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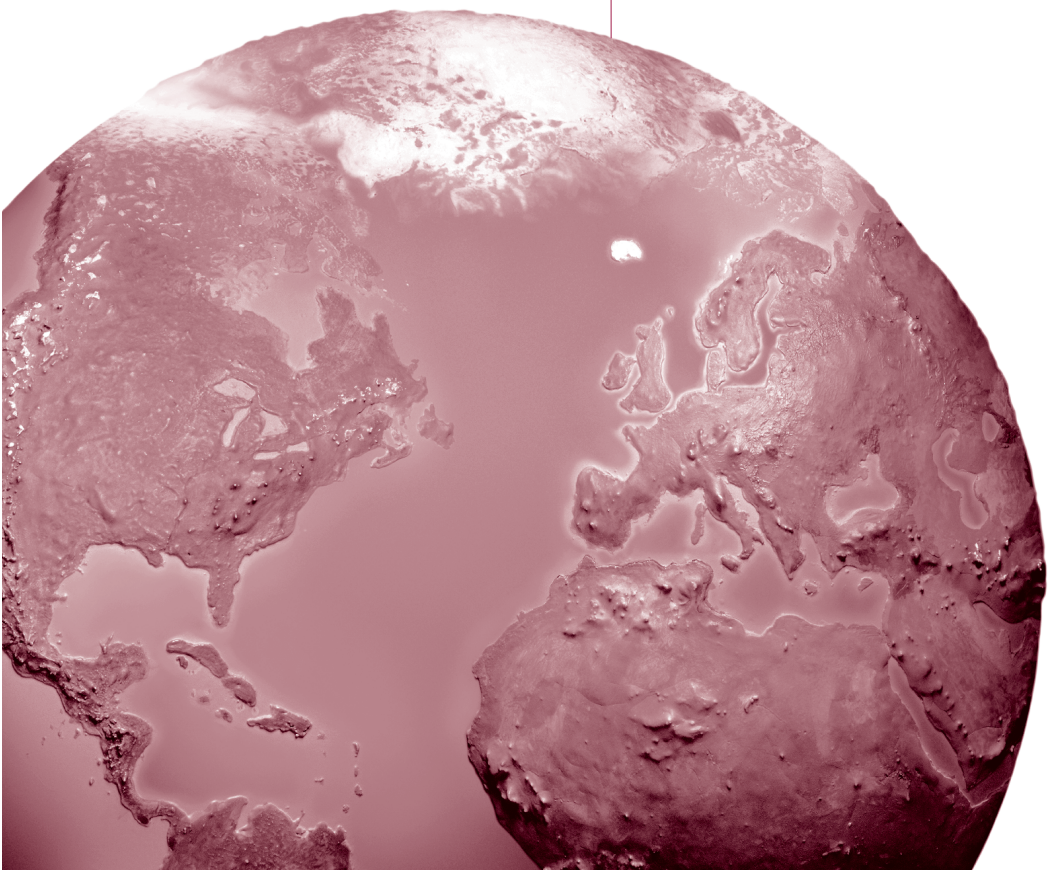
Ambient Air Pollution and All-Cause and Cause-Specific Mortality in an Analysis of Asian Cohorts

George S. Downward and Roel Vermeulen on behalf of the Asia Cohort Consortium Executive Board



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with a Commentary by the HEI Review Committee

Research Report 213
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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 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.

ABOUT THIS REPORT

Research Report 213, *Ambient Air Pollution and All-Cause and Cause-Specific Mortality in an Analysis of Asian Cohorts,* presents a research project funded by the Health Effects Institute and conducted by Drs. George S. Downward and Roel Vermeulen of Utrecht University, the Netherlands.

The report contains three main sections.

The **HEI Statement**, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Review Committee's comments on the study.

The **Investigators' Report**, prepared by Downward and Vermeulen, describes the scientific background, aims, methods, results, and conclusions of the study.

The **Commentary**, prepared by members of the Review Committee with the assistance of HEI staff, places the study in a broader scientific context, points out its strengths and limitations, and discusses remaining uncertainties and implications of the study's findings for public health and future research.

This report has gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. This draft report is first examined by outside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the Review Committee, an independent panel of distinguished scientists who are not involved in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Commentary reflects the information provided in the final version of the report.

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HEI STATEMENT

Synopsis of Research Report 213

Ambient Air Pollution and All-Cause and Cause-Specific Mortality in an Analysis of Asian Cohorts

BACKGROUND

Much of what is currently known about the adverse effects of ambient air pollution comes from studies conducted in high-income regions, especially North America and Europe, with relatively low air pollution levels. The study by Dr. George S. Downward and Dr. Roel Vermeulen from Utrecht University, the Netherlands, addresses a clear research gap by leveraging harmonized data from the *Asia Cohort Consortium*, a large multicenter collaborative research effort in Asia that began in 2008.

APPROACH

The study by Downward and Vermeulen assessed the association between long-term exposure to outdoor air pollution and all-cause and cause-specific mortality in an analysis of six Asian cohorts, with more than 340,000 participants in six countries (Statement Figure). The cohorts were general population studies and varied widely in size, study period, recruitment method, geographical scope, exposure assignment, and outcome assessment. The cohorts in India and Japan were the largest by far. Participants were recruited from 1991 to 2008 and followed up between 5 (India) and 23 years (Taiwan). Some cohorts were conducted in a single city or district (e.g., cohorts in India and Bangladesh). Others included much larger areas in a country (e.g., Japan).

The investigators estimated exposure for fine particles and nitrogen dioxide by using existing global satellite-based models. The estimates were assigned to study participants based on geocoded residential location for the year of recruitment only.

The study included all-cause mortality and nonaccidental, all-cancer, lung cancer, cardiovascular disease, and noncancer lung disease mortality. The outcome assessment was performed for each individual cohort, typically through active follow-up or linkage to death registries.

What This Study Adds

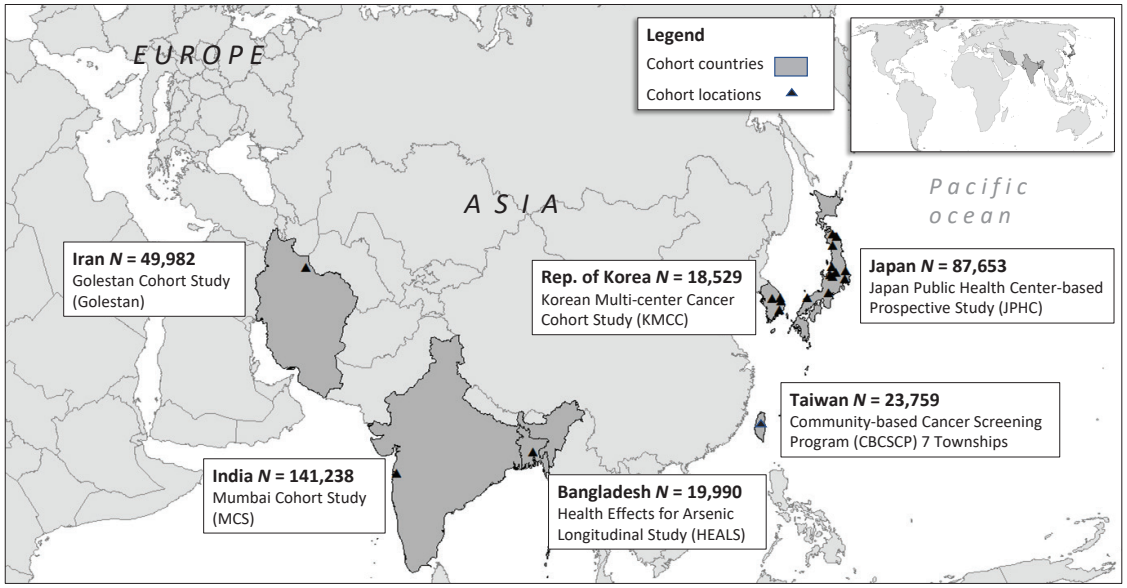
- The study assessed the association between long-term exposure to ambient air pollution and mortality in six Asian cohorts, addressing a clear research gap.
- Combined results across the cohorts documented no association between long-term exposure to ambient $PM_{2.5}$ and mortality, except for a borderline significant positive association with cardiovascular mortality. Several individual cohorts (i.e., in India, Japan, and Taiwan), however, did display positive significant associations between ambient $PM_{2.5}$ and cardiovascular mortality.
- For ambient NO_2, combined results showed positive associations for all mortality outcomes, in particular the cancer outcomes.
- Large heterogeneity of the findings was reported across the individual cohorts, with sometimes no apparent pattern. Furthermore, the combined NO_2 estimates were heavily driven by positive associations from a single cohort in Japan.
- Although uncertainty remains regarding the true size of the ambient air pollution and mortality associations in Asia, these populations are experiencing very high levels of air pollution, meriting attention and action to reduce ambient air pollution.

The investigators applied single-pollutant Cox proportional hazard models to assess the association between air pollution exposure and mortality with adjustment for important confounders, such as age, sex, recruitment year, smoking, body mass index, diet, and a measure of socioeconomic status (education or employment). The investigators calculated hazard ratios for each cohort separately and then combined the results using random effects meta-analysis. They conducted various sensitivity analyses in each cohort, including an adjustment for urbanicity. No meta-analyses were conducted on any of the sensitivity analysis results.

MAIN RESULTS AND INTERPRETATION

The study by Downward and Vermeulen documented no associations between long-term exposure to ambient

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. George S. Downward (first author) and Dr. Roel Vermeulen (principal investigator) at Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands, and Institute for Risk Assessment Sciences, Utrecht University, the Netherlands. Research Report 213 contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Review Committee.



Statement Figure. Geographical location of the six Asian cohorts.

fine particles and all-cause mortality and cause-specific mortality in meta-analyses, except for a borderline significant positive association with cardiovascular mortality (i.e., an adverse health effect of air pollution). Several individual cohorts (i.e., in India, Japan, and Taiwan), however, did display positive significant associations between ambient fine particles and cardiovascular mortality. For ambient nitrogen dioxide, the combined estimates showed positive associations for all mortality outcomes, in particular the cancer outcomes, although estimates were heavily driven by positive associations from a single cohort in Japan. The cohorts were very diverse, and large heterogeneity of the findings was reported across the individual cohorts, with null, negative, or positive findings, with sometimes no apparent pattern.

In its independent review of the study, the HEI Review Committee thought the research was well motivated and addressed a clear research gap. The large sample size and leverage of harmonized data from the Asia Cohort Consortium were considered to be strengths of the study. Furthermore, data were available for several individual-level lifestyle factors, such as smoking status and intensity, body mass index, and diet, and the analyses were adjusted accordingly. Application of existing global satellite-based models allowed for a uniform estimation of exposure at a reasonably high spatial resolution for large urban and rural populations in six Asian countries. Such a study would otherwise not have been possible given the paucity of ground-based monitors, particularly in low- and middle-income countries. Although the Review Committee broadly agreed with the investigators' conclusions, it identified limitations that should be considered when interpreting the results.

Importantly, the Committee was concerned that residual confounding was likely in the main analyses due to inadequate adjustment for characteristics that correlate with air pollution and mortality, most notably socioeconomic status and urbanicity. Findings sometimes differed for models that adjusted for urbanicity as compared to those that did not. The Committee would have been interested in better understanding potential sources of heterogeneity in the findings. There were also concerns about the exposure assessment approach because of the substantial temporal and spatial misalignment of the data, which might have influenced the analysis of mortality outcomes in unpredictable ways. For example, residential mobility was not taken into account and, for a few cohorts (in India and Iran), only aggregated residential address data were available (e.g., postal code). Also, the global models typically perform more poorly in Asia compared to North America and Europe.

CONCLUSIONS

Overall, there remains uncertainty about the true size of the ambient air pollution and mortality associations in Asia, where the levels of air pollution are often high and the types and sources of air pollution, including household air pollution, markedly differ from those in high-income settings. The study by Downward and Vermeulen highlights the urgent need for future studies that could prove to be useful in reducing this uncertainty. At the same time, these populations are experiencing very high levels of air pollution, meriting attention and action to reduce ambient air pollution regardless of the uncertainties.

Ambient Air Pollution and All-Cause and Cause-Specific Mortality in an Analysis of Asian Cohorts

George S. Downward[1,2] and Roel Vermeulen[1,2] on behalf of the Asia Cohort Consortium Executive Board

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ABSTRACT

Introduction Much of what is currently known about the adverse effects of ambient air pollution comes from studies conducted in high-income regions, with relatively low air pollution levels. The aim of the current project is to examine the relationship between exposure to ambient air pollution (as predicted from satellite-based models) and all-cause and cause-specific mortality in several Asian cohorts.

