respiratory Outcomes—Adults										
Asthma onset[b]	7	1.10 (1.01 to 1.21)	<3	NA	<3	NA	<3	NA	<3	NA
ALRI[b]	3	1.07 (0.71 to 1.61)	<3	NA	<3	NA	<3	NA	<3	NA
COPD[b]	7	1.03 (0.94 to 1.13)	3	1.03 (0.88 to 1.20)	<3	NA	<3	NA	4	0.91 (0.62 to 1.36)
Cardiometabolic Outcomes										
Ischemic heart disease events[b]	5	0.99 (0.94 to 1.05)	4	0.99 (0.96 to 1.03)	5	1.01 (0.99 to 1.03)	4	1.14 (0.99 to 1.31)	4	1.09 (0.86 to 1.39)
Coronary events[b]	7	1.03 (0.95 to 1.11)	<3	NA	<3	NA	<3	NA	<3	NA
Stroke events[b]	7	0.98 (0.92 to 1.05)	8	0.99 (0.94 to 1.04)	6	1.03 (0.98 to 1.09)	5	1.09 (0.96 to 1.23)	4	1.08 (0.89 to 1.32)
Diabetes[b]	7	1.04 (0.96 to 1.13)	4	1.02 (0.96 to 1.10)	3	1.16 (0.57 to 2.36)	<3	NA	4	1.05 (0.96 to 1.15)
Diabetes[c]	7	1.09 (1.02 to 1.17)	<3	NA	<3	NA	4	1.19 (0.87 to 1.63)	3	1.08 (0.70 to 1.67)

Continues next page

Table 14.1 (*Continued*). Meta-analytical Summary Estimates of Associations Between Long-Term Exposure to Various Traffic-Related Air Pollutants and Health Outcomes (NOTE: the individual pollutants are considered indicators of TRAP)

Health Outcome	NO_2 per 10-µg/m^3		NO_x per 20-µg/m^3		EC per 1-µg/m^3		PM_{10} per 10-µg/m^3		$PM_{2.5}$ per 5-µg/m^3	
	N	Relative Risk (95% CI)	*N*	Relative Risk (95% CI)	*N*	Relative Risk (95% CI)	*N*	Relative Risk (95% CI)	*N*	Relative Risk (95% CI)
Mortality										
All-cause	11	1.04 (1.01 to 1.06)	5	1.05 (0.97 to 1.14)	11	1.02 (1.00 to 1.04)	6	1.06 (0.97 to 1.16)	12	1.03 (1.01 to 1.05)
Circulatory	10	1.04 (1.00 to 1.09)	3	0.94 (0.61 to 1.46)	9	1.02 (1.00 to 1.04)	7	1.03 (0.98 to 1.10)	11	1.04 (1.01 to 1.08)
Respiratory	8	1.05 (1.00 to 1.09)	4	1.10 (0.86 to 1.41)	8	1.01 (0.98 to 1.05)	4	1.10 (0.84 to 1.44)	7	1.03 (0.97 to 1.10)
Lung cancer	5	1.04 (1.01 to 1.07)	<3	NA	3	1.02 (0.88 to 1.19)	3	1.09 (0.87 to 1.36)	6	1.06 (0.99 to 1.13)
Ischemic heart disease	6	1.05 (1.03 to 1.08)	4	1.04 (0.86 to 1.27)	6	1.05 (0.99 to 1.11)	<3	NA	7	1.07 (1.04 to 1.10)
Stroke	6	1.01 (0.98 to 1.04)	3	1.02 (0.93 to 1.12)	<3	NA	<3	NA	3	1.04 (1.01 to 1.07)
COPD	3	1.03 (1.00 to 1.05)	<3	NA	<3	NA	<3	NA	<3	NA

ALRI = acute lower respiratory infection; COPD = chronic obstructive pulmonary disease; EC = elemental carbon; NA = not applicable; NO_2 = nitrogen dioxide; NO_x = nitrogen oxides; and PM_{10} and $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤10 µm and ≤2.5 µm, respectively.

[a] Mean difference in grams.

[b] Incidence.

[c] Prevalence.

Table 14.2. Summary of the Level of Confidence in the Evidence for an Association Between Long-Term Exposure to TRAP and Selected Health Outcomes

Health Outcome	Assessment		
	Narrative	Modified OHAT	Overall
	To assess confidence in the presence of an association	To assess confidence in the quality of the body of evidence	A combination of the narrative assessment and the modified OHAT assessment
Birth Outcomes			
Term low birth weight	Moderate	Moderate	Moderate
Term birth weight	Low	Low	Low
Small for gestational age	Moderate	Moderate	Moderate
Preterm birth	Low	Low	Low
Respiratory Outcomes—Children			
Asthma onset[a]	Moderate	High	Moderate to high
Asthma ever[b]	Moderate	Moderate	Moderate
Active asthma[b]	Moderate	Moderate	Moderate
ALRI[a]	High	Moderate	Moderate to high
Respiratory Outcomes—Adults			
Asthma onset[a]	High	Moderate	Moderate to high
ALRI[a]	Low	Very low	Very low to low
COPD[a]	Low	Low	Low
Cardiometabolic Outcomes			
Ischemic heart disease events[a]	Moderate	Moderate	Moderate
Coronary events[a]	Low	Low	Low
Stroke events[a]	Moderate	Low	Low to moderate
Diabetes[a,b]	Moderate	Moderate	Moderate
Mortality			
All-cause	High	High	High
Circulatory	High	High	High
Respiratory	Moderate	Moderate	Moderate
Lung cancer	Moderate	High	Moderate to high
Ischemic heart disease	High	High	High
Stroke	Low	Moderate	Low to moderate
COPD	Low	Low	Low

ALRI = acute lower respiratory infection; COPD = chronic obstructive pulmonary disease; OHAT = Office of Health Assessment and Translation.

[a] Incidence.

[b] Prevalence.

SIDEBAR 14.1 OVERALL CONFIDENCE ASSESSMENT: DESCRIPTORS OF THE LEVEL OF CONFIDENCE IN THE EVIDENCE FOR AN ASSOCIATION[a]

High	Evidence is sufficient to conclude that the strength of the evidence for an association is high, that is, the exposure has been shown to be associated with health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. The determination is based on multiple high-quality studies conducted in different populations and geographical areas with consistent results for multiple exposure indicators.
	High confidence in the association between exposure and the outcome.
Moderate	Evidence is sufficient to conclude that an association is likely to exist, that is, the exposure has been shown to be associated with health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. The determination is based on some high-quality studies in different populations and geographical areas, but the results are not entirely consistent across areas and for multiple exposure indicators.
	Moderate confidence in the association between exposure and the outcome.
Low	Evidence is suggestive but limited, and chance, confounding, and other biases cannot be ruled out. Generally, the body of evidence is relatively small, with few high-quality studies available and at least one high-quality epidemiological study shows an association with a given health outcome and/or when the body of evidence is relatively large but the evidence from studies of varying quality and across multiple exposure indicators is generally supportive but not entirely consistent.
	Low confidence in the association between exposure and the outcome.
Very low	Evidence is inadequate to determine if an association exists with the relevant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association.
	Very low confidence in the association between exposure and the outcome.

[a] The overall confidence assessment of the association of each health outcome with long-term exposure to TRAP is a combination of the narrative assessment and the modified OHAT assessment. The descriptors are modified from the U.S. Environmental Protection Agency (2015) and the OHAT (2019).

meta-analyses or in single large studies. Most of the studies had a cohort design, were conducted in different populations, and were at a low or moderate risk of bias.

The Panel concluded that the overall level of confidence in the evidence for an association between exposure to TRAP and asthma onset in both children and adults and ALRI in children was considered moderate to high. Studies examining exposure to NO_2 have made the greatest contribution to this evaluation. The overall level of confidence in the evidence for an association between TRAP and asthma ever and active asthma in children was moderate. Asthma ever refers to lifetime asthma prevalence and active asthma refers to prevalence of asthma in the last 12 months. For most of the other respiratory outcomes investigated—including incidence of chronic obstructive pulmonary disease (COPD) and ALRI in adults, wheeze outcomes as well as exacerbation of asthma and COPD in diseased adults—the confidence was very low or low for an association with TRAP, hampered in part by the small number of qualifying studies.

14.2.3 CARDIOMETABOLIC OUTCOMES

The summary estimates were mostly positive and were consistent with an association of PM_{10} with IHD: 1.14 (95% CI: 0.99–1.31), per 10-μg/m^3, with evidence suggesting a monotonic exposure–response function. Evidence was suggestive for EC and $PM_{2.5}$, but less consistent overall. Associations were reported with NO_2 and diabetes prevalence with a summary estimate of 1.09 (1.02–1.17) per 10-μg/m^3, supported by consistent positive but imprecise estimates for the other pollutants. The summary estimates of EC, PM_{10}, and $PM_{2.5}$ with stroke incidence were slightly less precise, but the evidence was strengthened by several high-quality studies with a monotonic exposure–response function. Studies that were not included in meta-analyses provided additional support for an association between TRAP and IHD, diabetes, and stroke. In contrast, for coronary events, the number of studies was smaller and insufficient for meta-analyses, except for NO_2, which yielded a positive, but imprecise association.

Because cardiometabolic outcomes are likely influenced by traffic noise, some studies investigated possible confounding or effect modification by noise with mostly similar results after adjustment for co-exposure to noise. The Panel had overall moderate confidence in the evidence for associations between long-term exposure to TRAP and IHD and to TRAP and diabetes; low-to-moderate confidence in the evidence for an association of TRAP with stroke; and low confidence in the evidence for an association of TRAP with coronary events.

14.2.4 MORTALITY

The summary estimates showed that NO_2, EC, and $PM_{2.5}$ were associated with all-cause, circulatory, IHD, respiratory, and lung cancer mortality, ranging from 1.01 to 1.07. Associations of these pollutants with stroke and COPD mortality were less certain because fewer studies were available for consideration. The studies on pollutants not included in the meta-analyses and the studies with indirect traffic measures supported those associations. All studies on mortality had cohort designs, with outcome during follow-up determined by linkage to mortality registries. Most studies were conducted in North America and Europe; some were set in Asia. The majority of studies accounted for a large number of individual and area-level covariates—including smoking, BMI, and individual and area-level socioeconomic status (SES)—and were judged at a low or moderate risk for bias.

The overall confidence in the evidence for an association between TRAP exposure and mortality was high for all-cause, circulatory, and IHD mortality. The Panel's overall confidence was moderate to high for lung cancer, moderate for respiratory, low to moderate for stroke, and low for COPD mortality.

14.3 BIOLOGICAL PLAUSIBILITY

Comparisons of the findings from mechanistic and epidemiological studies to give informative insights into the toxicity of TRAP are challenging owing to the differences in methods adopted and the often-disparate focus of the two disciplines. As a consequence, the impact of exposure cannot be determined in the same way. A discussion of the coherence between the epidemiological findings and the mechanistic evidence presented in this Special Report is also restricted by the different approaches that were adopted in collating the presented data. The epidemiological work adopted a systematic approach, including meta-analyses and formal confidence assessments. The official task of the mechanistic review was not to produce a comprehensive review of all relevant studies and detailed critical analysis of individual assays, study designs, and inconsistences, but rather to present an overview of the biological mechanisms through which TRAP is believed to elicit the health outcomes included in the epidemiological systematic reviews and meta-analyses (Chapter 3).

14.3.1 BIRTH OUTCOMES

The limited number of mechanistic studies conducted in humans, although not fully supportive, suggests that exposure of pregnant women to higher concentrations of ambient NO_2 or NO_x affects placental growth and function by eliciting abnormal vascularization and/or hemodynamics (Carvalho et al. 2016; Contreras et al. 2018; van den Hooven et al. 2012). These findings provide some biological plausibility to the epidemiological evaluations of associations between NO_x and term low birth weight. A small number of animal studies demonstrating disturbances in placental morphology and function and umbilical cord structure following maternal exposure to (a) particulate air pollutants in real-world environments with high traffic density and (b) high concentrations of diesel exhaust, lend mechanistic support to the epidemiological findings of associations between $PM_{2.5}$ exposure during pregnancy and fetal growth restriction (term birth weight, term low birth weight, and small for gestational age) (Veras et al. 2008, 2012; Weldy et al. 2014). There is suggestive evidence from human and animal mechanistic studies that increased exposure to TRAP (including residential proximity to source and particulate urban air pollution) is associated with inflammation, oxidative/nitrosative stress and a lower degree of DNA methylation in the placental or cord blood (Herbstman et al. 2012; Kingsley et al. 2016; Saenen et al. 2016). These perturbations may represent potential mediators of associations observed between prenatal $PM_{2.5}$ exposure and compromised fetal growth.

14.3.2 RESPIRATORY OUTCOMES AND MORTALITY

The well-established literature base of experimental studies, describing airway inflammation, hyperresponsiveness, and oxidative stress following exposures to NO_2 and diesel exhaust supports an effect of TRAP on the onset of asthma as well as on the exacerbation of pre-existing respiratory disease. Such evidence provides biological plausibility to the epidemiological conclusions of moderate-to-high confidence in associations between TRAP and asthma onset in both children and adults. Mechanistic research is also well developed in defining underlying pathways involved in diesel exhaust or diesel exhaust particles induced modulation of epithelial function and inflammatory mediators (Muñoz et al. 2019). A direct interaction of diesel exhaust particles with airway C-fiber afferents to elicit respiratory reflexes is another mechanistic pathway that may explain how exposure to various components of TRAP could exacerbate asthmatic symptoms (Robinson et al. 2018). Studies also support interactions between TRAP and the epigenome in contributing to the development and persistence of disease (Ji et al. 2016), and particularly an impact of early life TRAP exposure on persistent wheezing and asthma.

The epidemiological evidence base for associations between TRAP and COPD is limited and the overall level

of confidence in the evidence for an association is low. Furthermore, very little experimental research, employing environmentally relevant models to reflect long-term exposures to ambient concentrations, has been conducted to identify a possible mechanism through which TRAP exposure could affect airway pathophysiology and thus contribute to the development or worsening of COPD.

Epidemiological evaluations strongly point toward an association between TRAP and incidence of ALRI in children, but not necessarily in adults, the latter hampered by the small numbers of included studies. Biological plausibility exists from experimental studies employing high exposure concentrations of NO_2 (U.S. EPA 2016) and diesel exhaust particles (Castranova et al. 2001; Yang et al. 2001). These studies have reported impaired pulmonary clearance of bacterial infections and increased susceptibility and response to viral respiratory infections. Mechanisms identified include a reduced capacity of alveolar macrophages to internalize bacteria and produce antimicrobial oxidants, inhibitory effects on the secretion of proinflammatory cytokines, increased production of immunosuppressive mediators, a reduction in expression and production of antimicrobial surfactant proteins, and a reduced cytotoxic potential in natural killer cells (Castranova et al. 2001; Ciencewicki et al. 2007; Müller et al. 2013; Yin et al. 2007).

The mechanisms described above lend biological plausibility to the evidence of an association between TRAP and respiratory mortality. In addition, that animal and in vitro studies have demonstrated the carcinogenicity of diesel exhaust and condensates of gasoline engine exhaust (IARC 2014) provides strong support to the current epidemiological evaluation that found a moderate-to-high level of confidence in the evidence for an association between exposure to TRAP and lung cancer mortality.

14.3.3 CARDIOMETABOLIC OUTCOMES AND MORTALITY

A large evidence base, dominated by studies using diesel exhaust or diesel exhaust particles describes the multifaceted nature of effects (vascular dysfunction, acceleration of atherosclerosis, increased propensity for thrombosis, and imbalance of the autonomic nervous system) on the cardiovascular system. Far fewer studies have focused on NO_2 exposures, but evidence does exist that exposures can lead to endothelial dysfunction and atherogenic effects. Given that all of these effects can contribute to IHD, coronary events, and stroke, the evidence base lends plausibility to an association between TRAP and cardiovascular outcomes. As the aforementioned cardiac events also increase the risk of death, the identified interconnecting mechanisms also lend biological support to the high evidence of an association between exposure to TRAP and all-cause, circulatory, and IHD mortality. The research effort documenting oxidative, inflammatory, and autonomic nervous system imbalances as potential junctures at which TRAP can exert adverse effects on the cardiovascular system supports their role in the underlying biological mechanisms (Miller and Newby 2020). Toxicological and mechanistic research investigating a role for TRAP in mediating stroke is less developed. However, atherosclerosis of extra- or intracranial arteries, increased thrombogenicity, and loss of vascular flexibility with resulting hypertension are also plausible pathways by which TRAP could induce stroke. Risk factors for cardiovascular disease are also intricately linked to those of diabetes mellitus, with endothelial dysfunction often preceding insulin resistance. A limited number of experimental studies have investigated more specific mechanisms underlying the moderate epidemiological association identified between TRAP and diabetes mellitus. These include disturbed glucose homeostasis, increased pulmonary, a systemic and adipose inflammatory response and altered lipid and fatty acid metabolism (Chen et al. 2017, 2019; Wei et al. 2016; Yan et al. 2011).

14.3.4 PROMOTION OF HARMONIZATION ACROSS MECHANISTIC TOXICOLOGY AND EPIDEMIOLOGY

Future research strategies that promote better harmonization across mechanistic toxicology and epidemiology will make it easier to compare the data generated from the two fields and facilitate clearer insights into the health effects of TRAP. For this to happen, experimental studies need to focus on optimal methods including realistic exposures (with respect to exposure length and concentrations of a single pollutant or real-world mixture) relevant models of human health and disease, and specific endpoints. Many studies of the effects of TRAP using animals have focused on acute exposures to single pollutants to investigate how specific pollutants mediate disease using controlled exposure systems (Shang and Sun 2018). As an important complementary approach, a move to environmentally relevant mixtures, frequencies, and concentrations is exemplified in a long-term study that exposed rats to TRAP for 14 months in a novel facility drawing air from a major freeway tunnel system (Edwards et al. 2020). This air contained gases and particles that are emitted by vehicle travel, without any modification, thereby providing a better approach for evaluating the adverse health effects of TRAP on individuals who live near highways and those who commute frequently. Epidemiologists and toxicologists need to integrate approaches, combining observational and novel experimental research, to expand our knowledge of disease mechanisms (Peters et al. 2021). For example, *omics* approaches that focus on identifying new markers of exposure and mechanistic processes may provide novel insights into the relationship between real-world exposure, toxicological consequences, and ultimate human health effects (Laine et al. 2020; Pinto et al. 2019).

14.4 COMPARISON WITH OTHER REVIEWS AND RECENT RESEARCH

Table 14.3 summarizes the causal determinations from some previous recent authoritative reviews relevant to our current review of epidemiological evidence regarding the associations between long-term exposure to TRAP and selected health outcomes. For this purpose, the Panel selected the 2010 HEI Traffic Review, IARC's evaluation of the carcinogenic effect of diesel and gasoline exhaust (IARC 2014), the IARC assessment of the carcinogenic effect of air pollution and PM (IARC 2016), the U.S. EPA Integrated Science

Table 14.3. Summary of Previous Authoritative Reviews on Causal Determinations Relevant to the Current Review

	HEI 2010[a]	IARC 2014[b]	IARC 2016[b]	U.S. EPA 2016[c]	Health Canada 2016[d]	U.S. EPA 2019[c]		
Health Outcome	TRAP	Diesel and Gasoline Engine Exhaust	Outdoor Air Pollution, PM_{10}, $PM_{2.5}$	NO_2	Diesel Exhaust	PM_{coarse}	$PM_{2.5}$	UFPs
Birth outcomes	Inadequate	—	—	Suggestive	—	Inadequate	Suggestive	Inadequate
Respiratory outcomes	Suggestive: asthma onset in children Sufficient: asthma exacerbation in children Inadequate: asthma onset in adults, COPD incidence	—	—	Likely	Likely	Inadequate	Likely	Inadequate
CVD and metabolic outcomes	Suggestive: CVD Metabolic outcomes not assessed	—	—	Suggestive	Suggestive	Suggestive	Causal: CVD Suggestive: metabolic outcomes	Inadequate
Mortality	Suggestive for total and CVD	—	—	Suggestive	—	Suggestive	Causal	Inadequate
Cancer	Inadequate	Diesel exhaust Group 1 carcinogen: lung cancer Gasoline exhaust Group 2b possible carcinogen: lung cancer	Group 1 carcinogen: lung cancer	Suggestive	Causal: lung cancer Suggestive: bladder cancer Inadequate: other cancers	Suggestive	Likely	Inadequate

CVD = cardiovascular disease.

[a] HEI 2010 classification—Sufficient evidence to infer a causal association (Sufficient); suggestive but not sufficient to infer a causal association (Suggestive); inadequate and insufficient to infer a causal association (Inadequate); evidence suggestive of no causal association.

[b] IARC classification—Group 1: carcinogenic to humans; Group 2A: probably carcinogenic to humans; Group 2B: possibly carcinogenic to humans; Group 3: not classifiable as to its carcinogenicity.

[c] U.S. EPA Integrated Science Assessment classification—Causal relationship (Causal); likely to be causal relationship (Likely); suggestive of, but not sufficient to infer, a causal relationship (Suggestive); inadequate to infer the presence or absence of a causal relationship (Inadequate); not likely to be a causal relationship.

[d] Health Canada classification—Same as U.S. EPA Integrated Science Assessment.

Assessments (ISA) of NO_2 (U.S. EPA 2016) and PM (U.S. EPA 2019), and the evaluation of a composite source, diesel exhaust from Health Canada (2016). The Panel notes that in the case of NO_2 and PM, the pollutant itself was evaluated, irrespective of the source. It should be emphasized that the assessments evaluated the weight of evidence in different ways and using different terminology as illustrated in the footnotes of Table 14.3. Sidebar 14.1 provides the descriptors of the level of confidence in the evidence for an association used in the current review. A direct comparison between the descriptors used in the current review and those used in other assessments is not possible because the Panel systematically evaluated only epidemiological studies and did not attempt an integrated assessment of causality. To this end, there has been no separate, independent systematic assessment of the mechanistic, toxicological, and human clinical studies relating TRAP exposure to human health.

In addition, a direct comparison between the current review and the 2010 HEI Traffic Review (HEI 2010) is difficult because of the difference in scope, methods, and criteria for study inclusion between the two reviews. The current review differed from the earlier critical review in 2010 in some important aspects: (1) it followed a systematic approach using common methods and a published protocol; (2) it evaluated the epidemiological literature only; (3) it evaluated only studies of long-term exposure and health; (4) it used a novel exposure framework and considered exposure contrasts both in the near-roadway and neighborhood environment; (5) it focused on a selected set of health outcomes chosen a priori, and (6) it drew conclusions about the confidence in the body of epidemiological evidence. The Panel in 2010 concluded that the evidence was sufficient to support a causal relationship between exposure to TRAP and exacerbation of asthma in children. The 2010 Panel also found suggestive evidence of a causal relationship with onset of childhood asthma, nonasthma respiratory symptoms in adults, impaired lung function in children and adults, total and cardiovascular mortality, and cardiovascular morbidity. For a number of other health outcomes, such as birth outcomes, asthma onset in adults, COPD incidence, and lung cancer mortality, the 2010 Panel found that there was limited evidence of associations, and the data were either inadequate or insufficient for drawing firmer conclusions.