Methods Cohorts were recruited from the Asia Cohort Consortium (ACC*). The geocoded residences of participants were assigned levels of ambient particulate material with aerodynamic diameter of 2.5 µm or less ($PM_{2.5}$) and nitrogen dioxide (NO_2) utilizing global satellite-derived models and assigned for the year of enrollment (or closest available year). The association between ambient exposure and mortality was established with Cox proportional hazard models, after adjustment for common confounders. Both single- and two-pollutant models were generated. Model robustness was evaluated, and hazard ratios were calculated for each cohort separately and combined via random effect meta-analysis for pooled risk estimates.

Results Six cohort studies from the ACC participated: the Community-based Cancer Screening Program (CBCSCP, Taiwan), the Golestan Cohort Study (Iran), the Health Effects for Arsenic Longitudinal Study (HEALS, Bangladesh), the Japan Public Health Center-based Prospective Study (JPHC), the Korean Multi-center Cancer Cohort Study (KMCC), and the Mumbai Cohort Study (MCS, India). The cohorts represented over 340,000 participants.

Mean exposures to $PM_{2.5}$ ranged from 8 to 58 µg/m^3. Mean exposures to NO_2 ranged from 7 to 23 ppb. For $PM_{2.5}$, a positive, borderline nonsignificant relationship was observed between $PM_{2.5}$ and cardiovascular mortality. Other relationships with $PM_{2.5}$ tended toward the null in meta-analysis. For NO_2, an overall positive relationship was observed between exposure to NO_2 and all cancers and lung cancer. A borderline association between NO_2 and nonmalignant lung disease was also observed. The findings within individual cohorts remained consistent across a variety of subgroups and alternative analyses, including two-pollutant models.

Conclusions In a pooled examination of cohort studies across Asia, ambient $PM_{2.5}$ exposure appears to be associated with an increased risk of cardiovascular mortality and ambient NO_2 exposure is associated with an increased cancer (and lung cancer) mortality. This project has shown that satellite-derived models of pollution can be used in examinations of mortality risk in areas with either incomplete or missing air pollution monitoring.

INTRODUCTION

Ambient air pollution represents a significant source of morbidity and mortality, being responsible for approximately 4 million deaths and 120 million lost disability adjusted life years (DALYs) for the year 2019 (Global Burden of Disease 2019). More than a quarter of these deaths are predicted to have occurred in Asia, where outdoor air pollution levels are typically high (Brauer et al. 2016). However, despite this high disease burden, the health effects of air pollution within this region remain relatively understudied (Chen and Hoek 2020). Further, owing to differences in exposure metrics, approaches, and source populations, the comparability and generalizability of findings are limited.

Much of what is currently known about the effects of ambient air pollution comes from studies performed in high income countries — especially in North America and Europe.

This Investigators' Report is one part of Health Effects Institute Research Report 213, which also includes a Commentary by the Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. George S. Downward, Institute for Risk Assessment Sciences, Utrecht University, P.O. Box 80178, 3508 TD Utrecht, the Netherlands; e-mail: *G.S.Downward@uu.nl*. No potential conflict of interest was reported by the authors.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83467701 to the Health Effects Institute, 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 and other terms appears at the end of this volume.

For example, the ESCAPE and subsequent ELAPSE projects in Europe as well as the Six City and American Cancer Society studies in the United States have provided major insights into the health of their populations and made major contributions toward policy recommendations (Beelen et al. 2014a; Dockery et al. 1993; Pope et al. 2002; Strak et al. 2021). Although earlier studies examined community- or city-level exposures, a key resource used more frequently has been the generation and application of land use regression (LUR) models. In these models, measured levels of ambient pollutants are examined in the context of local pollution sources and land use features to generate prediction models, which in turn can be used to predict environmental exposures throughout a region (Beelen et al. 2013; Eeftens et al. 2012).

The application of LUR models has allowed a wide range of examination of health effects across populations including studies of mortality, cardiovascular disease, cancer, and neurological diseases. In a large cohort of enrollees in the U.S. Medicare program for example, a 10-μg/m^3 increase in $PM_{2.5}$ was associated with a 7.3% increase in all-cause mortality (95% confidence interval [CI]: 7.1%, 7.5%) and a 10-ppb increase in ozone was associated with a 1.1% increase (95% CI: 1.0%, 1.2%) (Di et al. 2017). When looking across multiple countries or zones, it is also possible to observe high levels of variation between countries or regions, both in terms of pollution concentrations and health effects. This is well illustrated by the ESCAPE project, where concentrations of ambient $PM_{2.5}$ varied across 22 cohorts from 13 European countries from relatively "safe" levels (i.e., beneath the World Health Organization–recommended ambient level [which at the time was 10 μg/m^3]) to levels well above 30 μg/m^3. Similarly, observed relationships between ambient air pollution exposure and mortality also showed high levels of heterogeneity across cohorts and countries, which included null or nonsignificant findings that, only in meta-analysis, revealed a pooled, increased risk of death in association with increasing air pollution exposure (specifically that a 5-μg/m^3 increase in $PM_{2.5}$ was associated with a [hazard ratio] HR of 1.07 for all-cause mortality with a 95% CI of 1.02 to 1.13) (Beelen et al. 2014a). This heterogeneity in exposure levels and effects is likely a reflection of differences in specific pollution constituents and sources operating in combination with heterogeneity in the underlying infrastructure, culture, and resources available to each country.

A key difference in ambient air pollution between North America, Europe, and Asia is that there is a much wider range of air pollution exposures in Asia, ranging from levels comparable to that in Europe (e.g., Japan which in 2016 had a mean $PM_{2.5}$ concentration of 13 μg/m^3) to levels several times higher than that described in Europe (e.g., India which in 2016 had a mean $PM_{2.5}$ concentration of 69 μg/m^3) (WHO 2018). A feature further complicating the differences between these geographic areas is that low-and-middle-income countries (LMIC) typically experience relatively high levels of absolute exposure to ambient air pollutant while also, owing to infrastructural and economic limitation, experiencing challenges in healthcare access — which may potentially further compound any burden of disease.

Owing to these differences in both extremes of exposure and underlying infrastructures, applying disease burden estimates from European and North American studies to the Asian setting is limited. However, the majority (if not all) of Asian countries are lacking detailed LUR models, such as those described for Europe, meaning that examining and describing precise disease burden in these countries is challenging. A frequent approach is to extrapolate the exposure–response relationships observed in Europe to the higher values in Asia to predict potential disease burdens in these areas (Burnett et al. 2014). However as already described, the generalizability of these findings is limited, resulting in high levels of uncertainty in these estimates.

A powerful resource, which may assist in addressing some of these challenges, has been the development of global LUR models, derived from satellite measurements of ambient pollutants and supplemented by ground-based monitors (Larkin et al. 2017; van Donkelaar et al. 2015, 2016). These models now provide an opportunity for the examination of the health effects of air pollution in areas of the world where it was previously impossible to do so, including many LMIC. An example of the applicability of these models has been the recently published Prospective Urban and Rural Epidemiology (PURE) study, which examined exposure to ambient $PM_{2.5}$ to more than 150 thousand individuals from 21 nations of differing income level (Hystad et al. 2020). This study reported that across these nations, a 10-μg/m^3 increase in $PM_{2.5}$ exposure was associated with a 3% increase in cardiovascular disease mortality (HR): 1.03, 95% CI: 1.00, 1.06). This highlights the important role of global LUR models and their potential power when being applied to diverse settings.

SPECIFIC AIMS

The aim of the project is to use satellite-derived estimates of ambient air pollution to assess the association between long-term exposure to ambient air pollution and all-cause and cause-specific mortality in an analysis of diverse Asian cohorts. The air pollutants examined in this project are $PM_{2.5}$ and NO_2. Exposure to either of these pollutants has been identified as a major risk factor for the development of (and death from) a variety of noncommunicable diseases, including lung cancer, cardiovascular disease, and chronic lung diseases.

Specific causes of death examined within the current project are all-cause mortality, nonaccidental mortality, deaths from cancer (and lung cancer in particular), cardiovascular deaths, and deaths from nonmalignant lung diseases.

METHODS AND STUDY DESIGN

GENERATION OF AMBIENT AIR POLLUTION DATA

Ambient air pollution was assigned to the residential addresses of participants of the Asia Cohort Consortium (ACC) at the year of recruitment, following the general

approach of the ESCAPE project (Beelen et al. 2014a). The pollutants examined were $PM_{2.5}$ and NO_2. Both have received much study from European and American studies and have been associated with a diverse range of outcomes including cardiovascular disease and cancer.

Values of $PM_{2.5}$ and NO_2 were assigned based on global maps that had been derived from the application of a geographically weighted regression model of satellite-derived estimates, the latest versions of which are made available by the developers at *https://sites.wustl.edu/acag/datasets/*. The full details of the model construction are described elsewhere (Larkin et al. 2017; van Donkelaar et al. 2015, 2016). Briefly, for $PM_{2.5}$, measurements from the Moderate Resolution Imaging Spectroradiometer (MODIS), Multi-angle Imaging SpectroRadiometer (MISR), and Sea-Viewing Wide Field-of View Sensor (SeaWIFS) were integrated, providing a near continuous planetary surface of $PM_{2.5}$. The GEOS-Chem chemical transport model and ground-based sun photometer (AERONET) observations were utilized to convert these values to near-ground concentrations. Values of $PM_{2.5}$ were produced at a spatial scale of approximately 1 km × 1 km and were found to correlate well with available ground-based data with an overall R^2 of 0.81 and calculated bias and variance values of a global variance of 1.3 and 7.9 μg/m^3, respectively (for the year 2010). However, it should be noted that bias and variance varied by global location. For example, within North America these values were 0.4 and 2.1 μg/m^3. By contrast across Asia bias varied from 3.2 (Central Asia) to 11.6 (East Asia) μg/m^3 and variance varied from 15.9 (Southeast Asia) to 33.9 μg/m^3 (South Asia).

For NO_2, measurements of the SCanning Imaging Absorption spectroMeter for Atmospheric CartograpHY (SCIAMACHY) and Global Ozone Monitoring Experiment–2 (GOME-2) satellites were combined with output from the global GEOS-Chem model to produce gridded surface estimates of NO_2 at an approximate resolution of 10 km × 10 km. The resolution of these estimates was further refined by land-based measurements from 5,220 air monitors in 57 countries, improving the resolution to approximately 100 m × 100 m. This global model had an adjusted R^2 of 0.54, had a mean absolute error of 3.7 ppb and a mean percent bias of 25%. There was variation in model performance between geographic sites, albeit not to the same extent as what was noted for $PM_{2.5}$. Within North America, the adjusted R^2 was 0.52 with a mean absolute error of 4.4 ppb and mean percent bias of 52%. Within Asia, the adjusted R^2 was 0.51 with a mean absolute error of 3.7 ppb and mean percent bias of 16%. Annual estimates of NO_2 from 1997 to 2008 were generated by replacing the satellite-based NO_2 predictor with the corresponding annual (three-year rolling average) estimates reported by Geddes and colleagues (2016), which were available from 1996 to 2012.

Levels of $PM_{2.5}$ and NO_2 for the year in which participants were recruited (1991–2008) were assigned to the residential coordinates of study participants within each cohort (details below) using ArcGIS and an automated script made specifically for each cohort. If a participant was recruited outside of the time period in which pollutant predictions were available (1998 to 2008 for $PM_{2.5}$ and 1997 to 2008 for NO_2), the nearest applicable time period was instead used. Not all locations were able to have predictions generated, especially with regard to NO_2 in coastal areas, in which case the number of valid predictions was reported. For quality control purposes, a subset of assigned exposures (maximum 200 per cohort, representing approximately 0.4% of all assigned exposures) was manually reviewed for each cohort. As the expectation was that manually assigned exposures would match those assigned via automated script, zero error was allowed (or observed) during this check.