The current systematic review found strengthened confidence in the presence of an association for many health outcomes. The findings of the current review confirmed the 2010 assessment for some outcomes; for example, confidence in the evidence was moderate to high for asthma onset in children and moderate for IHD. The findings strengthened the confidence for some other outcomes, such as term low birth weight, asthma onset in adults, and all-cause, circulatory, and lung cancer mortality. The Panel emphasized that a different definition of cases or population under risk in some instances may explain the difference in the determinations. Of particular note are the differences in respiratory outcome definitions. For example, in the 2010 HEI Traffic Review most studies on exacerbations of asthma (classified as causal) were categorized either as general population studies on active asthma or asthma ever in the current review. In contrast, in the current review, asthma exacerbation was limited to patients with asthma. This may partly explain the difference in conclusions.

The IARC monographs reviewed epidemiological evidence, animal bioassays, and mechanistic and other relevant data to reach conclusions as to the carcinogenic hazard to humans of environmental or occupational exposure to diesel and gasoline engine exhausts (IARC 2014). The conclusion was that diesel engine exhaust is carcinogenic to humans (Group 1)—in particular for lung cancer—whereas gasoline engine exhaust is possibly carcinogenic to humans (Group 2B), because of inadequate evidence in humans, whereas the evidence was sufficient in animals. Another IARC evaluation (IARC 2016) considered outdoor air pollution and PM to evaluate all the evidence on carcinogenicity (human, animal, and mechanistic); it determined that there was sufficient evidence that both air pollution in general, and PM in particular, caused lung cancer (Group 1 Carcinogen). The evidence for other types of cancer was inadequate, although some indications were present for bladder cancer. The current review judged the confidence in the presence of an association between long-term TRAP and lung cancer mortality as moderate to high.

Governmental environmental and health agencies have provided comprehensive evaluations of the health effects related to ambient NO_2 in 2016. As indicated in Table 14.3, the U.S. EPA's ISA for NO_2 concluded that there was *likely to be a causal relationship* for respiratory outcomes and *suggestive* evidence of a causal relationship for birth outcomes, cardiometabolic diseases, mortality, and cancer (U.S. EPA 2016). The independent assessment of Health Canada in the same year on diesel exhaust arrived at similar conclusions for respiratory and cardiometabolic diseases (Health Canada 2016). In 2018, the Committee on the Medical Effects of Air Pollutants in the United Kingdom (COMEAP 2018) evaluated the evidence regarding the association between NO_2 and mortality. They evaluated whether NO_2 is a causal agent or only an indicator of TRAP, given that correlations in space and time between concentrations of NO_2 and other traffic-related air pollutants are often high. Perhaps not surprisingly given such challenges, COMEAP members were unable to reach a consensus view regarding the causality assessment for NO_2. This discussion, although relevant, does not influence the evaluation of NO_2 in the current review because the Panel considered the individual pollutants—including NO_2—as indicators of the TRAP mixture. It does point, however, to a key question that remains largely unresolved so far (Section 14.10 Future Research Directions). A moderate or high level of confidence for the association between long-term

exposure to NO_2 and mortality for all-cause, respiratory, COPD, and ALRI mortality was found in a recent systematic review that serves as input for the updated WHO Air Quality Guidelines (Huangfu and Atkinson 2020).

The U.S. EPA ISA for particulate air pollution (U.S. EPA 2019) has considered $PM_{2.5}$, PM with aerodynamic diameter between 10 μm and 2.5 μm (PM_{coarse}), and UFPs. The evidence for $PM_{2.5}$ was considered *causal* for mortality and cardiovascular morbidity, *likely to be causal* for respiratory diseases and cancer, and *suggestive* for birth outcomes and metabolic outcomes. A moderate or high level of confidence for an association between long-term exposure to $PM_{2.5}$ and increased mortality from all causes, cardiovascular disease, respiratory disease, and lung cancer was found in a systematic review recently commissioned by WHO (Chen and Hoek 2020).

The Panel performed a comparison between some of the effect estimates listed in Table 14.1 and effect estimates for the same exposure–outcome pairs from recent meta-analyses, using the same increment. As an example, for all-cause mortality the effect estimates in the current report for NO_2 and $PM_{2.5}$ were 1.04 (95% CI: 1.01–1.06) and 1.06 (1.02–1.10) per 10-μg/m^3, respectively. They were 1.02 (1.01–1.04) and 1.08 (1.06–1.09) per 10-μg/m^3, respectively, in WHO air quality guidelines systematic reviews (Chen and Hoek 2020; Huangfu and Atkinson 2020), showing reasonable coherence. On the other hand, the results of the current TRAP review indicate a lower effect size for asthma and ALRI in children when compared with other recent meta-analyses (Khreis et al. 2017; Mehta et al. 2013).

The mortality and morbidity effects of long-term exposure to low-level $PM_{2.5}$, black carbon (BC), and NO_2 have been recently evaluated in the large ELAPSE project that has examined various European adult cohorts with individual detailed information on lifestyle covariates. The study was based on fine resolution (100 × 100 m) Europewide hybrid land use regression models, evaluating only within-cohort exposure contrasts. The ELAPSE study documented consistent associations between $PM_{2.5}$, NO_2, and BC and all-cause, circulatory, and respiratory mortality in the large pooled European cohort with detailed lifestyle covariates (Strak et al. 2021), as well as in the administrative cohorts including about 28 million participants (Brunekreef et al. 2021; Stafoggia et al. 2022). The analyses of morbidity outcomes in the same pooled cohort indicated associations of NO_2 and BC with incidence of asthma (Liu et al. 2020) and COPD (Liu et al. 2021). In addition, in the pooled cohort, incidence of stroke were associated with $PM_{2.5}$ (1.10 [95% CI: 1.01–1.21] per 5-μg/m^3 increase), NO_2 (1.08 [1.04–1.12] per 10-μg/m^3 increase), and BC (1.06 [1.02–1.10] per 0.5-10^{-5}/m increase), whereas coronary heart disease incidence were only associated with NO_2 (1.04 [1.01–1.07] per 10-μg/m^3 increase) (Wolf et al. 2021). Lung cancer incidence was associated with long-term exposure to $PM_{2.5}$ in the same cohort (Hvidtfeldt et al. 2021a); examination of PM components, however, suggested that the increased risk of lung cancer was related more with sources of combustion particles from oil and biomass burning and less from traffic emissions (Hvidtfeldt et al. 2021b).

14.5 EXPOSURE-ASSESSMENT CHALLENGES

TRAP is a complex mixture of tailpipe and nontailpipe emissions. Perhaps the single largest challenge in assessing exposure to TRAP stems from the absence of a measurable toxic constituent that is unique to traffic emissions. Vehicle exhaust emissions contain gases and particles with chemical and physical characteristics that are common among fossil fuel combustion sources. In the absence of a unique toxic agent, assessments rely on measurements and models of pollutants that in many geographic settings are thought to arise primarily from traffic-related combustion sources, such as NO_x, carbon monoxide (CO), EC, and UFPs. We additionally included studies based on $PM_{2.5}$ and PM_{10}, but only in restricted settings where the measures used are thought to reflect a large contribution from local traffic sources, because otherwise both pollutants are primarily regional pollutants with a large contribution of long-range transported pollution. The Panel included PM studies because the (small) spatial variation of PM within metropolitan areas is driven by traffic emissions, to an important extent (Hoek et al. 2011; Levy et al. 2014).

Many epidemiological studies in this review use land use regression models for assessment of long-term concentrations of these individual pollutants, but even when traffic and roadway characteristics are important predictors in these models, uncertainty remains in their traffic specificity. Likewise, chemical transport and dispersion models have been used with vehicle- and other sources of emissions to estimate long-term concentrations contributed specifically by traffic, but these estimates suffer from uncertainties in emissions inputs and modeling of atmospheric processes. Although substantial progress was made in this review, as discussed later, on identifying traffic exposure-assessment methods, further research is needed to understand how well and in what circumstances the key traffic-related pollutants and modeling techniques represent the exposure to traffic, compared with other sources.

Another challenge in assessing the evidence of the health effects of TRAP is interpreting the chemical agent(s) associated with health effects, as ambient concentrations of chemical components of the TRAP mixture are often highly correlated. As such, several important questions need to be considered. To what extent should epidemiological associations be interpreted as direct effects of individual pollutants (e.g., NO_2) or to the broader mixture of correlated components indicative of TRAP? When the association with a single pollutant stands

out among those for several traffic-related pollutants, is the association informative about the role of that specific pollutant or might it reflect more accurate exposure modeling of the mixture by one pollutant than the others? Cases with similar epidemiological associations for several traffic-related pollutants lend support to individual pollutants acting as surrogates for the mixture, but the understanding of this issue is limited and deserving of further research. For this review, this issue is less important as the Panel considered pollutants as indicators of TRAP and did not attempt to attribute health outcomes to specific components of TRAP. For policy purposes, however, the issue remains an important consideration. The issue is further complicated by changes in the TRAP composition over time. The evidence for decreases in vehicle emissions in developed countries over the last 30 years is very strong; however, reliable evidence for how a unit of TRAP emissions has changed is lacking. The absolute and relative amounts of NO_2, BC, UFPs, trace metals, and toxic organic gases and particles in vehicle emissions clearly have and will continue to change with the implementation of advanced control technologies and fuels (Chapter 2).

A strength of this review is the detailed consideration of how well a given study reflects exposure to TRAP. The Panel developed a novel exposure framework to define exposure characterization approach(es) most likely to specifically assess TRAP as opposed to air pollution exposure more generally. Specifically, the framework identified methods, pollutants, and spatial resolution of participant locations and pollution surfaces that together provide criteria for identifying studies where the exposure contrast is primarily from traffic sources. The Panel's approach includes studies of exposure of individuals beyond the near-road environment, but excludes, for example, studies that exclusively made use of between-city contrasts, such as the original Six Cities Study and the American Cancer Society study (Dockery et al. 1993; Pope et al. 2002). Studies or reviews that focus only on the near-road environment potentially underestimate the contribution of TRAP to population health, whereas studies or reviews focused on a single component (e.g., NO_2), regardless of source potentially, overestimate the contribution of TRAP to population health.

The exposure framework emphasized rigor, transparency, and reproducibility, at the expense of excluding some studies that could have provided useful insights. The Panel acknowledges that application of the exposure framework was not always straightforward to select studies, and the Panel may have included studies that have a significant contribution to exposure contrast from sources other than traffic or excluded studies that did have an important traffic signal. In particular, the selection was difficult for the studies outside the near-road environment. An example is the exclusion of multicity studies, resulting from the Panel's conservative approach of requiring adjustment for city (or area) to ensure that reported associations with health effects are driven by within-city variations in exposure rather than by between-city or regional differences in exposure. This choice was guided by the understanding that traffic is often the major source of within-city variability in exposure, and that contrasts between cities cannot reliably be ascribed to traffic contrast only. However, between-city exposure contrast can also reflect true differences in exposure to TRAP, even though it is commonly confounded by contributions from other sources. The Panel acknowledges that its framework may have excluded some informative studies. Thus, despite the improvements in evaluating the exposure-assessment approach of individual studies achieved in this review, further research is needed to refine methods for assessing the exposure contrast from TRAP and other sources for key traffic-related air pollutants.

Having adopted a broader and more inclusive exposure framework than the 2010 review, the Panel developed a traffic specificity classification to further categorize qualifying studies based on the level of confidence that the pollutant signal associated with the reported outcome(s) represented traffic. High traffic specificity was assigned using a restrictive form of the general exposure framework. 279 of 353 studies (79%) had at least one pollutant classified as high traffic specificity. The classifications illustrated the selectivity of the exposure framework, and the large number of included studies, with high confidence that the exposure contrast was from traffic. The expectation was that the high specificity studies would provide more reliable evidence of associations with traffic than the moderate specificity studies would. Sensitivity analyses stratifying the high and moderate traffic specificity studies informed the overall evaluation of the epidemiological evidence.

The exposure framework includes studies of primary TRAP and tends to result in exclusion of studies of secondary TRAP. The rationale was that at the large spatial scales relevant for secondary TRAP it is not possible to disentangle TRAP from other sources. The framework does not explicitly exclude secondary TRAP, but many of the exposure models cannot identify it. Thus, the epidemiological analyses techniques that largely focus on within-city variations ignore it. As described in Chapter 6, the contribution of vehicle NO_x and volatile organic compounds emissions are believed to be substantial for secondary nitrate and organic aerosols, and for ozone on the urban and regional scales. Secondary TRAP is understood to be part of the urban and regional background $PM_{2.5}$ and ozone, for which numerous adverse health effects are well established (U.S. EPA 2019, 2020). Thus, the associations derived from primary TRAP in all likelihood represent the lower limit of the overall burden of disease from TRAP. Because the studies reviewed by the Panel have largely excluded secondary TRAP, the benefits of policy analyses based on these meta-analysis results will most likely underestimate the actual benefits of emissions reductions.

14.5.1 THE INFLUENCE OF TRAFFIC NOISE

Beyond air pollution, traffic can be a source of other exposures with potential relevance to health, most notably noise. These exposures may either confound or modify the health effect of TRAP. Traffic noise has been associated with various adverse health outcomes, most notably cardiovascular morbidity and mortality including hypertension and IHD, but also neurocognitive development and function in children and adults, adverse birth outcomes, and possible metabolic outcomes such as diabetes mellitus (WHO 2018). In the current review, a limited number of studies adjusted for traffic noise (N = 24 studies of 353, 7%). The majority of those studies investigated cardiometabolic outcomes (N = 13 studies of 57, 23%). Cardiometabolic studies investigating associations with TRAP were mostly robust to adjustment for co-exposure to noise. This finding was consistent with results from the large European ELAPSE study, where no relevant impact of noise on the association of air pollutants with coronary events and stroke was found (Brunekreef et al. 2021).

Two studies of IHD that considered this question found that additional adjustment for noise had no material impact on estimates of the association with NO_x (Carey et al. 2016) or PM_{10} (Cesaroni et al. 2014) and only slightly attenuated the association with $PM_{2.5}$ (Cesaroni et al. 2014). A study of fatal IHD in Vancouver, Canada, found that adjustment for community noise somewhat attenuated EC associations (Gan et al. 2012). In the Scania Public Health Cohort study, where noise exposure was a covariate in all multivariable-adjusted associations of NO_x with IHD, the unadjusted and adjusted associations were nearly identical (Bodin et al. 2016).

Adjustment for the moderately correlated noise indicator in the DDCH study substantially reduced the positive NO_2 associations for both fatal and nonfatal coronary events (Roswall et al. 2017). On the other hand, very strong associations of both traffic density and noise annoyance with coronary events were found in a small cross-sectional study in Toronto (Chum and O'Campo 2015) where only mutually adjusted results were available. However, in larger studies, adjustment for noise slightly attenuated coronary events associations with $PM_{2.5}$ but not with EC or traffic density in Germany (Hoffmann et al. 2015), whereas positive associations of UFPs with coronary events were not affected by adjustment for traffic noise in Ontario, Canada (Bai et al. 2019).

Four studies of stroke incidence that examined the influence of noise adjustment for one or more traffic-related pollutants showed stable or even larger effect estimates (Gan et al. 2012; Hoffmann et al. 2015; Sørensen et al. 2014; Stafoggia et al. 2014). Likewise, five studies of diabetes reported similar results with traffic noise adjustment (Clark et al. 2017; Dzhambov and Dimitrova 2016; Eze et al. 2014, 2017; Renzi et al. 2018).

The Panel also assessed the influence of traffic noise on TRAP estimates for mortality. Four studies investigating all-cause mortality reported associations adjusted for road traffic noise. In three studies air pollution effect estimates were not or very mildly attenuated (Nieuwenhuijsen et al. 2018; Raaschou-Nielsen et al. 2012; Tonne et al. 2016). In the most recent DDCH study (Hvidtfeldt et al. 2019), effect estimates were substantially attenuated but still indicative of an association with all-cause mortality. In most studies the correlation between air pollutants and noise was generally low to moderate (~0.2. to 0.6). A similar robust pattern was seen in the four circulatory mortality studies adjusted for traffic noise (Beelen et al. 2014; Huss et al. 2010; Hvidtfeldt et al. 2019; Raaschou-Nielsen et al. 2012).

For birth outcomes, few studies compared the noise-adjusted TRAP estimates with the estimates that did not control for noise. From those, effect estimates were either similar or attenuated after adjustment for noise in most studies (Gehring et al. 2014; Hjortebjerg et al. 2016; Smith et al. 2017).

In summary, in most cases examined, estimates of the health effects of TRAP were robust to adjustment for traffic noise. The limited number of studies and regions (Europe and Canada), and sporadic inconsistencies, suggest a clear need for more TRAP studies with comparable quality and resolution of noise assessment in other geographic areas.

14.5.2 RELEVANT EXPOSURE WINDOWS AND TIME-RELATED FACTORS

Another important issue is the relevant exposure period for health outcomes. For example, the birth outcome analyses focused primarily on evidence from exposure during the entire pregnancy, as this was assessed in the majority of the studies reviewed. However, this may have masked associations with exposure during particular critical windows. For example, if TRAP impacts fetal growth only during a specific trimester, focusing on the entire pregnancy would likely attenuate estimated associations toward the null. The Panel did conduct ancillary analyses looking at trimesters of exposure; however, the number of studies was smaller and therefore the results were less reliable. Nonetheless, the Panel did identify some associations that were stronger in specific trimesters. The focus on long-term exposure also did not include potential triggering effects of daily variation in TRAP on preterm birth (Schifano et al. 2016).

An additional example of the difficulties in evaluating the relevant exposure window was illustrated in the respiratory chapter (Chapter 9), as a higher risk of asthma onset or ALRI observed during childhood could be due to exposure during pregnancy, in the early period of life, or during the most recent months or years. The meta-analyses for asthma onset and ALRI in children were similar when considering the earliest versus most recent exposure, thus failing to provide clear

insights as to which exposure window was most etiologically relevant. Additional studies are needed to identify the most relevant period of exposure for all respiratory outcomes, but in particular for asthma onset in children.

Likewise, the most relevant time period of TRAP exposure for the elicitation of cardiometabolic outcomes is unclear. By design, the Panel only evaluated the potential adverse health effects of long-term exposure to TRAP. However, long-term exposure is a very broad category that can extend from early life to the final years before death. Specifically, for cardiometabolic disease, more evidence suggests that underlying pathology may be underway as early as childhood and adolescence (Raghuveer et al. 2016).

The studies included here did not investigate cardiometabolic outcomes in early life, as such outcomes are typically preclinical while the focus of this review was deliberately on clinically manifested diseases. Within adulthood, the timing of exposure and outcome was only systematically addressed in a few studies, and issues of timing could be biased by other aspects of exposure assessments (stability of exposure models back in time, availability of accurate residential histories, selective survival, etc.). Hence, more could be learned from studies designed to include and identify the biologically most relevant time periods of exposure over the life course.

An additional issue that is difficult to address in the current literature is the relationship between short-term and long-term exposure in eliciting the health effects. The short-term exposure effects have been summarized in Chapter 4 and a large body of literature convincingly demonstrates an association of short-term exposure to traffic-related air pollutants and respiratory and cardiovascular morbidity outcomes and mortality. It is possible that the effects of long-term exposure to TRAP result from the progressive accumulation of short-term health insults over time. This hypothesis is biologically plausible at least for some outcomes, but few studies have explicitly addressed this question. A few studies have estimated the mortality effects of short- and long-term exposure to general $PM_{2.5}$ simultaneously; they found both short and long-term exposure effects, but also a suggestion that the effects of long-term exposure are larger than the sum of short-term effects (Shi et al. 2016; Yitshak-Sade et al. 2018). Furthermore, it is plausible that susceptibility to acute effects is increased through long-term exposure to TRAP.

In addition, time-related factors, such as latency since first exposure and latency since cessation of exposure, may play an important role, but the evidence is limited. Several intervention studies documented improvements in respiratory and cardiovascular health outcomes within a relatively short period after a drastic change in air pollution levels (Burns et al. 2020; Rich 2017). Also, a substudy in the Children's Health Study reported an improvement in lung function growth within a year among children who moved from areas of high-to-low air pollution (Avol et al. 2001). Likewise, evidence from other related research fields also indicate the importance of recent exposures rather than exposure happening in the long past, with rapid health improvements after cessation. For example, several studies investigating the lung function of bar workers before and after a smoking ban in public places showed beneficial effects of up to 8% within a few months after the ban (Eisner 1998; Menzies et al. 2006). Studies have also documented fairly immediate changes in cardiovascular diseases related to smoking bans (Gao et al. 2019; Tan and Glantz 2012).

14.5.3 TRENDS IN VEHICLE TECHNOLOGIES AND EMISSIONS

The time of exposure assessment is also a concern because TRAP emissions and exposures in North America and Europe have generally decreased over the past 30 years. This decreasing trend is a result of air quality regulations and improvements in vehicular emission-control technologies, and it is likely to continue (Chapter 2). The timing of exposure assessment relative to the observation time in a study can influence the magnitude (size) of the association. If an estimate is based on today's smaller exposure contrast, but was biologically determined by an earlier, much larger exposure contrast, the effect estimate may be inflated. Although the Panel has discussed this potential concern when evaluating the risk of bias for a specific study in the exposure domain, the issue is more complicated if the air pollution decline has been heterogenous in the areas under investigation. Although the magnitude of the effect estimate may be affected, it seems unlikely that the presence of a consistent association is influenced by these temporal trends, as some studies have shown stability of spatial contrasts over a decade. For example, the recently completed ELAPSE study documented this issue for mortality: significant associations were found with 2010 exposure, and with back-extrapolated exposures, but with a different effect size (Brunekreef et al. 2021). In addition, relationships can be nonlinear and influenced by the slope of the exposure–response function at low concentrations. That the vast majority of studies that looked specifically at the shape of the exposure–response function did report a monotonic and plausible exposure–response function—with health effects remaining at relatively low levels and no evidence of a threshold—lends confidence to the Panel's findings. Moreover, the results of recent low-level air pollution epidemiological studies investigating general $PM_{2.5}$ (Brauer et al. 2019; Dominici et al. 2019; Hales et al. 2021) and the evidence that relatively recent exposure (past 1–5 years) contributes to health effects related to long-term air pollution exposure, support the judgment of the Panel that the findings of the review are relevant to recent traffic exposures and not just to the higher exposures in the past.