STUDY POPULATIONS

The Asia Cohort Consortium

Ambient air pollution was assigned to the residential information of participants in the ACC, which is a multicenter collaborative epidemiology project consisting of (to date) more than one million people from several dozen cohorts from ten Asian countries. Originally formed in 2008, the ACC was developed to explore the relationships between genetics, environmental exposures, and disease across a broad geographic scope (Chen et al. 2013, 2017; Song et al. 2012). Cohorts were identified for potential inclusion within the ACC through thorough literature search, after which cohort investigators were contacted to gauge interest in participating in the consortium. Willing cohorts were subsequently administered surveys to determine available data and whether that data were suitable for inclusion within the consortium. To be eligible for inclusion in the ACC, cohorts must have information on mortality outcomes and common confounding variables, such as smoking, sex, and body mass index. To ensure consistency between cohorts, study covariates were standardized via internal "harmonization" procedures at the ACC. Harmonization occurred over several rounds of data review and internal discussion, including logic/missing data checks. Any harmonization queries were resolved between the ACC and the individual cohort investigators before being included within the consortium's dataset.

At the beginning of the current project, the principal investigators of each member cohort at the time (23 cohorts from 9 countries) were contacted, inviting their involvement in the current project. Of those 23, 6 (representing 6 countries) agreed to participate in the current project and provided access to residential and covariate information.

The level of access to residential information varied between cohorts on the basis of privacy legislation, internal ethics requirements, and staff availability at each cohort (described below). Air pollution predictions were generated for all participants who had complete information on age, sex, recruitment year, follow-up time, and vital status.

DESCRIPTION OF PARTICIPATING COHORTS AND ASSIGNMENT OF POLLUTION HEALTH OUTCOMES

The Community-based Cancer Screening Program

The CBCSCP was established in 1991 to examine cancer (and other cause mortality) and recruited participants via household registration offices from seven townships across Taiwan (Sanchi, Chutung, Potzu, Makung, Paihsa, Kaoshu, and Huhsi) from January 1991 to December 1992 (Chen et al. 2006; Liao et al. 2012). Participants have been followed up for cancer incidence and causes of death through health examinations, the review of medical records, and linkage to national cancer and death registries.

Exposure to ambient pollutants in the CBCSCP were assigned to all participants in the cohort (N = 23,759), which had been geocoded by members of the CBCSCP research team. The accuracy of predictions to the specific coordinates was established and confirmed via manual check.

The Golestan Cohort Study

The Golestan Cohort Study was established in the Golestan region of Iran to identify risk factors for esophageal cancer via an assessment of multiple personal factors including occupation, socioeconomic status, and smoking (Pourshams et al. 2010). Participants were randomly recruited from Gonbad city and surrounding rural areas from 2004 to 2008 and thus included residents of both urban and rural settings. Participants were followed up at approximately one-year intervals but were also instructed to inform the Golestan research team in the case of major medical event.

Individual address information was unavailable for participants within the Golestan cohort. Instead, exposure to ambient pollutants was assigned at the local community or village level, representing 624 unique locations, each containing a median of 38 participants. Individual communities were relatively small, generally being no more than 1 km^2 in area, and thus individual point estimates (centroids) were considered sufficient for assigning pollution to the participants within each village. Quality control of estimates was performed by both examining individual point estimates and comparing point estimates to those derived from creating a 500-m "buffer" around each point (to represent uncertainty arising from only using community-level information). This buffer information had a correlation >0.9 with point estimates. Thus, point estimates were retained in final analysis.

Health Effects for Arsenic Longitudinal Study

The HEALS was established in Araihazar, Bangladesh, to evaluate the effects of arsenic exposure on various health outcomes, including cancer (Ahsan et al. 2006). Participant recruitment began in 2000 until 2008 with participants recruited from individuals and households using specific wells across Araihazar, Bangladesh, and followed up at approximately 2-year intervals and monitored for all-cause and cause-specific mortality outcomes.

Exposure to ambient pollutants in HEALS was assigned at the level of individual residence. Both the geocoding of addresses and assignment of environmental pollutants was performed by the HEALS research team. Quality control of the predictions was performed by having both the HEALS and Utrecht research team assign pollution levels to a series of random GPS coordinates and compare results — expecting (and finding) complete agreement.

Japan Public Health Center-based Prospective Study

The JPHC study was established to identify risk factors for noncommunicable diseases, specifically cancer and cardiovascular diseases (Tsugane and Sawada 2014; Tsugane and Sobue 2001). A first round of recruitment (JPHC 1) began in 1990, recruiting residents, 40–59 years old from Yokote, Ninohe, Saku, Chubu, and Katsushika. A second round of recruitment (JPHC 2) was initiated in 1993–1995, targeting residents 40–69 years of age from Nagaoka, Mito, Chuo-higashi, Kamigoto, Miyako, and Suita. Mortality outcomes were established via examining registered deaths as recorded by the Japanese Ministry of Health, Labor, and Welfare.

Exposure to ambient pollutants within the JPHC study were assigned to those within the cohort with long-term residential stability (N = 87,653). Exposures were assigned to the residential addresses of JPHC participants, which had been geocoded by members of the JPHC member team. The accuracy of predictions to the specific coordinates was established via manual check.

Korean Multi-center Cancer Cohort Study

The KMCC study recruited adults from the Haman, Choongjum Uljin, and Pophan areas of the Republic of Korea (Yoo et al. 2002). The purpose of the KMCC study was to investigate the relationship between cancer risk and personal, environmental, and host factors in Korea. Participant recruitment began in 1993 to 2005, and participants were recruited from those who had participated in cancer screening. Participant information was linked to health insurance, cancer, and death databases, allowing regular follow-up of study participants.

In this study, exposure to ambient pollutants were assigned to the residential addresses of participants (N = 18,529). Addresses were geocoded using a Google Maps API, which subsequently underwent random review to ensure data quality. Complete geocodes were unable to be completed for approximately 2,000 individuals. Instead, these participants were assigned middle-of-street or nearby neighbor geocodes, both of which were expected to be within the general precision of the maps used. Regardless, these sites were flagged for exclusion in sensitivity analyses. Pollution predictions were assigned to each geocoded address, which were in turn manually checked for quality control purposes.

Mumbai Cohort Study

The MCS is based in the city of Mumbai, India with participants recruited from polling stations across Mumbai. It was established in the early to mid-1990s with the goal of examining personal risk factors for mortality in men and women residing in Mumbai (Pednekar et al. 2009). Deaths were identified through active follow-up of participants.

The exact residential address residential information was not available for MCS, meaning that an alternative approach to pollution assignment was required. Exposures to ambient air pollutants were assigned at the postal code level instead. In total there were 100 postal codes in Mumbai that included MCS participants.

HEALTH OUTCOMES

The current project examined all-cause and cause-specific mortality (information on morbidity was not routinely recorded at the ACC at this time). The collection of information on mortality and cause of death was performed by each individual cohort, typically through linkage to death or cancer registries and/or active follow-up and coded via either International Classification of Diseases (ICD) 9 or 10 coding system depending on the year of death.

The specific causes of death used in the current project were all-cause mortality, accidental mortality, all cancer, lung cancer, cardiovascular disease (which incorporated both cardiovascular and cerebrovascular events), and nonmalignant lung disease. These causes of death, and their ICD 9 or ICD 10 definitions, are provided in Table 1. The only exception to this is the JPHC cohort, which provided their own specific outcomes (ICD 10 codes): all-cause mortality, all cancer (C00–C97), lung cancer (C34), heart disease (I20–I52), cerebrovascular disease (I60–I69), lung (J10–J18 and J40–J47), or otherwise nonspecified.

STATISTICAL METHODS AND DATA ANALYSIS

The population, outcome, and exposure characteristics of the individual cohorts contributing to the current project were examined through descriptive statistics. The relationship between ambient air pollution (assigned at the year of enrollment into their respective cohort) and mortality outcomes was examined through the development of Cox proportional hazard models. Model construction and confounder/covariate selection was based on the analytical protocols utilized in the ESCAPE project. Age was assigned as the time scale utilized and censoring was defined as death, emigration, loss to follow-up, or the completion of the follow-up period, whichever occurred first. Exposures to ambient $PM_{2.5}$ and NO_2 at baseline (or nearest applicable year) were assigned as the primary variables of interest and models with increasing levels of covariate inclusion were developed. First, models containing only pollution and outcomes were developed (model 1), followed by the addition of recruitment year and sex (model 2), and subsequently the addition of smoking, body mass index, and socioeconomic (education or occupation) and dietary factors (e.g., alcohol intake) (model 3). Covariate selection was based on the covariates identified within the previous ESCAPE project. The MCS and HEALS cohorts lacked information regarding dietary factors. With the Golestan cohort, information on domestic fuel use was available. Therefore, as this is an important contributor to personal air pollution exposure, domestic fuel use was included in model 3 for this group. Hazard ratios (HRs) were derived and reported for a 5-μg/m^3 increment in $PM_{2.5}$ and a 10-ppb increment in NO_2.

The findings for model 3 were the focus of this report and were generally consistent with the findings of models 1 and 2, which are in the Appendix (available on the HEI website).

Subgroup and Sensitivity Analyses

In addition to the main analyses as described, several additional levels of analyses were performed to evaluate the robustness of findings and potential variation of findings across different settings.

Table 1. Causes of Death and Their Respective ICD 9 and ICD 10 Codes

Cause of Death Group	ICD 9 Codes	ICD 10 Codes
Nonaccidental	001–799	A00–R99
All cancer	140–239	C00–D49
Lung cancer	162	C34
Cardiovascular disease	410–414, 415.1, 427, 428, 430–438, 440–442, 444, 798.1, 798.2, 798.9	G45, I20–I26, I46, I50, I60–I67, I69, I70–I74, R96
Nonmalignant lung disease	460–519	J00–J99

- Any potential interaction between the two pollutants studied within the current project were examined through the generation of two-pollutant models.
- To examine any differences in risk estimates between individuals with differing smoking statuses, analysis was reperformed after stratification by smoking status. Specific focus was placed on female nonsmokers by additionally examining this group.
- To examine whether the risks observed differ between those with and without pre-existing disease, analysis was performed examining those who were disease-free at recruitment (i.e., answered no to all questions related to pre-existing disease). However, this information was only available for the Golestan, JPHC, and KMCC cohorts.
- Restriction of cohorts to allow more precise temporal adjustments. Predictions of $PM_{2.5}$ were only available for the years 1998 to 2008 and NO_2 for the years only 1997 to 2008. However, several cohorts recruited outside of these time periods, meaning that, for our primary analysis, pollution was assigned on the basis of the closest available year. This may lead to exposure miss-classification, especially among those within the cohorts who had died prior to 1998. Therefore, to evaluate any impact of this, analysis was repeated by restricting cohort populations to those who were alive in 1998 and generating a "new" cohort among this group. Within these "new" cohorts, 1998 (or the actual year of recruitment if later) was assigned as the new baseline point for the prediction of pollutants. Ages and follow-up times were updated to reflect this newly generated groups.
- To further evaluate the role of solid fuel on health within the Golestan cohort, analysis was repeated with ambient air pollution removed.
- To evaluate whether findings were influenced by urban/rural status (urbanicity) additional analysis was performed after additionally adjusting for urbanicity at the residence of each study participant. Two methods for assigning urbanicity were used. The primary approach was to apply a gradient approach via the global models derived by Gao and O'Neill who applied a global gradient for relative urbanicity (based on remote satellite observations and land use patterns) in the year 2000 and modeled subsequent trends in urban spread for future applications (Gao and O'Neill 2020). Data, in the forms of global maps, are publicly available and levels of urbanicity were applied in the same manner as for air pollution. In this project, levels from the year 2000 were used in the first instance but levels from 2010 were also examined to consider any impacts of changing urbanicity over time. As a second approach, a "yes/no" approach was used by applying maps of the Global Human Settlement Layer Urbanicity for 2015, which describes urban centers, defined by resident population (Florczyk et al. 2019). Participants within these centers were considered "urban" and those living outside of these centers were considered "nonurban." As Mumbai is already a large urban center, it was excluded from this analysis. Additionally, there was insufficient contrast in the Global Human Settlement Layer Urbanicity for the HEALS to allow analysis. As urban features can be expected to contribute to ambient $PM_{2.5}$ and NO_2, correlation and summary (mean) values for $PM_{2.5}$ and NO_2 were examined for the scenarios of urbanicity described above.
- To examine differentials in risk estimates at different levels of exposure (i.e., nonlinear relationships), penalized splines and quartile-based models were generated. Penalized splines were generated with four degrees of freedom across all cohorts and pollutants. The number of degrees of freedom was chosen after manual inspection of varying degrees of freedom for all cohorts. Significance (*P*) levels for a nonlinear component and figures for each model were evaluated and compared with the linear models for potential nonlinear interactions.
- The validity of the assumption for proportional hazards was evaluated for the main models of each cohort via the examination of Schoenfeld residuals. Model covariates that indicated that they may violate the proportional hazards assumption were stratified (i.e., analysis was performed for each stratum of the offending variable and the resulting HRs were pooled) or removed and analysis was repeated. If either of the main pollutants indicated that they may violate the proportional hazards assumption, analysis was repeated after adding an interaction by follow-up time term to the model.

We additionally sought to evaluate exposure misclassification through individuals changing residence during the follow-up process. However, information on long-term residential mobility was not available.

Meta-analysis

Following the generation of models for each cohort, findings were pooled via random effects meta-analysis. During this process, the JPHC mortality definitions were considered equivalent to the definitions used in the remainder of the project with the exception for heart and cerebrovascular disease, which were merged to approximate the cardiovascular disease endpoint utilized in the rest of the project.

This project was reviewed and approved by both the ACC executive committee and the University Medical Center Utrecht institutional review board prior to its initiation.

All statistical analysis was performed in R (Version 3.5) utilizing the Survival package (R Core Team 2018; Therneau 2021). *P* values less than 0.05 were considered to reflect statistical significance.

RESULTS

OVERALL RESULTS

Six cohorts accepted the invitation to participate in the current project: CBCSCP, Golestan study, HEALS, JPHC, KMCC, and MCS as described in the *Methods and Study Design* section. Specific findings for the individual cohorts are described below. In summary, these cohorts had between 18,529 (KMCC) and 141,238 (MCS) participants with a combined total of 341,151 participants across six countries. Selected demographics and information on each cohort are provided in Table 2. Cohorts tended to have a higher proportion of female than male participants (50%–60% female) and mean ages at recruitment ranged from late thirties to early/mid-fifties. There was a wide range in the amount of total follow-up, ranging from 5 (MCS) to 23 (CBCSCP) years. Participants tended to have a "healthy" body mass index (in the range of 20–25), with the exception of HEALS where 60% of participants had a body mass index less than 20. Participants were generally nonsmokers. More detailed overviews of covariate information for each cohort (including information on any missing covariates) are presented in the Appendix (available on the HEI website).

Descriptions of the predicted pollutants are provided in Table 3. Overall, a wide range in exposures across the different cohorts was observed. Mean exposures to $PM_{2.5}$ ranged from 7.9 μg/m^3 (CBCSCP) to 57.9 μg/m^3 (HEALS). Similarly, exposures to NO_2 ranged from 6.6 ppb (HEALS) to 23 ppb (MCS). NO_2 and $PM_{2.5}$ were moderately correlated with each other (coefficient = approx. 0.5) for four of the cohorts (Golestan, HEALS, JPHC, and KMCC) but weakly or not correlated (coefficient = approx. 0) for the CBCSCP and MCS cohorts.

Graphical depictions of the generated HRs for each cohort, in both single and two-pollutant models are provided in Figure 1 (numerical values are provided when examining each cohort one-by-one below). In general, high levels of variation in HRs between the different cohorts were observed, including both increased and reduced likelihoods of mortality. In particular, the JPHC and MCS cohorts tended to display positive relationships between ambient exposures and mortality outcomes whereas the other cohorts tended toward null relationships. Within the JPHC, positive relationships between both ambient $PM_{2.5}$ and NO_2 with multiple causes of mortality were observed, including all-cause (HR for $PM_{2.5}$: 1.06, 95% CI: 1.03, 1.09; HR for NO_2: 1.16, 95% CI: 1.12, 1.19) and cancer (HR for $PM_{2.5}$: 1.10, 95% CI: 1.06, 1.16; HR for NO_2: 1.18, 95% CI: 1.13, 1.23) mortality. Within the MCS, $PM_{2.5}$ was associated with both all-cause (HR: 1.15, 95% CI: 1.07, 1.24) and cardiovascular (HR: 1.25, 95% CI: 1.08, 1.46) mortality whereas NO_2 was associated with all-cause (HR: 1.27, 95% CI: 1.17, 1.38), cancer (HR: 1.51, 95% CI: 1.07, 2.14), and cardiovascular (HR: 1.38, 95% CI: 1.16, 1.65) mortality. Two-pollutant models typically showed findings that were directionally consistent with those reported for the single-pollutant models with typically very little alteration.

The findings within individual cohorts generally remained consistent across a wide variety of subgroup and alternative analyses. The minimally adjusted analyses (i.e., models 1 and 2) showed directionally consistent findings with those of the final models, with the addition of extra covariates when generating the final models tending the HRs to migrate toward the null point. Findings were likewise consistent across several layers of additional sensitivity analysis, including stratification by smoking status, examination of nonsmoking women, restricting to those alive from 1998, and restricting to those who were disease-free at recruitment. Adjusting for urbanicity tended not to have any appreciable effect on the directionality of the findings, with the exception of CBCSCP where several null findings became significantly positive and Golestan where several findings became more positive, albeit without statistical significance.

The findings from each individual cohort were pooled via random effects meta-analysis. Forest plots, markers of heterogeneity, and pooled estimates for both $PM_{2.5}$ and NO_2 are provided in Figure 2 and Figure 3, respectively.

When examining the pooled estimates for $PM_{2.5}$, a borderline nonsignificant positive relationship between $PM_{2.5}$ exposure and cardiovascular mortality was observed. A 5-μg/m^3 increase in $PM_{2.5}$ was associated with an increased pooled HR of 1.05, with a 95% CI of 0.99 to 1.12. Within the remaining analyses for $PM_{2.5}$ there was an overall trend toward null findings with HRs consistently approximating 1.

When examining NO_2, an overall positive relationship was observed between exposure to ambient NO_2 and all cancer (HR for a 10-ppb increase: 1.18, 95% CI: 1.13, 1.23) and lung cancer (HR: 1.13, 95% CI: 1.01, 1.26). Additionally, there was a borderline nonsignificant association between ambient NO_2 and nonmalignant lung disease (HR: 1.10, 95% CI: 0.98, 1.23). Null or nonsignificant relationships were observed for NO_2 and all-cause (HR: 1.06, 95% CI: 0.85, 1.32), nonaccidental (HR: 1.07, 95% CI: 0.78, 1.48), and cardiovascular (HR: 1.14, 95% CI: 0.89, 1.47) mortality.

THE COMMUNITY-BASED CANCER SCREENING PROGRAM

The study population of the CBCSCP cohort consisted of an approximately equal number of men and women with an average age at recruitment of 47 years. Participants were followed for an average of 23 years, after which time 74% (17,464) were still alive. Among those who were deceased, cancer was the most common cause of death (2,189 deaths) followed by cardiovascular disease (1,089 deaths). Participants tended to be never smokers (71%), and never drinkers (89%). They had achieved at least an elementary education (42%) and had an average body mass index of 24. Demographic details are described in the Appendix (Table A1).

Table 2. Mean (sd) or *N* (%) Key Population Demographics at Recruitment[a]

	CBCSCP	Golestan	HEALS	JPHC	KMCC	MCS
Country	Taiwan	Iran	Bangladesh	Japan	Korea	India
Total *N*	23,759	49,982	19,990	87,653	18,529	141,238
Age	47 (10)	52 (9)	37 (10)	52 (8)	55 (14)	51 (11)
% Male	50%	42%	41%	47%	40%	58%
Recruitment years	1991–1992	2004–2008	2000–2008	1990–1995	1993–2005	1991–1997
Years of follow-up	23 (6)	11 (2)	10(3)	20 (5)	13 (5)	5 (2)
Smoking status						
Never	16,858 (71%)	39,141 (78%)	13,483 (67%)	51,994 (60%)	11,456 (63%)	115,340 (82%)
Former	6,861 (29%)[b]	3,318 (7%)	1,249 (6%)	10,791 (12%)	1,971 (11%)	5,126 (4%)
Current		7,523 (15%)	5,250 (26%)	24,551 (28%)	4,893 (27%)	20,772 (15%)
Pack-years[c]	24 (20)	17 (18)	15 (15)	30 (21)	27 (23)	7 (15)
BMI[a]	24 (3)	27 (5)	20 (3)	23 (3)	24 (3)	22 (4)
<20	2,423 (10%)	5,229 (10%)	11,870 (60%)	9,915 (11%)	2,197 (13%)	43,020 (30%)
20–25	12,761 (54%)	15,117 (30%)	6,442 (33%)	53,440 (62%)	9,557 (56%)	63,746 (45%)
25–30	7,374 (31%)	16,917 (34%)	1,266 (6%)	21,150 (24%)	4,830 (28%)	28,144 (20%)
>30	1,145 (5%)	12,711 (25%)	132 (1%)	2,136 (2%)	603 (4%)	6,328 (4%)
Number of deaths	6,295 (26%)	7,060 (14%)	1,532 (8%)	17,931 (20%)	3,411 (18%)	12,934 (9%)
Causes of death						
Nonaccidental	5,821	5,966	1,467	—	2,983	8,689
All cancer	2,189	1,401	268	7,331	1,072	793
Lung cancer	466	94	63	1,462	282	78
Cardiovascular disease	1,089	3,022	513	4,318	666	3,306
Nonmalignant lung disease	587	403	219	1,196	285	1,255
Original research interest	Cancer and cause-specific mortality	Risk factors for esophageal cancer	Evaluate the health effects of arsenic exposure	Risk factors for noncommunicable diseases	Risk factors for cancer	All-cause and cause-specific mortality
Recruitment procedure	Participants were invited from household registration offices in seven townships in Taiwan	Participants were randomly recruited from Gonbad city and surrounding rural areas	Participants were recruited from individuals using wells across Araihazar, Bangladesh	Participants were randomly recruited from 11 public health center areas in Japan	Eligible subjects were those who had participated in a cancer screening survey across four areas in Korea	Participants were recruited from polling stations across Mumbai
Mean (sd) urbanicity score[d]	0.23 (0.21)	0.07 (0.15)	0.03 (0.02)	0.31 (0.33)	0.12 (0.21)	NA[e]

[a] Missing values not shown (available in the Appendix). Percentage calculations are rounded to the nearest whole number and calculated with missing values excluded.
[b] CBCSCP only supplied ever/never smoking information.
[c] Former and current smokers only.
[d] Score from 0 (fully rural) to 1 (fully urban). Based on urbanicity score in 2000 (Gao and O'Neill 2020).
[e] As participants were only recruited from Mumbai, assumed to be completely urban.

Levels of $PM_{2.5}$ could be predicted for 23,390 members of CBCSCP (98% of total) whereas for NO_2 only 13,035 predictions could be made (55%). The lower proportion of NO_2 predictions was attributed to challenges with assigning NO_2 predictions to coastal areas. The mean (standard deviation [sd]) estimated concentration for ambient $PM_{2.5}$ was 7.9 (6.5) $\mu g/m^3$ and 9.4 (2.4) ppb for NO_2. There was no notable correlation between levels of $PM_{2.5}$ and NO_2 (0.14).

After removing participants with missing information on covariates, fully adjusted $PM_{2.5}$ models were generated for 22,952 participants (98% of those with predictions) and fully adjusted NO_2 models for 12,844 (99%). The findings from unadjusted and partially adjusted models are directionally consistent with the fully adjusted models (Appendix Tables A2 and A3). In fully adjusted models (Table 4 and Table 5), a 5-$\mu g/m^3$ increase in $PM_{2.5}$ was positively associated with an increased likelihood of death from cardiovascular disease (HR: 1.05, 95% CI: 1.00, 1.10). However, $PM_{2.5}$ was not associated with an increased likelihood of any other cause of death including overall deaths (HR: 1.00, 95% CI: 0.98, 1.02) and cancer (HR: 1.00, 95% CI: 0.97, 1.04). In contrast to $PM_{2.5}$, a 10-ppb increase in NO_2 was associated with a reduced likelihood of death from any cause (HR: 0.76, 95% CI: 0.65, 0.90) and nonmalignant lung disease (HR: 0.58, 95% CI: 0.34, 1.00). Positive (but nonsignificant) associations were observed for deaths from all cancer (HR: 1.15, 95% CI: 0.87, 1.51) and lung cancer (HR: 1.44, 95% CI: 0.79, 2.60). The findings for $PM_{2.5}$ and NO_2 observed in single-pollutant models persisted for two-pollutant models with no appreciable difference observed (Table A4). This included the increased HR observed for cardiovascular disease where, in the two-pollutant model, a 5-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with an HR of 1.05 (95% CI: 1.00, 1.11).