The Panel notes that newer implemented technologies have reduced, but not eliminated, pollutants that have been used in this review as markers of TRAP, including NO_2, EC,

and UFPs, especially in view of the slow turnover of the vehicle fleet and other challenges described in Chapter 2. Because the conclusions of the Panel were primarily based on markers of exhaust emission, it is uncertain how the conclusions could apply to a future scenario where the fleet predominantly consists of electric vehicles. Although the proportion of electric vehicles is small at this time, their sale is growing rapidly, as technical and infrastructural barriers are overcome and government policies and manufacturers' pledges to boost their adoption come to fruition. The reduction in greenhouse gas emissions from electrification is highly dependent on the carbon intensity of the power generation (Chapter 2). Finally, the convergence of new technological developments outside the transportation sphere—particularly digital connectivity and artificial intelligence—and a change in mobility preferences could significantly change the current transportation sector with its heavy reliance on private automobile ownership. Such changes also have the potential for reductions in greenhouse gas and TRAP emissions, especially if they are combined with electrification and if they succeed in long-lasting reductions in total travel demand. Because fleet turnover is a relatively slow process, some of the challenges related to TRAP emissions and exposures are likely to continue to be of concern. These include higher emissions exposures in environmental justice communities and higher emissions due to cold starts and from older and high-emitting vehicles. Additionally, urban areas will continue to suffer from the ills of congestion and sprawl, including the lack of green space and the suboptimal use of urban space. Finally, technology alone, whether old or new, will not solve all these problems. Active transport—that is walking, scootering and bicycling (but with little or no electrification)—could substantially assist in addressing the challenges of modern mobility. Redesign of urban roads and added greenspace encourages active transport and physical activity, while also reducing the heat-island effect. Also, active transport helps to overcome a sedentary lifestyle, which is a growing trend in most high-income countries and is associated with several adverse health outcomes.

Thus, despite the noteworthy improvements in vehicular emissions and air quality, concerns about TRAP and its impact on human health, even at somewhat reduced levels, are likely to continue in the near and medium-term future. The overall impact of transportation and mobility choices on air quality and human exposure is a highly dynamic and rapidly changing area; its consideration should be a part of any future research planning.

14.6 OUTCOME-ASSESSMENT CHALLENGES

The selected morbidity outcomes were measured in various ways across studies, and the Panel did not impose restrictions regarding the source of outcome data (e.g., official registry, hospital data, clinical examinations, and questionnaire) except for COPD, where the Panel excluded studies based only on questionnaires following the Global Initiative for Chronic Obstructive Lung Disease guidelines (Pauwels et al. 2001). The validity of the outcome measure can influence both the magnitude and direction of the association. It is well known that nondifferential misclassification (i.e., independent of the exposure status) of a dichotomous outcome will generally create bias toward the null, thus an underestimate of the effect measure, and a diminished possibility to detect an association (Chen et al. 2013; Copeland et al. 1977). However, differential outcome misclassification (i.e., dependent of the exposure status) can create bias toward or away from the null in unpredictable ways, in particular when conflated with confounding. For example, in health studies of TRAP, differential misclassification of the outcome can happen through SES and access to or utilization of the health care system. The effects of individual and neighborhood SES on health are now widely accepted, and it is understood that there are relationships between TRAP and SES. In many settings, low-SES communities reside in the vicinity of roads and transportation corridors, and therefore are disproportionately exposed to air pollution. Such communities may also be more susceptible to air pollution due to lack of access to or utilization of the health care system, and there may be other underlying disparities (Clark et al. 2014; Hajat et al. 2015; O'Neill et al. 2003). However, some studies have reported opposite associations between SES and air pollution exposure, for example in New York and Rome, highlighting the importance of investigating the SES–air pollution associations in a specific setting (Cesaroni et al. 2010; Hajat et al. 2013). Through those varying associations, differential outcome misclassification can lead to unpredictable bias in either direction.

Bias due to nondifferential outcome misclassification depends on two components of validity: sensitivity (the probability that someone who truly has the outcome will be identified as such) and specificity (the probability that someone who does not have the outcome will be identified as such), with low specificity being the most important factor generating bias toward the null in epidemiological studies. In addition to sensitivity and specificity of the outcome measure, the exposure and disease distribution also play a role (Copeland et al. 1977). In general, an outcome with low sensitivity but high specificity will not lead to measures of relative risk bias. Because most of the studies in the current review use relative risk as the measure of association, and many have an outcome-assessment strategy that yields high or very high specificity, outcome misclassification is not likely to be a major source of bias in most of the studies reviewed in the report.

The Panel considered the issue of outcome validity and potential outcome misclassification in the risk of bias assessment. As discussed in the specific chapters, the outcome assessment was particularly an issue for COPD and ALRI in adults; such difficulties may partly explain the very low to low confidence determinations for these outcomes. For COPD,

the criteria often used in epidemiological studies (e.g., use of health services) have high specificity but rather poor sensitivity as they represent only those patients with severe or poorly controlled COPD. Moreover, for ALRI in adults, studies were largely based on administrative datasets from hospitals relying on specific Internal Classification of Diseases codes for pneumonia, which do not distinguish between community and hospital-acquired pneumonia. Moreover, community-acquired pneumonia can also be treated at home; these cases are missed when only hospitalizations are considered (Millett et al. 2013).

Validity of diagnoses for cardiovascular disease has been shown to be lower in older compared with younger ages, in specific subtypes of disease compared with others, and on death certificates compared with hospital-based diagnoses (Davidson et al. 2020; Lloyd-Jones et al. 1998; McCormick et al. 2014). IHD can also be misclassified as congestive heart failure, particularly in primary health care (Remes et al. 1991). Moreover, diagnostic criteria for the classification of coronary events and access to diagnostic tests (i.e., availability of computerized tomography and magnetic resonance imaging scans for diagnosis of stroke) have changed during the period covered in this review, which may have led to differences in case definition and methods of detection during this time span. For diabetes, a disease with a long oligosymptomatic prediagnostic phase, reliance on self-report or documented disease will typically miss 40% of cases in North America or Europe, while in-depth study center examinations will have a much higher sensitivity (IDF 2019).

In general, several outcome challenges remain, even when the specificity of the outcome measure was considered high, in particular when data from only a specific fraction of the diseased individuals were captured (e.g., the more severe cases, cases with more symptoms, and cases with better access to health care services). Such epidemiological studies do not represent the complete prevalence or incidence of those diseases, but rather, may only indicate the burden of moderate to severe disease or milder disease in which the person is at risk of exacerbations. This conclusion and caveat suggest future studies would need to characterize the disease entity in a better way by considering its full spectrum.

14.7 METHODOLOGICAL STRENGTHS AND LESSONS LEARNED

This review is the largest systematic effort to date that evaluates the epidemiological evidence regarding the associations between long-term exposure to TRAP and the specified health outcomes. The use of systematic review methods within the field of environmental health has been expanding over the last 10 years or so and has become quite common. One of the drivers of this growing interest is the increasing recognition of the potential for the methods of systematic reviews to offer a new benchmark in best practices for aggregating and summarizing evidence in support of policy decisions (Whaley et al. 2020).

The Panel used a systematic, transparent approach throughout the evaluation. The Panel carefully developed and tested a search strategy, developed a new exposure framework to transparently select studies and developed confidence assessment methods that was applied with frequent internal meetings in subgroups and the full Panel. The allocation of the search task to an independent organization that was experienced in literature searches contributed significantly to the completeness and accuracy of the literature search. The performance of all meta-analyses by two Panel members contributed largely to the standardization of the analyses. HEI staff and the chairs provided further harmonization in the evaluation of studies and evidence. The systematic effort is considered a strength and an important difference compared with the earlier critical review of 2010.

Another major strength of this review was the methods adopted to evaluate the confidence in the evidence. The conclusions were based on a narrative assessment and a modified OHAT assessment, with the two approaches considered complementary, that reflected the complex issues in determining the level of confidence. The two approaches differed in some important respects. In the modified OHAT assessment, there was more emphasis on the studies entering meta-analyses and on the quality of the body of evidence. In contrast, for the narrative assessment the Panel considered evidence from *all* studies included in the systematic review. This was considered particularly important because only about half of all relevant studies were judged by the Panel to be appropriate for including in the meta-analyses. Moreover, the narrative assessment assessed the confidence in the presence of an association and included some aspects that are not or are only partially covered in the OHAT assessment, such as the number and size of the evidence base, the strength (magnitude) of the association, and the consistency of the findings across locations, time periods, study designs, and different pollutants and indirect traffic measures. This narrative approach links more directly to current and widely accepted evidence synthesis frameworks, such as those of the U.S. EPA and IARC (e.g., Owens et al. 2017; Samet et al. 2020). For future assessments, the Panel would recommend taking a broader narrative approach to maximize what can be learned from observational studies in environmental health to complement the formal assessment.

Table 14.4 summarizes key elements of GRADE-type approaches and suggested improvements for evidence synthesis, following the Panel's experience in this review. Below we elaborate further on those issues.

There is a fundamental distinction between clinical medicine and environmental epidemiology, which makes it difficult to apply formal assessments like Grading of Recommendations Assessment, Development and Evaluation (GRADE) or OHAT

Table 14.4. Key Elements of GRADE-Type Approaches and Suggested Improvements for Evidence Synthesis of Observational Studies in Environmental Health

Key Elements	Suggested Improvement
Evidence Synthesis	
Use only GRADE to assess confidence in the quality of the body of evidence	Take a broader (narrative) approach to maximize what can be learned from observational studies in environmental health to complement the formal assessment
Assign an initial level of low or moderate confidence for all observational studies	Consider that observational studies can offer high confidence evidence in environmental health, where randomized controlled trials are generally not feasible
Derive overall judgments based primarily on meta-analyses results only	Consider evidence from *all* studies included in a systematic review; the studies entering meta-analysis are often a subset
Assess the statistical heterogeneity of results and downgrade the evidence if substantial heterogeneity is found	Sources of heterogeneity can both strengthen or weaken the confidence in the evidence, and should be carefully explored Some heterogeneity is expected in studies of the health effects of environmental exposures, due to different exposures, populations, and study settings Consider primarily the direction of the associations rather than its magnitude; different methods and study designs that generate similar findings may strengthen the confidence; add a separate upgrading factor for consistency
Always suspect publication bias. Assess publication bias using the Egger test and funnel plots then downgrade accordingly	Do not expect publication bias in case of large and collaborative (multicenter) studies Explore additional tools to explore the possibility of publication bias
Risk of Bias in Individual Studies	
Compare to randomized controlled trials or hypothetical target experiments as ideal study	Do not consider randomized controlled trials as ideal study
Evaluate bias in different domains (e.g., confounding, selection bias, measurement error)	Focus on identifying the most likely influential sources of bias, classifying each study on the basis of how effectively it has addressed each potential bias and determining whether results differ across studies in relation to susceptibility to each hypothesized source of bias
Rank potential biases (e.g., low, moderate, high) using a risk of bias tool	Rank biases considering the suggestions in the row above

in epidemiology. GRADE was initially implemented for evaluating evidence to develop clinical guidelines for therapeutic beneficial interventions, ranking randomized studies as providing higher-confidence evidence than nonrandomized designs in the clinical setting. Environmental health research and policy evaluate, identify, and mitigate environmental hazards. Randomized controlled trials are often not feasible and unethical for studies of environmental exposures and health outcomes (intervention studies being the exception). Randomized controlled trials typically involve short follow-up times and limited sample sizes, but investigations of health effects of environmental exposures may require follow-up over many years to capture long etiologicical induction periods and investigations of rare health outcomes necessitate a very-large sample size (up to millions). Typically, a limited number of dose levels are studied in a randomized controlled trial, in contrast to a wide spectrum of exposure levels studied in observational investigations of environmental exposures.

Finally, randomized controlled trials often have limited generalizability, because they enroll highly selected samples of persons meeting specified criteria—healthier and with fewer underlying conditions, than the population that might eventually use the treatment (Steenland et al. 2020). By contrast, a large epidemiological study in the general population can include the full spread of susceptibility.

These fundamental differences require a different approach to evaluating the confidence in a body of evidence in environmental health. For future assessments, the Panel recommends that observational studies, especially cohort and case-control studies of incident cases, start with a high confidence rating. This initial confidence rating for a body of evidence from this

type of studies can be then downgraded if substantial biases are likely that would affect the effect estimates significantly. The Panel prefers the approach of explicitly describing biases in a body of evidence to the automatic assignment of lower initial confidence to all observational studies.

The downgrading factor in the confidence assessment of the body of evidence most often used in the current review was imprecision (49% of all meta-analyses), pointing to the need for additional (larger) studies (Table 14.5). The upgrading factor that was most often used was evidence for a monotonic exposure–response relationship, which was applied to 29% of the meta-analyses. The Panel decided that at least two influential studies should have evaluated the actual form of the relationship using, for example, splines or categorical analyses, and should document a monotonic exposure–response function. Note that to avoid upgrading null findings, this factor was used only if the linear association was at least borderline significant.

The GRADE-type application was challenging, partly due to the mechanistic up- and downgrading of confidence related to certain factors. Some features of the GRADE and OHAT methods were particularly controversial, such as downgrading the body of evidence because of unexplained inconsistency across studies. This downgrading factor was applied in only 13% of the assessments in this review. Some heterogeneity is expected due to the nature of observational studies and the different populations involved. The Panel therefore decided to evaluate this factor after careful review of the potential sources of heterogeneity, including risk of bias, and primarily consider the direction of an association rather than its magnitude. The Panel would argue that sources of heterogeneity can strengthen or weaken the confidence in the evidence. Hence, the Panel appreciated that OHAT—in contrast to GRADE—uses consistency as an extra upgrading factor, and so have almost all frameworks for review and evaluation of environmental hazards and risks to inform policy.

Another issue that was discussed in the application of OHAT was the criteria for downgrading when there was evidence suggestive of publication bias. The methods to address this sort of bias are relatively crude (Egger test, funnel plots) and are limited to situations with a relatively large number of studies, while false-positive indications can arise from other factors (heterogeneity is one, sometimes due to the nonlinearity of the association). The Panel a priori did not necessarily expect publication bias, especially when large and collaborative (multi center) studies were involved. In an attempt to further explore the possibility of publication bias, the Panel conducted a sensitivity analysis for studies before versus after 2008. Furthermore, the Panel prepared plots of the number of participants versus publication year, colored by the direction of the association and the statistical significance of the results for all estimates—and only for those included in meta-analysis (all the results are available in Additional Materials 14.1; available on the HEI website). From all these analyses, there was no clear sign of publication bias, and this downgrading factor was never applied in this review.

The Panel systematically evaluated differences between high versus moderate or low risk of bias studies in sensitivity

Table 14.5. Summary of Number of Up- and Downgrading Factors Used in the Confidence Assessment of the Body of Evidence for TRAP per Health Outcome Category

		Factors Decreasing Confidence				Factors Increasing Confidence		
Health Outcome Category	Total Meta-analyses	Risk of Bias	Unexplained Inconsistency	Imprecision	Publication Bias	Monotonic Exposure–Response Function	Consideration of Residual Confounding	Consistency Across Populations
Birth outcomes	19	12	4	4	0	6	2	0
Respiratory outcomes—children[a]	16	1	1	10	0	1	0	2
Respiratory outcomes—adults[a]	5	0	3	4	0	0	0	0
Cardiometabolic outcomes	18	0	1	13	0	6	1	0
Mortality	29	3	2	12	0	12	0	2
Total	87	16 (18%)	11 (13%)	43 (49%)	0 (0%)	25 (29%)	3 (3%)	4 (5%)

[a] Wheeze outcomes not included in the total sum for respiratory outcomes.

analyses and applied the downgrading factor in 18% of the meta-analyses (N = 87) (although much higher at 63% in the birth outcomes). Most of the studies in meta-analyses were rated as low-to-moderate risk of bias for all but the important confounder domain, for which about one-third of the meta-analyzed studies were rated as high risk of bias. In most meta-analyses, however, differences in effect estimates between low or moderate and high risk of bias studies were small, and hence no downgrade was applied. Partly based on subject matter-informed directed acyclic graphs (DAGs), the Panel developed a list of important confounders which included age, sex, individual-level or neighborhood SES, BMI, and smoking (Chapter 5). The definition of an important confounder is rather subjective because confounding is not always easy to recognize, and it may differ widely among study populations and settings. Moreover, risk of bias indicates the *potential* for the results of an individual study to be biased and does not inform on *actual* bias in a particular study. Neither does a score of moderate or high risk of bias inform about the size of a potential bias (e.g., while risk of bias can be high due to a methodological problem, actual bias might be very small and vice versa). A high risk of bias determination also does not indicate the direction of bias, which can vary according to specific study conditions, with the potential for different biases to operate in countervailing directions.

Although various risk of bias tools exist, there is no consensus about the best approach for assessing risk of bias in observational studies (Bero et al. 2018; Eick et al. 2020; Savitz et al. 2019). For future assessments, the Panel advocates that risk of bias assessments should be focused more on identifying the most likely influential sources of bias—based on methodological and subject matter expertise—classifying each specific study on the basis of how effectively it has addressed each potential bias and determining whether results differ across studies in relation to susceptibility to each hypothesized source of bias, as described in Savitz and colleagues (2019). Such an approach can provide insight into the potential impact of each specific bias, identifies a subset of studies likely to best approximate the true association, and suggests features needed to improve future research.

Lastly, an important choice in the application of the OHAT approach was whether upgrades in confidence should be assigned without consideration to downgrades that have been assigned, and vice versa. The Panel opted to evaluate the downgrading and the upgrading factors independently, following the GRADE application in WHO systematic reviews of air pollution and traffic noise for use in guideline development (Chen and Hoek 2020; Huangfu and Atkinson 2020; WHO 2018). There may be some clear exceptions, for example if a downgrade for risk of bias has been made, one should not upgrade for large magnitude of the effect. Note that the latter factor was not considered in the traffic review, because the Panel considered a large effect to be both ambiguous to define and unlikely to occur in the traffic review.

14.8 USE OF META-ANALYSIS ESTIMATES IN BURDEN OF DISEASE AND HEALTH IMPACT ASSESSMENTS OF TRAP

Burden of disease estimates seek to quantify the mortality or morbidity attributable to long-term exposure to current levels of air pollution. In contrast, health impact assessments seek to estimate the health benefits likely to arise under plausible alternative counterfactual scenarios, such as from the future implementation of air pollution abatement policies. It was beyond the scope of this review to perform a burden or health impact assessment of TRAP. The Panel encourages future risk and health impact assessments of TRAP; however, it is important to note the limitations of such an assessment considering several issues that will be described later.

Burden can be quantified as the number of years of life a person loses as a consequence of dying prematurely because of disease and the number of years of life a person lives with disability caused by the disease (WHO 2016). Burden calculations require the following:

- An exposure–response function quantifying the association between long-term concentrations of a pollutant and health outcome
- An estimate of the distribution of exposure to an air pollutant across a given population
- Disease measures (incidence or prevalence) and cause-specific or all-cause mortality
- A suitable *counterfactual* or minimum exposure level

Years of life lost can be expressed as an equivalent number of deaths attributable to air pollution, a concept more easily communicated to a nonscientific audience, although often misinterpreted as the number of deaths caused by air pollution. The global burden of air pollution has been assessed in the State of Global Air study (HEI 2020). Burden assessments specific to TRAP have also been conducted. For example, the World Bank Group estimated 184,000 deaths worldwide in 2010 attributable to TRAP as indicated by $PM_{2.5}$ derived from vehicular emissions (Bhalla et al. 2014). Lelieveld and colleagues (2015) estimated that TRAP is responsible for one-fifth of deaths from air pollution in the United States, the United Kingdom, and Germany. In a study of asthma incidence in the U.S. contiguous states in 2000 and 2010, TRAP accounted for 27%–42% and 18%–36%, respectively (Alotaibi et al. 2019). Khreis and colleagues (2018) estimated the number of cases of asthma in children in Bradford, England, which were attributable to TRAP, as indicated by traffic-related emissions of NO_2 and NO_x to be 3% and 6%, respectively (Khreis et al. 2018).

Burden calculations imply a causal relationship between the pollutant and health outcome; they should therefore be preceded by a causal determination based on an evaluation of epidemiological and other evidence. For some pollutants and outcomes, such evaluations have previously been completed

(e.g., U.S. EPA 2019). The biological underpinnings of TRAP effects are summarized in Chapter 3.

Burden calculations conducted individually on correlated pollutants, such as those considered to be TRAP indicators in this review, should not be added together as this could lead to overestimation of the total burden attributable to a specific source. Rather, careful consideration of the extent to which the pollutant under investigation has effects independent from other pollutants or whether it is interpreted as marker of the TRAP mixture is required to inform any burden assessment (COMEAP 2018).

TRAP comprises a mixture of tailpipe emissions (e.g., NO_x, CO, PM) and nontailpipe emissions (e.g., brake and tire wear), and it is likely that their individual meta-analytic summary estimates represent some or all of this mixture. Consequently, while this review addressed a range of traffic-related pollutants, the Panel recognized their high correlation, but attempts to estimate associations for individual pollutants independent of the other traffic-related pollutants were beyond the scope of this Special Report.

It is also important to note that this review only assessed the evidence for TRAP with pollutants reflecting the near-roadway and neighborhood environment; hence, our assessment does not explicitly include the health impacts of secondary air pollutants resulting from traffic. Consideration of the range of primary and secondary pollutants resulting from traffic should be included, therefore, in any burden assessment exercises to provide a more complete picture.

Evaluation of the linearity of the exposure–response function across the range of pollutant concentrations observed in epidemiological studies is also important. Existence of a threshold or lack of evidence of associations below counterfactual values also has a substantial impact on burden estimation. A further consideration is transferability of evidence from studies included in this review to the target population(s). Factors to examine include the population characteristics and the nature of the TRAP mixture. For example, an exposure–response function derived in locations with little diesel use in motor vehicles may not be applicable to a location with a high proportion of motor vehicles using diesel fuel.

Health impact calculations utilize the same data inputs as for burden calculations but are applied to hypothetical scenarios that assume reductions in pollutants or pollutant mixtures arising from potential abatement strategies. Such strategies may aim to reduce traffic volumes in general (and so reducing concentrations of a number of pollutants at the same time) or target reductions in specific pollutants by imposing design criteria on engine manufacturers, for example. In a health impact assessment, the reliability of the exposure–response function used is of less importance than for burden calculations, because the nature of the assessment is one of comparison between policies (i.e., relative), rather than quantification of absolute numbers. Health impact assessments can be estimated and so contribute to cost benefit analyses for selected policy options. Examples of such analyses include assessments by Malmqvist and colleagues (2018), Smargiassi and colleagues (2020), and COMEAP (2018).

The focus of this review was an assessment of the level of confidence in the evidence for an association between TRAP and a range of health outcomes, rather than the estimation of the magnitude and precision of the associations. A moderate-to-high level of confidence was found for an association for a number of pollutant–outcome pairs. However, in air pollution epidemiology, the relative risks reported in any individual study are typically small, and with substantial variability (heterogeneity) between studies. Hence, the choice of included studies (based on geographical location, population characteristics, pollution mixtures, etc.) and the selection of study results for meta-analysis can influence the magnitude and precision of the meta-analytic estimate. The specificity to TRAP of the exposure assessment is a key issue. In this review, included studies met exposure-assessment criteria, ensuring a focus on pollutants arising from traffic and excluding studies where exposure contrasts were likely dominated by nontraffic sources. Hence, this review summarizes the evidence base and provides exposure–response functions that are relevant to TRAP compared with other reviews based on general ambient air pollutant concentrations that likely reflect contributions from multiple sources. Given the large populations at risk in burden and impact assessments, a careful assessment of the evidence including the precision of meta-analytical estimates and how this may impact on subsequent burden calculations is also recommended (Spiegelhalter 2017).