Subgroup and Sensitivity Analysis

Smoking Status Tables with results stratified by smoking status (ever and never) and examining nonsmoking females specifically are shown in the Appendix (Tables A5 to A7). When stratifying by smoking status, the directionality observed in the primary models generally remained, albeit with greater uncertainty due to the reduced sample sizes. This included the previously observed positive relationship between $PM_{2.5}$ and cardiovascular disease, which remained for both ever smokers (HR: 1.05, 95% CI: 0.97, 1.14) and never smokers (HR: 1.06, 95% CI: 0.99, 1.13), and the negative relationship between NO_2 and all-cause (and nonaccidental) mortality, which, for all-cause mortality, had an HR of 0.86 (95% CI: 0.66, 1.11) for ever smokers and 0.71 (95% CI: 0.57, 0.88) for never smokers. The only exception to this general pattern was the relationship between NO_2 and all cancer where, for ever smokers, an elevated and significant relationship (HR: 1.52, 95% CI: 1.01, 2.28) was observed. When examining only female nonsmokers, findings consistent with those from the primary models were observed, including $PM_{2.5}$ and cardiovascular disease (HR: 1.06, 95% CI: 0.98, 1.14) and NO_2 and all-cause (and nonaccidental) mortality (HR: 0.69, 95% CI: 0.52, 0.91).

Restriction to Those Alive in 1998 The majority of those for whom predictions could be made were still alive in 1998, resulting in 22,286 predictions for $PM_{2.5}$ and 12,499 for NO_2 (Table A8). As this population was largely unchanged from that in the main analyses, the overall findings of these models were consistent with those already presented, including the positive relationship between $PM_{2.5}$ and cardiovascular disease (HR: 1.05, 95% CI: 0.99, 1.11) and the negative relationship between NO_2 and all-cause (and nonaccidental) mortality (HR: 0.73, 95%, CI: 0.61, 0.87).

Table 3. Pollution Characteristics for Each Cohort at Recruitment

	CBCSCP		Golestan		HEALS		JPHC		KMCC		MCS	
Country	Taiwan		Iran		Bangladesh		Japan		Korea		India	
	N[a]	Mean (sd) [P5, P95]	*N*[a]	Mean (sd) [P5, P95]	*N*[a]	Mean (sd) [P5, P95]	*N*[a]	Mean (sd) [P5, P95]	*N*[a]	Mean (sd) [P5, P95]	*N*[a]	Mean (sd) [P5, P95]
$PM_{2.5}$ ($\mu g/m^3$)	23,390	7.9 (6.5) [1.2, 24.7]	49,982	32.2 (3.7) [27.1, 38.4]	19,990	57.9 (2.4) [55.2, 61.4]	87,600	10.9 (3.3) [6.1, 16.9]	18,529	22.8 (3.1) [19.9, 28.8]	126,377	34 (1.3) [32.7, 37.8]
NO_2 (ppb)	13,035	9.4 (2.4) [6, 13]	49,982	8.8 (1.3) [7, 11]	19,983	6.6 (0.8) [6, 8]	85,177	9.4 (7.8) [<1, 30]	18,517	11.2 (2.7) [7, 16]	126,401	23 (2.3) [21, 27]
Correlation $PM_{2.5}/NO_2$		0.14		0.54		0.46		0.50		0.57		<0.01

P5 = 5th percentile; P95 = 95th percentile.

Study cohorts: CBCSCP = Community-based Cancer Screening Program (Taiwan); Golestan = Golestan region, Iran; HEALS = Health Effects for Arsenic Longitudinal Study (Bangladesh); JPHC = Japan Public Health Center-based Prospective Study; KMCC = Korean Multi-center Cancer Cohort Study; MCS = Mumbai Cohort Study (India).

[a] *N* represents the total number for whom predictions could be made.

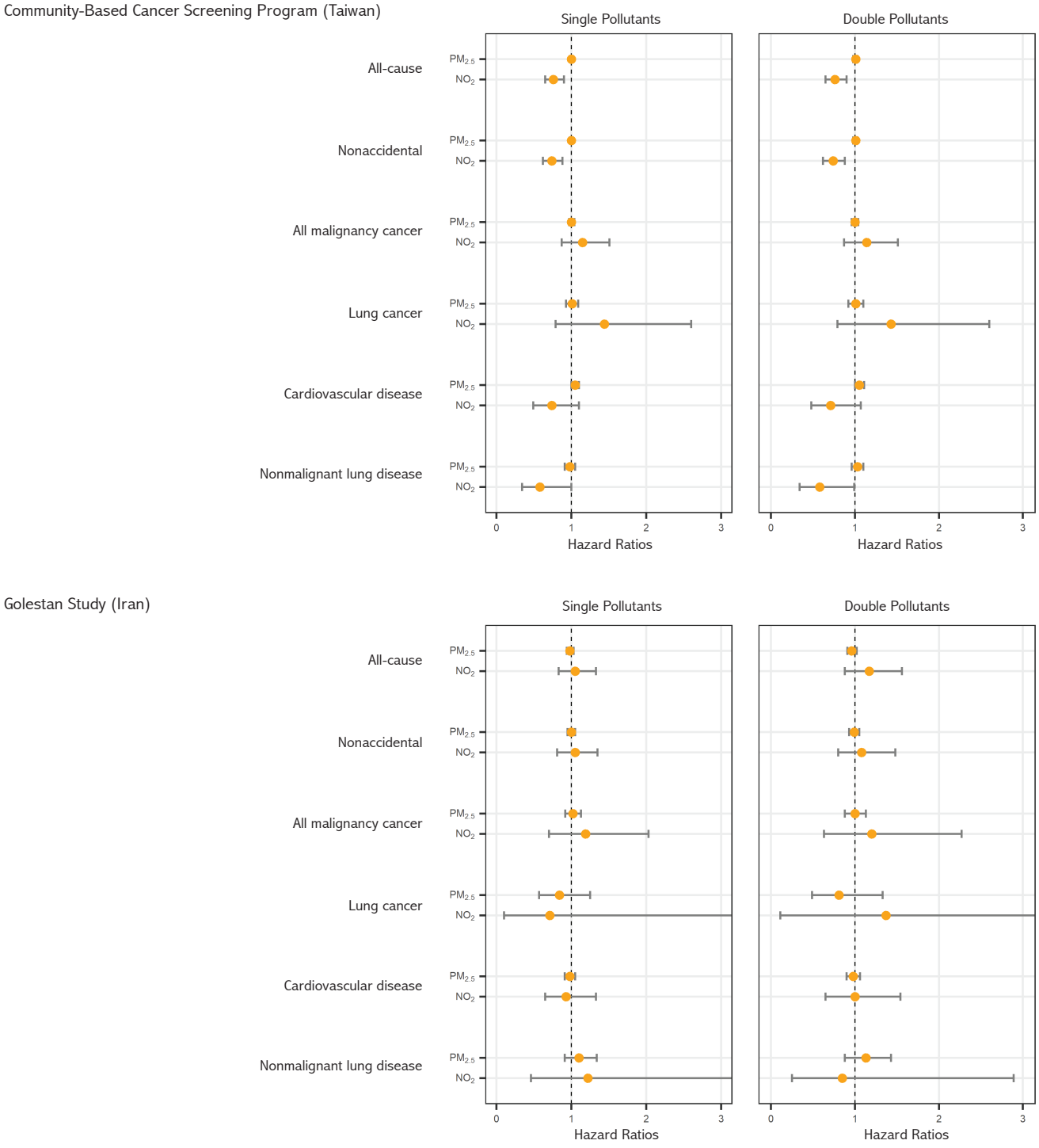

Figure 1. Fully adjusted hazard ratios derived from single- and two-pollutant models examining the relationship between ambient air pollution exposure and all-cause and cause-specific mortality. Hazard ratios are calculated per 5-μg/m^3 increase in $PM_{2.5}$ and 10-ppb increase in NO_2. Models are adjusted for year of recruitment, gender, smoking status and intensity, BMI, socioeconomic status, alcohol intake, and diet. The Golestan cohort was additionally adjusted for domestic fuel use. Note: Hazard ratio scale restricted to range of 0 to 3 for ease of viewing. Some points will fall outside this range.

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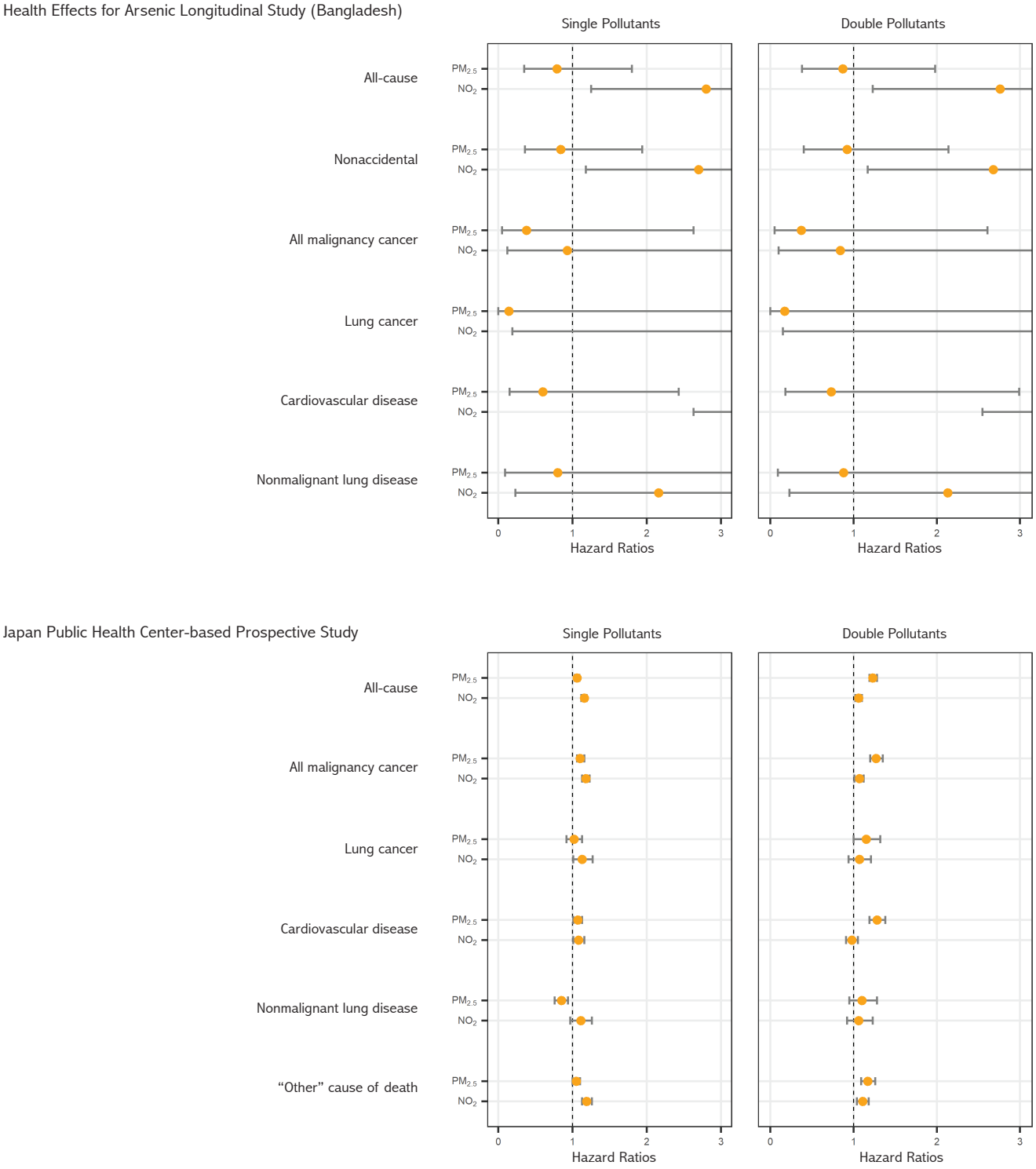

Figure 1 (*Continued*). Fully adjusted hazard ratios derived from single- and two-pollutant models examining the relationship between ambient air pollution exposure and all-cause and cause-specific mortality.

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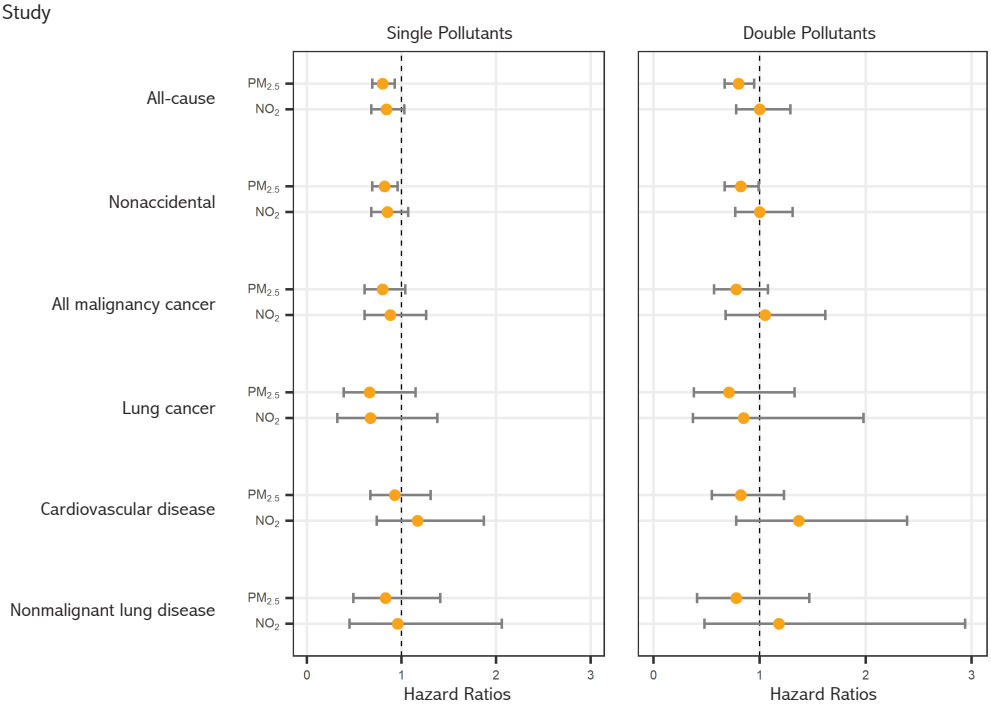
Korean Multi-center Cancer Cohort Study



Mumbai Cohort Study

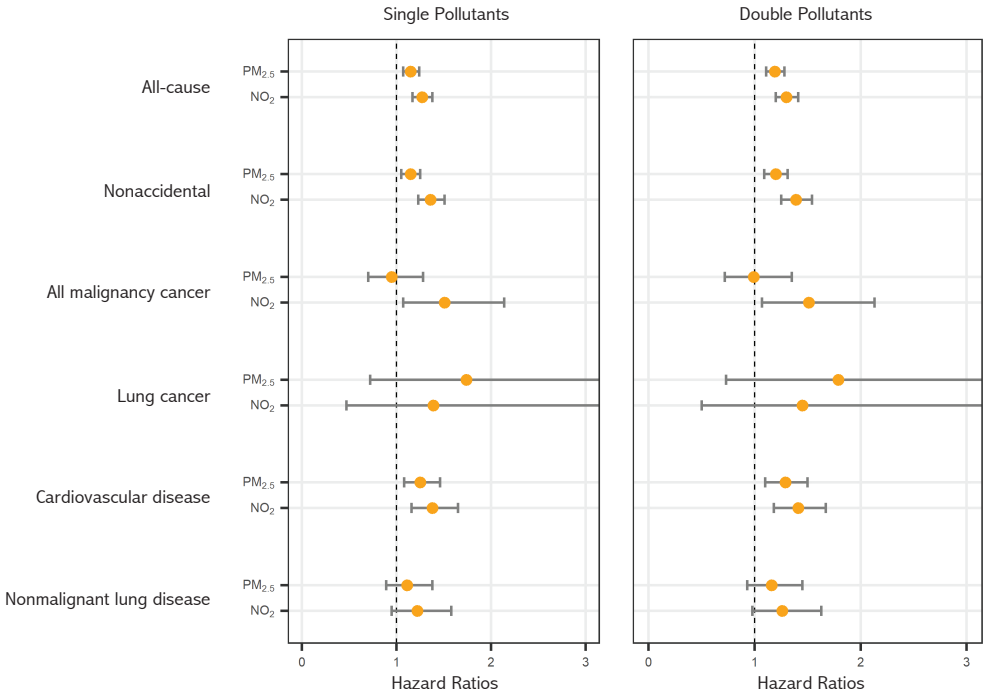


Figure 1 (*Continued*). Fully adjusted hazard ratios derived from single- and two-pollutant models examining the relationship between ambient air pollution exposure and all-cause and cause-specific mortality.

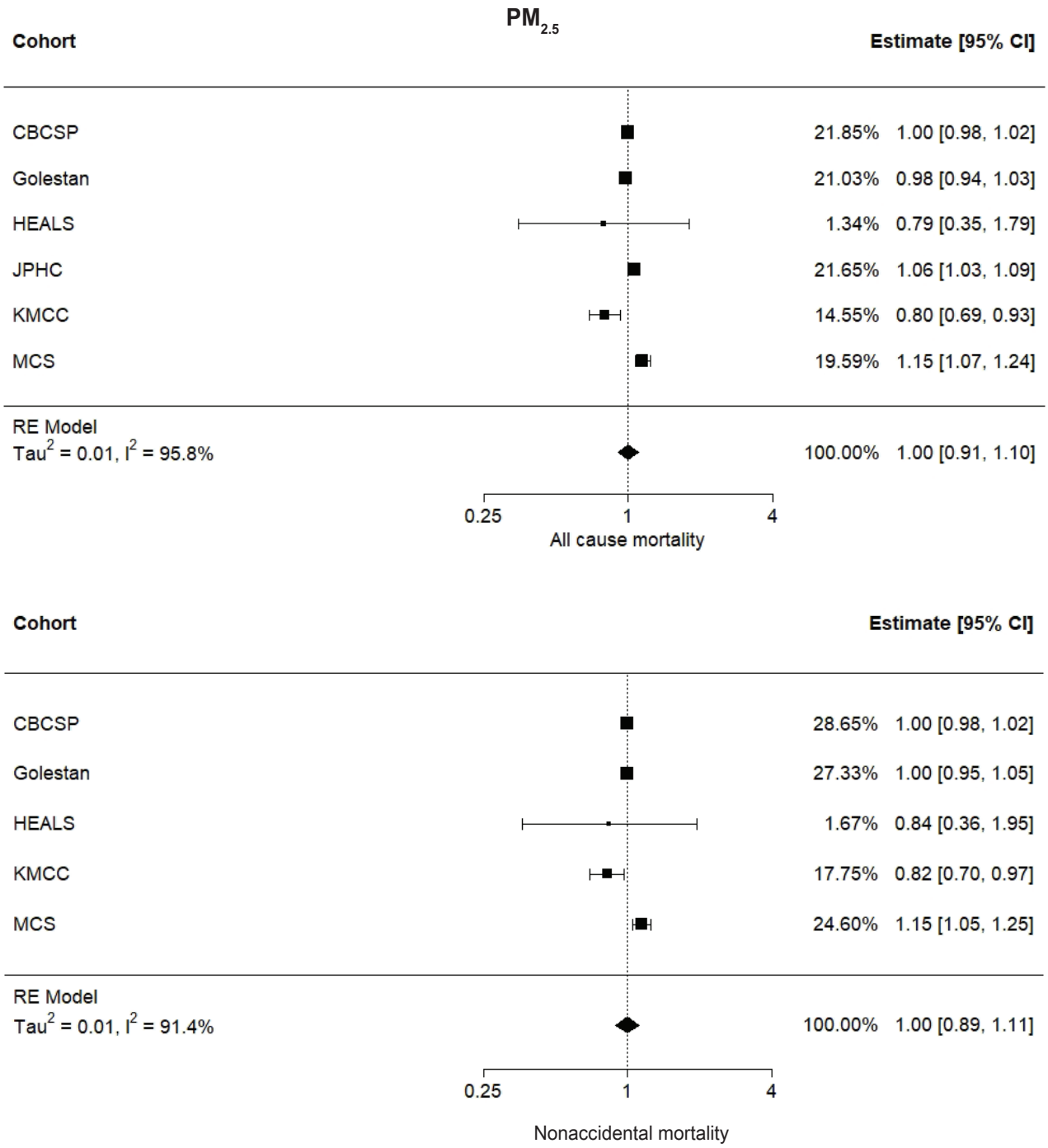


Figure 2. Random effects meta-analysis for association between 5-μg/m³ increase in $PM_{2.5}$ and all-cause and cause-specific mortality. Models adjusted for sex, recruitment year, smoking status and pack-years, body mass index, socioeconomic status, alcohol intake, and diet. Golestan cohort was additionally adjusted for domestic fuel use. Percentage weights based on variance value.

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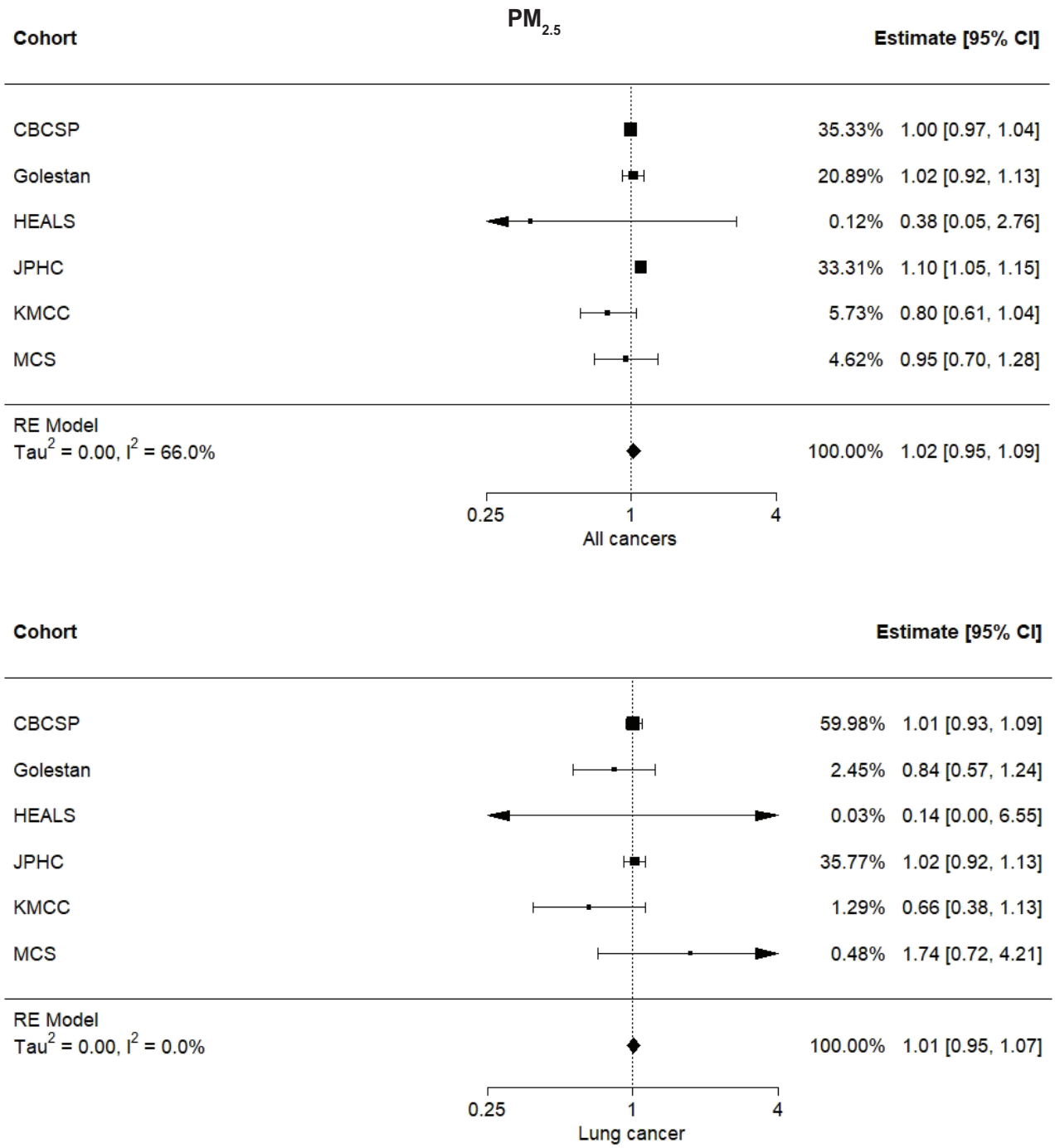

Figure 2 (*Continued*). Random effects meta-analysis for association between 5-μg/m³ increase in $PM_{2.5}$ and all-cause and cause-specific mortality.