In addition to the above issues, this review has identified a number of deficiencies in the evidence base underpinning these meta-analytical estimates that can have a direct bearing on subsequent burden and health impact assessment exercises. These include a paucity of studies in key areas including outcomes (e.g., COPD incidence), pollutants (e.g., CO, EC), geographical location (the majority of studies are conducted in North America and Europe), and unexplained heterogeneity between studies. Increasing the number of studies on certain pollutants in the TRAP mixture, such as nontailpipe PM and UFPs, could provide additional evidence of the presence of an association; it could also provide insight into how variations in the mixture may influence the effect size (i.e., further explain heterogeneity). A better understanding of the contribution of TRAP to secondary pollutants is also needed to determine whether they influence the current review, which is largely focused on primary TRAP. The lack of independent evidence of secondary pollutant health impacts on top of the impacts of primary TRAP is also an important deficiency in current research. Additional epidemiological studies in these areas will facilitate a greater understanding of factors modifying the magnitude of associations worldwide and increase the precision, and hence, confidence in associations used in burden and health impact assessments.

14.9 LIMITATIONS OF THE REVIEW

The Panel acknowledges the limitations in the selection of health outcomes and prioritization. The Panel decided to focus efforts on reviewing the evidence for a selected number of clinical outcomes, rather than trying to review every possible important outcome. It is recommended that future reviews seek to evaluate the mechanisms behind the association of TRAP with the selected outcomes by studying the (subclinical) outcomes initially considered in the review, such as lung function, blood pressure, atherosclerosis, certain pregnancy outcomes (e.g., preeclampsia), and others.

As the Panel focused on the effects of long-term exposure only, the potential triggering effects of short-term exposure to TRAP have not been addressed systematically in this review. We did include a narrative nonsystematic review of short-term exposure studies, concluding that the overall evidence is consistent in reporting positive associations between short-term exposures to several traffic-related air pollutants and a suite of adverse health outcomes. Observed associations range from early, preclinical changes through in-depth examinations of pulmonary inflammation, lung function, and changes in biomarkers; to increased symptom exacerbation and health service use (i.e., emergency department visits and hospital admissions); and finally to increased mortality observed at the population level. However, the short-term exposure review is only meant to provide background information and serve as complementary and supporting evidence to the systematic review on long-term exposures.

As described in the methods, the final search date was July 2019, thus the most current studies are not included in the systematic review. In the final section of each outcome chapter (Chapters 8–11) some key recent studies were discussed that generally confirmed the assessment, but it is clear that this represents a very active field of study.

The small number of studies for some pollutant–outcome pairs present challenges in the interpretation of the meta-analyses. Random effects models estimate the mean and the between-study variance and the precision of the latter is likely to be low when the number of studies is very small. A random-effects model assumes that study estimates are sampled from a normal distribution, the validity of which is difficult to assess with small numbers of studies. A high degree of heterogeneity between study estimates and imbalance in the precision of these estimates further complicates the interpretation of the meta-analysis. Judicious assessment of the strengths and limitations of individual studies were sometimes necessary to arrive at an appropriate interpretation of the analysis. For example, the Panel had more confidence in a meta-analysis with a larger number of studies than in a meta-analysis with only three studies.

The Panel was charged with drawing conclusions about the confidence in the quality of the body of evidence and with assessing the level of confidence in the presence of an association between TRAP and selected health outcomes. It is worth noting, therefore, that the review did not focus on quantifying the exact magnitude of the associations of TRAP. Also, as individual studies analyze associations between air pollutants and health on a pollutant by pollutant basis, our review, meta-analysis, and assessment are therefore on a pollutant by pollutant basis. It is important to note that while the results are presented for a particular pollutant, the individual pollutants are considered as indicators of the TRAP mixture; associations therefore relate to the traffic pollution mixture rather than to each pollutant, independent of other traffic pollutants.

The Panel drew conclusions about the confidence in the strength of only the epidemiological evidence. This is a narrower focus than the ISAs such as from the U.S. EPA and other available authoritative reviews, which draw from all types of evidence (e.g., animal studies and mechanistic evidence), and then reach conclusions as to whether a particular association is causal. This Special Report includes a high-level succinct review on the mechanistic evidence, and the Panel did consider coherence with mechanistic research as supporting the plausibility of TRAP effects. Admittedly, the consideration of other types of evidence is limited; therefore, the Panel refrained from assessing causal determinations. For these reasons, the descriptors of the overall confidence assessment (Sidebar 14.1) only mention *association* rather than causal association, causal relationship or effect. We note, however, that a similar confidence assessment of epidemiological studies by WHO was considered sufficient to develop air quality guideline values (WHO 2021).

More broadly the review was limited to TRAP, although consideration was given to other factors of traffic, most notably noise. There is a clear need to evaluate TRAP in the broader context of transportation and mobility impacts on public health. Emerging knowledge suggests that transportation can affect health through many intertwined pathways such as traffic accidents, noise, climate change, temperature, stress, and the lack of physical activity and green space. Studies on the interactions and effect modifications of air pollution effects through other exposures such as green space, heat, noise, and physical activity are relatively scarce, but are needed as they reflect real-world conditions and may further advance our understanding of the implications of transportation activities and TRAP (Khreis et al. 2020).

14.10 FUTURE RESEARCH DIRECTIONS

The current review helped to identify several areas for future research. Although the evidence is already compelling for some of the outcomes investigated, a number of future research opportunities emerged from the results of this review, including research in low- and middle-income countries. The Panel's suggestions for future research directions can be found in Table 14.6.

Table 14.6. Several Future Research Directions Identified in the Systematic Review of Selected Health Effects of Long-Term Exposure to Traffic-Related Air Pollution

Broad Research Area	Research Directions
Exposure assessment	• Improve methods to assess exposure contrast from TRAP and other sources for key traffic-related pollutants, currently and as control technologies and fuels change, the fleet turns over, and electrification makes greater inroads. This research should investigate methods to incorporate within-city and between-city exposure to TRAP that accounts for the potential confounding from other sources. • Harness low-cost sensors to improve the understanding of local-scale exposure to TRAP and hot spots within communities. • As transportation systems evolve, take advantage of modern tracking devices (e.g., GPS, cell phones) to improve understanding of human activity and the intersection of people with traffic and the transportation system. • Develop noise exposure databases and models like those in Europe and make them available for use in epidemiological studies to properly characterize potential confounding by noise on other continents. • Conduct studies to characterize and build models for exposure to UFPs and nontailpipe PM emissions from vehicles. The analyses should incorporate sufficient PM chemical speciation and PM size resolution to properly characterize emissions from these sources and pay attention to changes in them over time. • Examine the role of TRAP as part of the broader exposome using new sensors and omics methods and identify biomarkers of exposure or disease.
Epidemiology—overarching areas	• Conduct additional epidemiological studies that assess long-term exposure of an array of traffic pollutants including UFP and nontailpipe PM indicators. Few studies were available, and there are good reasons to suspect they might be health relevant beyond what is already known. • More traffic-specific studies are needed, including adjustment for pollution from nontraffic air pollution sources. Most studies were set up to study pollutants rather than sources, related to regulatory standards. • More studies are needed in areas outside North America and Europe, particularly in low- and middle-income countries. The small number of studies outside these areas was due to fewer air pollution studies in general and fewer sufficiently traffic-specific studies, even though air pollution levels in such locations can be very high. • Investigate whether one or more of the TRAP indicators can be shown to have health effects independent of the other traffic pollutants. Gain a better understanding of whether the epidemiological associations found for TRAP are due to direct effects of NO_2, to another component of TRAP, or to the broader mixture of correlated components indicative of TRAP. • Analyze and evaluate exposure–response function(s) for traffic pollutants using, for example, splines, or quartile/quantile analyses. • Study the interaction with other environmental, social, and behavioral factors such as SES, traffic noise, green space and allergen exposure; physical activity and diet; and high and low temperatures and other climatic conditions. • Evaluate the fuller range of potential impacts of transportation and (new) mobility on public health. This includes the opportunities for physical activity and active transport to mitigate the adverse health effects of TRAP. • Evaluate the mechanisms behind the association of TRAP with the selected outcomes by studying the (subclinical) outcomes initially considered in the review as well, such as pregnancy outcomes, lung function, blood pressure, atherosclerosis, and others. This would have aided the Panel's interpretation. • Define sensitive subgroups of the population that need to be protected (e.g., related to SES, nutrition, pregnancy, critical windows of development, age) due to the risk of immediate, delayed, or lifetime effects. The current review focused on general population studies. • Evaluate the effectiveness of key traffic policy measures on reducing TRAP and improving public health.

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Table 14.6 (*Continued*). Several Future Research Directions Identified in the Systematic Review of Selected Health Effects of Long-Term Exposure to Traffic-Related Air Pollution

Broad Research Area	Research Directions
Methods in study design, analysis and evidence synthesis	• Future studies should improve standardization across studies to the extent possible and analyze the data so they can be used in meta-analysis. Studies should also focus on complete and detailed reporting of all relevant study aspects. • Expand statistical methods used in epidemiological studies, such as causal modeling methods, methods to correct for exposure measurement error in health analyses, methods to correct for confounding, and multipollutant modeling approaches. • Improve the methodological aspects related to confidence assessment in the body of evidence for use in environmental epidemiology.
Birth outcomes	• More research on the critical windows of exposure in birth outcome studies. • Apply exposome approaches and biomarkers of TRAP in the study of birth outcomes (e.g., soot in placental tissues).
Respiratory outcomes	• Additional research on outcomes for which there are suggestions of an association with TRAP, but for which the evidence is still limited, specifically COPD incidence and ALRI in adults. • The incidence of COVID-19 infection and acute lung injury that have occurred worldwide due to the pandemic presents an opportunity to explore the connection with TRAP in the future, particularly given early evidence that air pollution might affect COVID-19 incidence and mortality (Chen et al. 2021; Kogevinas et al. 2021; Lipsitt et al. 2021; Stieb et al. 2020, 2021). • Although there is strong evidence that short-term exposure to some traffic-related air pollutants (particularly NO_2 and CO) is related to exacerbation of asthma and COPD in both children and adults, the evidence for long-term exposure needs to be further studied. • A robust association has been found between TRAP and asthma onset in children and corroborated by the results for asthma ever and active asthma. However, the relevant period of exposure (prenatal, first years of life, later childhood) is not well established, and more research is warranted into the relevant exposure windows for asthma onset in children. In addition, more research is needed regarding the specific age at which air pollution-related asthma initiates.
Cardiometabolic outcomes	• Additional studies are needed for cardiometabolic outcomes. • Pay more attention to the outcome assessment to reduce misclassification for cardiometabolic outcomes. This issue is equally applicable to respiratory outcomes, in particular COPD. • Pay specific attention to traffic noise and adequate noise assessment including housing characteristics, behavioral factors, and hearing loss. • More research is needed on the critical windows of exposure in cardiometabolic studies. • Future experimental studies may clarify some issues that currently remain unanswered, such as whether PM pollutants influence cardiovascular morbidity more than gaseous pollutants, and maybe only in highly susceptible individuals.
Mortality	• Additional studies on COPD, stroke, and ALRI mortality would be useful as there are few studies, and these outcomes are important (e.g., in the Global Burden of Disease assessment).