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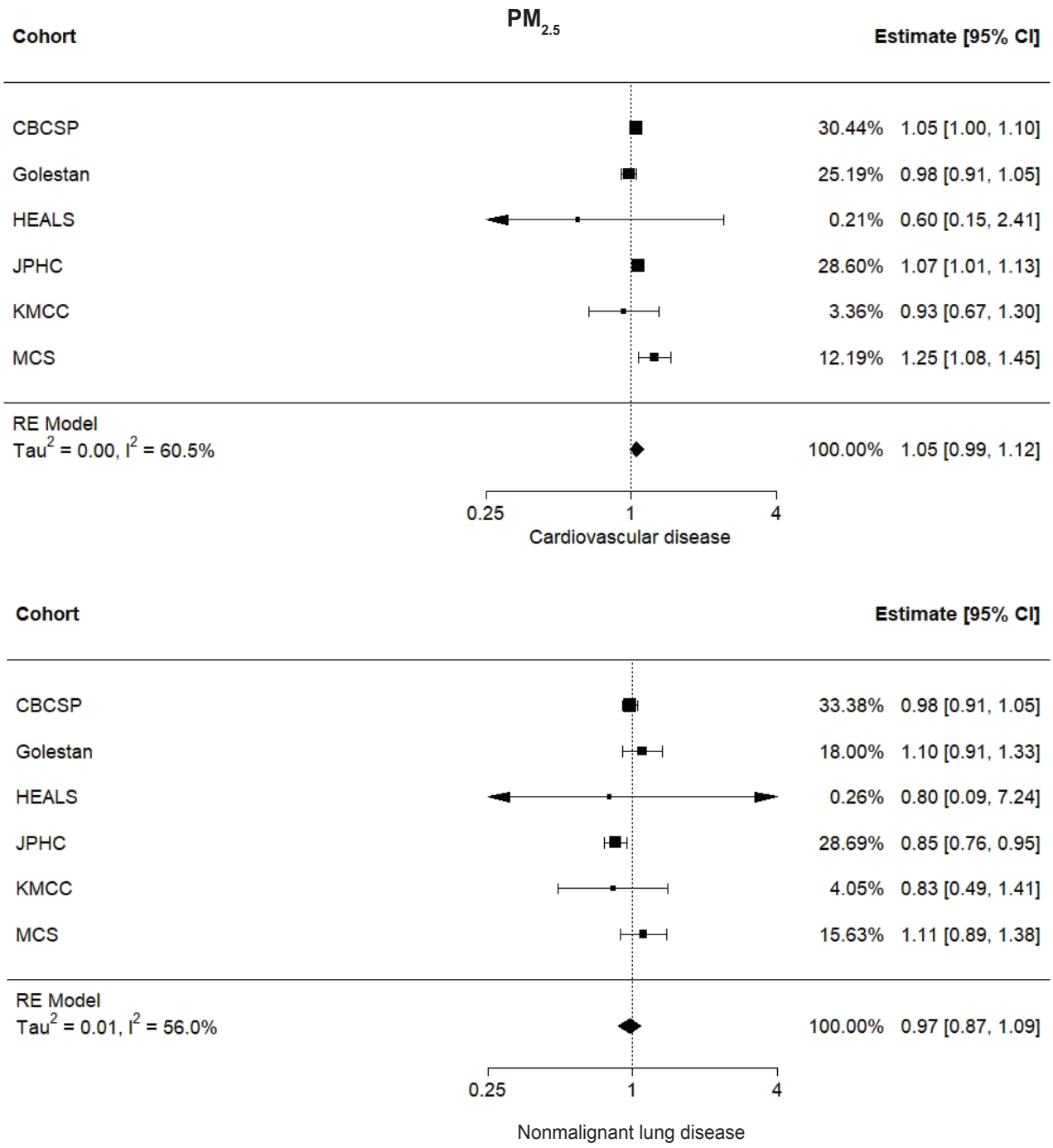

Figure 2 (*Continued*). Random effects meta-analysis for association between 5-μg/m³ increase in $PM_{2.5}$ and all-cause and cause-specific mortality.

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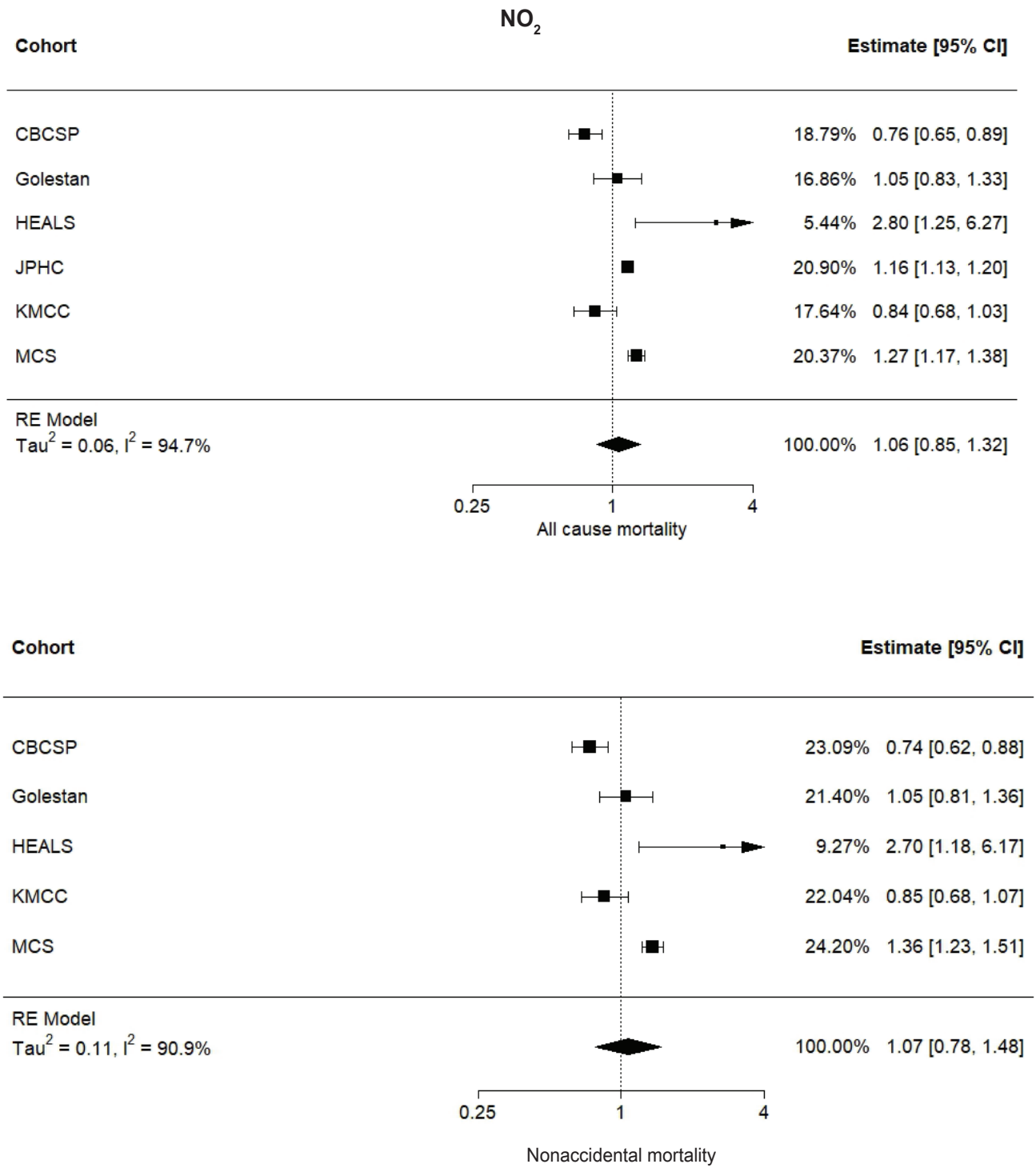

Figure 3. Random effects meta-analysis for association between 10-ppb increase in NO_2 and all-cause and cause-specific mortality. Models adjusted for sex, recruitment year, smoking status and pack-years, body mass index, socioeconomic status, alcohol intake, and diet. Golestan cohort additionally adjusted for domestic fuel use. Percentage weights based on variance value.

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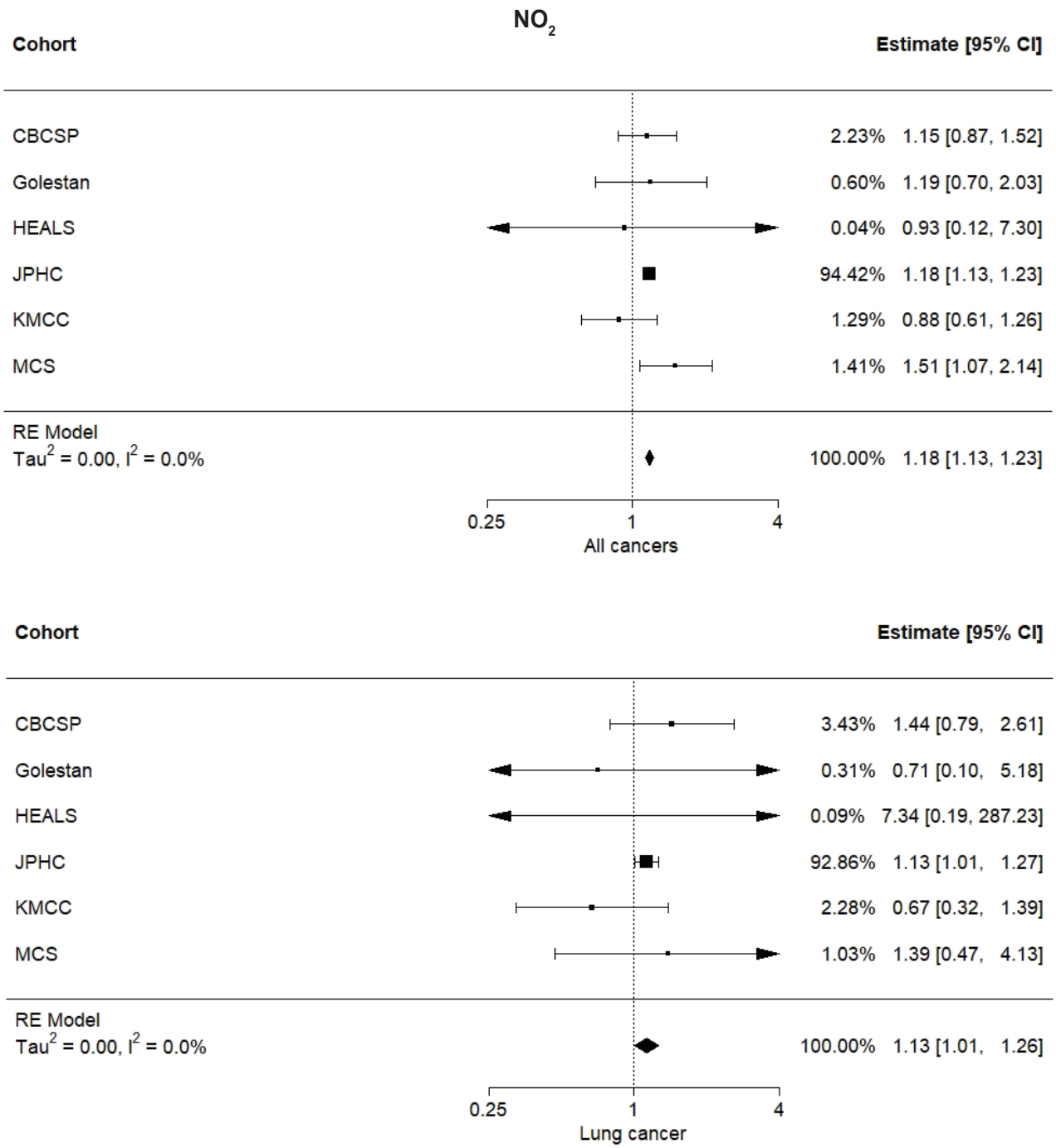

Figure 3 (*Continued*). Random effects meta-analysis for association between 10-ppb increase in NO_2 and all-cause and cause-specific mortality.