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Table 14.6 (*Continued*). Several Future Research Directions Identified in the Systematic Review of Selected Health Effects of Long-Term Exposure to Traffic-Related Air Pollution

Broad Research Area	Research Directions
Neurological outcomes	• More research is needed on the critical window(s) of exposure for neurodevelopmental outcomes (cognitive function, attention-deficit hyperactivity disorder, autism spectrum disorder) and in the etiologies of dementia and Parkinson disease. • Studies of clinical diagnosis (for autism spectrum disorder and, in a small number of studies, attention-deficit hyperactivity disorder) rely on presentation at a clinic or health care center. They are also vulnerable to changes in diagnostic criteria. Finally, they may be less sensitive, making it harder to detect more subtle associations with environmental exposures. Future studies that use instruments assessing quantitative, dimensional traits may be able to overcome some of these limitations. • Expanding the range of outcomes to include other neurodevelopmental endpoints, such as internalizing behaviors (e.g., anxiety and depression), will be important as more data become available for these outcomes. • More studies are needed that use regularly occurring, uniform, standard criteria-based methods to evaluate all study participants for dementia and Parkinson disease. Misclassification in medical records and claims is highly prevalent. Before using these sources, we need more explicit understanding of how to leverage them in ways that do not introduce biases emerging from variations in how community health care is accessed and how diagnoses are rendered. • The emerging literature on neuroimaging in research on neurodevelopment, dementia, and other adult cognitive outcomes may provide clues about mechanisms and should be explored further. However, attention should be paid to addressing and mitigating selection bias (i.e., the possibility that participation could be related to exposure and cognitive status).
Mechanistic evidence	• Further research into the potential health risk of nontailpipe PM (e.g., from brake and tire wear). • Controlled human exposure studies: Move away from simple exposures of single components under acute conditions to real-world exposures and state-of-the-art analytics (e.g. metabolomics); investigate how exposures play out across age and vulnerable groups. • Animal toxicology: use of realistic exposures and relevant models of optimal health and disease/susceptibility that assess temporal responses; design studies that address a range of questions, analyzed by a number of research groups with complementary interests and expertise—so that multiple tissues and organs are studied. • In vitro studies: test emerging hypotheses from informative in vitro assays/sophisticated in vitro systems with in vivo models to extrapolate to human exposure. • Conduct further research into possible interactions of TRAP with COVID-19 in a way that may increase vulnerability to infection (e.g., via increased cellular expression of the receptor angiotensin-converting enzyme 2).

14.11 OVERALL CONCLUSIONS

The findings from the systematic review, meta-analyses, and evaluation of the quality of the studies and potential biases have provided an overall high or moderate-to-high level of confidence in an association between long-term exposure to TRAP and the adverse health outcomes all-cause, circulatory, IHD, and lung cancer mortality, asthma onset in both children and adults, and ALRI in children. The Panel's confidence in the evidence was considered moderate, low, or very low for the other selected outcomes.

Tailpipe emissions from motor vehicles and ambient concentrations of most monitored traffic-related pollutants have decreased steadily over the last several decades in most high-income countries. The Panel's main findings were derived from studies conducted when exposure levels were generally higher than present-day levels in high-income countries, and comparable to or lower than present-day levels in low-income countries.

In light of the large number of people exposed to TRAP—both in and beyond the near-road environment, the Panel concluded that the overall high or moderate-to-high level of confidence in the evidence for an association between long-term exposure to TRAP and several adverse health outcomes indicates that exposures to TRAP remains an important public health concern and deserve greater attention from the public and from policymakers.

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MATERIALS AVAILABLE ON THE HEI WEBSITE

Additional Materials 14.1 contains supplemental material not included in the main report. It is available on the HEI website at *www.healtheffects.org/publications*.

Additional Materials

14.1 HEI-Traffic Review Plots for Examination of Potential Publication Bias

ABBREVIATIONS

ALRI	acute lower respiratory infection
BC	black carbon
BMI	body mass index
CVD	cardiovascular disease
CI	confidence interval
CO	carbon monoxide
COMEAP	Committee on the Medical Effects of Air Pollutants in the United Kingdom
COPD	chronic obstructive pulmonary disease
EC	elemental carbon
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IARC	International Agency for Research on Cancer
IHD	ischemic heart disease
ISA	Integrated Science Assessment
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
OHAT	Office of Health Assessment and Translation
PM	particulate matter
PM_{10}	particulate matter ≤10 µm in aerodynamic diameter
$PM_{2.5}$	particulate matter ≤2.5 µm in aerodynamic diameter
PM_{coarse}	particulate matter with aerodynamic diameter between 10 µm and 2.5 µm
SES	socioeconomic status
TRAP	traffic-related air pollution
UFPs	ultrafine particles
U.S. EPA	U.S. Environmental Protection Agency
WHO	World Health Organization

STUDY NAME ABBREVIATIONS

ABCD	Amsterdam Born Children and their Development
ACCESS	Asthma Coalition on Community Environment and Social Stress Project
ACHAPS	Australian Child Health and Air Pollution Study
ACS-CPS II	American Cancer Society—Cancer Prevention Study II
ALSWH	Australian Longitudinal Study on Women's Health
ARIC	Atherosclerosis Risk in Communities Study
BAMSE	Children, Allergy, Milieu, Stockholm, Epidemiology (Swedish abbreviation)
BiB	Born in Bradford
BORN	Better Outcomes Registry & Network
BREATHE	Biomedical REAl-Time Health Evaluation
BWHS	Black Women's Health Study
CAFEH	Community Assessment of Freeway Exposure and Health
CanCHEC 1991	Canadian Census Health and Environment Cohort
CANDLE	Conditions Affecting Neurocognitive Development and Learning in Early Childhood
CANHEART	Cardiovascular Health in Ambulatory Care Research Team
CAPS	Childhood Asthma Prevention Study
CATSS	Child and Adolescent Twin Study in Sweden
CCAAPS	Cincinnati Childhood Allergy and Air Pollution Study
CCCEH	Columbia Center for Children's Environmental Health
CCHH	China, Children, Homes, Health Study
CCHS	Canadian Community Health Surveys
CHAMPIONS	Calculating How Air Pollution Impacts Our Society
CHARGE	Childhood Autism Risk from Genetics and the Environment
CHEER	Children's Health and Environmental Research
CHIS 2001	California Health Interview Survey 2001
CHS	Children's Health Study
COGNAC	COGNition and Air pollution in Children
CPRD	Clinical Practice Research Datalink
Danish ASD	Danish Autism Spectrum Disorder
DDCH	Danish Diet, Cancer and Health
DNBC	Danish National Birth Cohort
EBCRHS	East Bay Children's Respiratory Health Study
EBNHC	East Boston Neighborhood Health Center
ECHO	Environmental influences on Child Health Outcomes
ECRHS	European Community Respiratory Health Survey
EDEN	Study on the pre- and early postnatal determinants of child health and development
EGEA	Epidemiological Study on Genetics and Environment of Asthma
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
ELISABET	Enquete Littoral Souffle Air Biologie Environnement
ENVIRONAGE	ENVIRonmental influence ON early AGEing
EPIC	European Prospective Investigation on Cancer and Nutrition
ESCAPE	European Study of Cohorts for Air Pollution Effects
GASPII	Gene and Environment Prospective Study on Infancy in Italy
GCARS	Greater Cincinnati Asthma Risks Study
GINI	German Infant Nutritional Intervention
GINIplus	German Infant Study on the Influence of Nutrition Intervention plus air pollution and genetics on allergy development
GOT-MON	Gothenburg–Multinational MONItoring of trends and determinants in CArdiovascular disease
HELIX	Human Early-Life Exposome
HIMS	Health in Men Study
HNR	Heinz Nixdorf Recall Study

Continues next page

STUDY NAME ABBREVIATIONS

IAS Girona	Institut Assistència Sanitària
INMA	Infancia y Medio Ambiente
ISAAC	International Study of Asthma and Allergies in Childhood
KAPPA	Kaiser Air Pollution and Pediatric Asthma
KPNC Oakland	Kaiser Permanente Northern California Oakland
LA FANS	Los Angeles Family and Neighborhood Survey
LISA	Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood
LISAplus	Lifestyle Immune System Allergy plus Air Pollution and Genetics
Los Angeles County DDS	Los Angeles County Department of Developmental Services
MAAS	Manchester Asthma and Allergy Study
MAPSS	Maternal Air Pollution in Southern Sweden
MESA	Multi-Ethnic Study of Atherosclerosis
MINAP	Myocardial Ischeamia National Audit Project
MISSEB	Maternal–Infant Smoking Study of East Boston
MoBa	Norwegian Mother and Child Cohort Study
MOBILIZE	Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston
NII Israel	National Insurance Institute of Israel
NLCS-AIR	Netherlands Cohort Study on Diet and Cancer
NOMAS	Northern Manhattan Study
NWPSU	North West Perinatal Survey Unit
NYCNAAS	New York City Neighborhood Asthma and Allergy Study
OLIN	Obstructive Lung Disease in Northern Sweden
OMCHS	Osaka Maternal and Child Health Study
ONPHEC	Ontario Population Health and Environment Cohort
ONS-Longitudinal	Office for National Statistics Longitudinal Study
PASIDA	Parkinson's Disease in Denmark
PIAMA	Prevention and Incidence of Asthma and Mite Allergy
POSGRAD	Prenatal Omega-3 Supplementation on child Growth and Development
PPS	Primary Prevention Study
PRECEE	PREgnancy and Combined Environmental Exposure
PRISM	Programming of Intergenerational Stress Mechanisms
PROGRESS	Programming Research in Obesity, Growth, Environment and Social Stressors
RANCH	Road traffic noise and Aircraft Noise exposure and children's Cognition and Health
RFAB	Twin Study of Risk Factors for Antisocial Behavior
RHINE	Respiratory Health in Northern Europe
RICHS	Rhode Island Child Health Study
SAGE	Study of Air Pollution, Genetics and Early Life Events
SALIA	Study on the Influence of Air Pollution on Lung Function, Inflammation and Ageing
SALT	Screening Across the Lifespan Twin Study
SAPALDIA	Swiss Study on Air Pollution and Lung Disease in Adults
SAVIAH	Small Area Variations in Air quality and Health
SDPP	Stockholm Diabetes Prevention Program
SHEEP	Stockholm Heart Epidemiology Program
SIDRIA	Italian Studies on Respiratory Disorders in Childhood and Environment
SIMSAM	Swedish Initiative for Research on Microdata in the Social And Medical Sciences
SIXTY	Cohort Study of 60-Year-Olds
SNAC-K	Swedish National Study on Aging and Care in Kungsholmen
SNEC	Seven Northeastern Cities

Continues next page

STUDY NAME ABBREVIATIONS

SORA	Study on Respiratory Disease and Automobile Exhaust
SW PA Children	Southwestern Pennsylvania children
T-CHEQ	Toronto Child Health Evaluation Questionnaire
TAHS	Tasmanian Longitudinal Health Study
THUA OHIP	Toronto–Hamilton Urban Airshed Ontario Health Insurance
TRANSPHORM	Transport-related Air Pollution and Health impacts–Integrated Methodologies for Assessing Particulate Matter
VESTA	Five [V] Epidemiological Studies on Transport and Asthma
VIVA	Project Viva
33 CCHS	33 Communities Chinese Health Study

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EFFECTS
INSTITUTE

75 Federal Street, Suite 1400
Boston, MA 02110, USA
+1-617-488-2300
www.healtheffects.org

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