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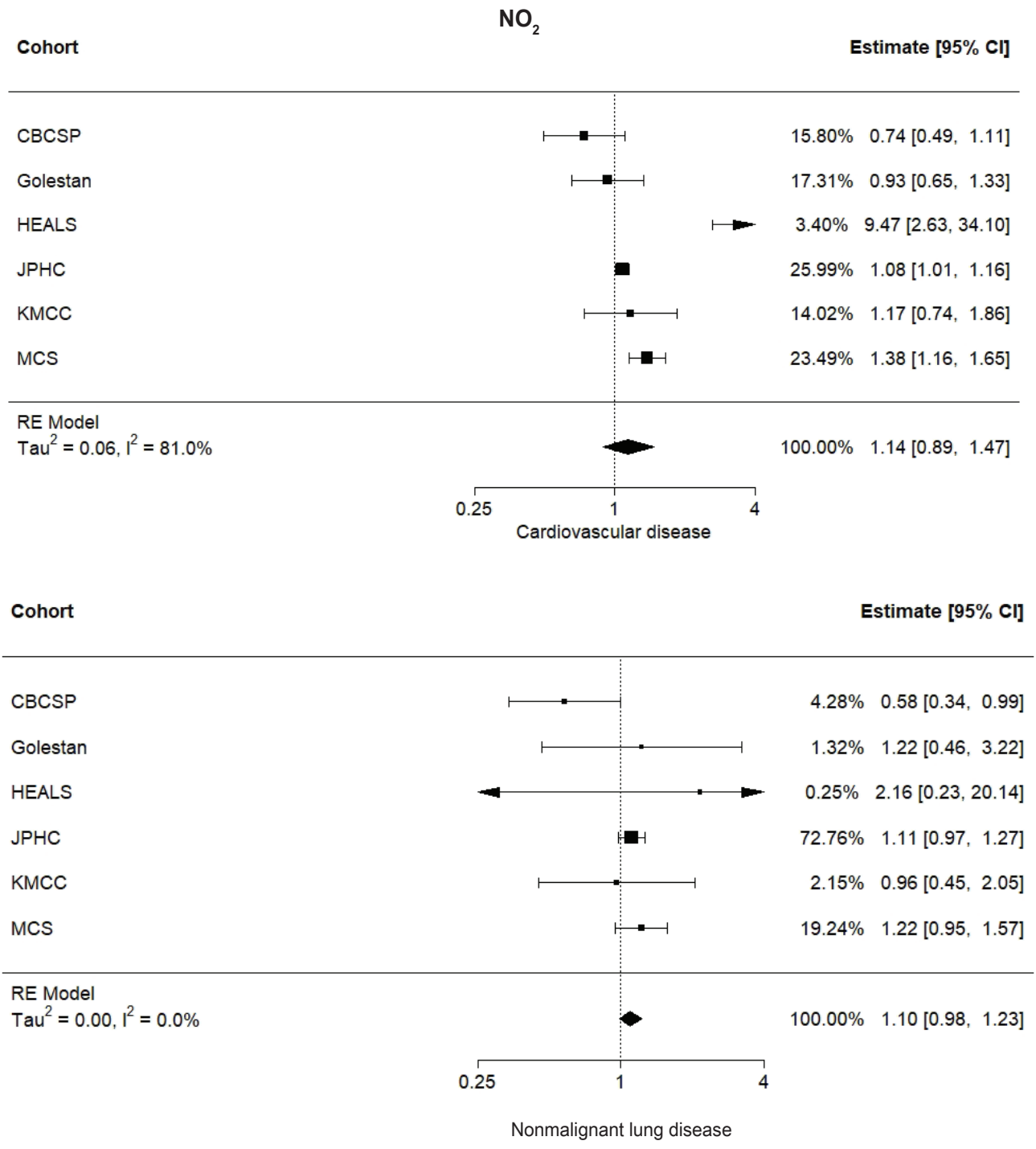

Figure 3 (*Continued*). Random effects meta-analysis for association between 10-ppb increase in NO_2 and all-cause and cause-specific mortality.

Urbanicity The degree of urbanicity for the year 2000 was moderately correlated with the assigned value of $PM_{2.5}$ (0.63) but less so for NO_2 (0.41). Mean concentrations of $PM_{2.5}$ were higher for individuals living in urban areas than those living in nonurban areas (17.2 μg/m^3 vs. 5.3 μg/m^3) but were more similar for NO_2 (9.7 ppb vs. 9.2 ppb). After additionally adjusting the models for the degree of urbanicity in 2000 (Tables 4 and 5), the previously observed null relationships between $PM_{2.5}$ and deaths from all cancer became positive (HR: 1.05, 95% CI: 1.01, 1.10). Further, the null relationship between $PM_{2.5}$ and nonaccidental mortality became positive (HR: 1.03, 95% CI: 1.00, 1.06). Similar findings were observed after adjusting for urbanicity in 2010 instead, with the exception of the positive association between $PM_{2.5}$ and nonaccidental mortality losing statistical significance (HR: 1.02, 95% CI: 0.99, 1.05) (Appendix Table A9). When adjusting for participants living in a major urban center or not, both the association with all cancer and lung cancer became positive (HR for all cancer: 1.09, 95% CI: 1.03, 1.15; HR for lung cancer: 1.16, 95% CI: 1.03, 1.31, Appendix Table A9). A positive association between $PM_{2.5}$ and lung cancer was observed when additionally adjusting by urbanicity in 2000, but this was nonsignificant (HR: 1.05, 0.95, 1.16). No change of note was observed after adjusting for urbanicity in the NO_2 models (Table 5 and Appendix Table A10)

Penalized Splines and Quartile Analysis The findings for penalized spline analysis for all-cause mortality and $PM_{2.5}$ and NO_2 are presented in Figure 4. (All outcomes are presented in Appendix Figures A1 and A2). The *P* values for the nonlinear spline analysis were nonsignificant for $PM_{2.5}$ and all-cause, accidental, lung cancer, and cardiovascular disease mortality and NO_2 and all outcomes. The spline analysis for $PM_{2.5}$ and cancer mortality (which was significant) indicated an increasing hazard at low concentrations of $PM_{2.5}$ (approx. 5 μg/m^3), which declined afterward. Likewise, when examining $PM_{2.5}$ and nonmalignant lung disease (also significant), higher hazards were observed at $PM_{2.5}$ levels below 5 μg/m^3 with hazards being "flatter" after that point.

Tables showing analysis repeated with $PM_{2.5}$ and NO_2 divided into quartiles are presented in Appendix Tables A11 and A12. The HRs for those in the highest exposed quartile (compared with those in the lowest) showed findings generally consistent with those reported in the main models. For example, those in the highest quartile of $PM_{2.5}$ exposure (>8.8 μg/m^3) had a significantly higher likelihood of cardiovascular death than those in the lowest (<2.5 μg/m^3, HR: 1.28, 95% CI: 1.07, 1.54). Similarly, those in the highest quartile of NO_2 exposure (>10 ppb) had a reduced likelihood of death from any cause than those in the lowest (<8 ppb, HR: 0.87, 95% CI: 0.79, 0.96). Examinations of HRs across differing quartiles of exposure showed inconsistent findings in terms of dose–response relationships. For example, the HR for $PM_{2.5}$ and cardiovascular disease appears to follow a dose–response relationship across the second (HR: 0.99), third (HR: 1.03), and fourth (1.28) quartiles. However, the relationship between $PM_{2.5}$ exposure and all cancer appeared to follow a reverse pattern across the second (HR: 1.34), third (HR 1.13), and fourth (1.01) quartiles.

Evaluation of the Assumption for Proportional Hazards Several variables may have potentially violated the proportional hazards assumption: smoking status, pack-years, sex, and alcohol intake. After removing the continuous variable (pack-years) and stratifying the remaining categorical variables, no appreciable difference in observed HRs between pollutant and outcomes was observed (Appendix Table A13), including the positive association between $PM_{2.5}$ and cardiovascular mortality (HR: 1.08, 95% CI: 1.01, 1.15).

THE GOLESTAN COHORT STUDY

The population of the Golestan cohort had an average age of 52 at recruitment and consisted of more women (58%) than men. Participants were followed for an average of 11 years, after which time 86% (42,922) were still alive. Among those who were dead, cardiovascular disease (3,022) and cancer (1,401) were the most common causes of death. Participants tended to be never smokers (78%) and never drinkers (97%). The average body mass index of participants was 27 and the majority of the population was illiterate (70%). In addition to the demographics recorded for the other ACC cohorts, the Golestan cohort also included information on domestic fuel use. The majority of participants used some form of fuel for domestic heating and cooking. The most common fuel was kerosene (63%, N = 31,548) with fewer participants using firewood (2%, N = 971) or other organic fuels (<1%, N = 100). Demographic details, including fuel use, are provided in Appendix Tables A14 and A15.

Ambient levels of $PM_{2.5}$ and NO_2 were assigned to the community/village level for each participant. These assignments represented 624 unique locations throughout the Golestan area, each containing a median of 38 participants. The mean (sd) estimated concentration for $PM_{2.5}$ was of 32.2 (3.7) μg/m^3 and 8.8 (1.3) ppb for NO_2. $PM_{2.5}$ and NO_2 were moderately correlated with each other (0.54).

As the use of household fuels were identified as important risk factors for mortality, they were included in the fully adjusted models of $PM_{2.5}$ and NO_2 and mortality (Tables 6 and 7). After removing participants with missing information on covariates, fully adjusted $PM_{2.5}$ and NO_2 models were generated for 49,106 participants (98% of those with pollutant predictions). Within the fully adjusted models no relationship was observed between ambient $PM_{2.5}$ or NO_2 and mortality outcomes. For example, a 5-μg/m^3 increase in $PM_{2.5}$ was associated with an HR of 0.98 (95% CI: 0.94, 1.03) for all-cause mortality. Similarly, a 10-ppb increase in NO_2 was associated with an HR of 1.05 (95% CI: 0.83, 1.33). The findings from unadjusted and partially adjusted models are directionally consistent with the fully adjusted models (Appendix Tables A16 and A17). These findings remained in two-pollutant models, with no notable change in HR values (Appendix Table A18).

Table 4. All-Cause and Cause-Specific Mortality in Relation to Ambient $PM_{2.5}$ Exposure, With and Without Adjustment for Urbanicity in the Community-based Cancer Screening Program (CBCSCP)

	Unadjusted for Urbanicity		After Adjustment for Urbanicity[a]	
	N events (total = 22,952)	HR[b] (95% CI)	*N* events (total = 22,612)	HR[b] (95% CI)
All-cause	6,016	1.00 (0.98, 1.02)	5,909	1.02 (0.99, 1.05)
Nonaccidental	5,564	1.00 (0.98, 1.02)	5,458	1.03 (1.00, 1.06)
All cancer	2,089	1.00 (0.97, 1.04)	2,049	1.05 (1.01, 1.10)
Lung cancer	449	1.01 (0.93, 1.09)	445	1.05 (0.95, 1.16)
Cardiovascular disease	1,049	1.05 (1.00, 1.10)	1,034	1.07 (1.00, 1.14)
Nonmalignant lung disease	551	0.98 (0.91, 1.05)	542	0.99 (0.90, 1.09)

[a] Additionally adjusted for degree of urbanicity in the year 2000.

[b] HRs are per 5-μg/m^3 increase in $PM_{2.5}$. Models are adjusted for age (time-axis), sex, recruitment year, smoking status and intensity, body mass index, education, and alcohol intake.

Table 5. All-Cause and Cause-Specific Mortality in Relation to Ambient NO_2 Exposure, With and Without Adjustment for Urbanicity in the Community-based Cancer Screening Program (CBCSCP)

	Unadjusted for Urbanicity		After Adjustment for Urbanicity[a]	
	N events (total = 12,844)	HR[b] (95% CI)	*N* events (total = 12,844)	HR[b] (95% CI)
All-cause	3,321	0.76 (0.65, 0.90)	3,321	0.78 (0.65, 0.93)
Nonaccidental	3,041	0.74 (0.62, 0.88)	3,041	0.76 (0.63, 0.91)
All cancer	1,035	1.15 (0.87, 1.51)	1,035	1.23 (0.91, 1.67)
Lung cancer	218	1.44 (0.79, 2.60)	218	1.51 (0.78, 2.90)
Cardiovascular disease	581	0.73 (0.49, 1.10)	581	0.66 (0.43, 1.01)
Nonmalignant lung disease	360	0.58 (0.34, 1.00)	360	0.61 (0.34, 1.10)

[a] Additionally adjusted for degree of urbanicity in the year 2000.

[b] HRs are per 10-ppb increase in NO_2. Models are adjusted for age (time-axis), sex, recruitment year, smoking status and intensity, body mass index, education, and alcohol intake.

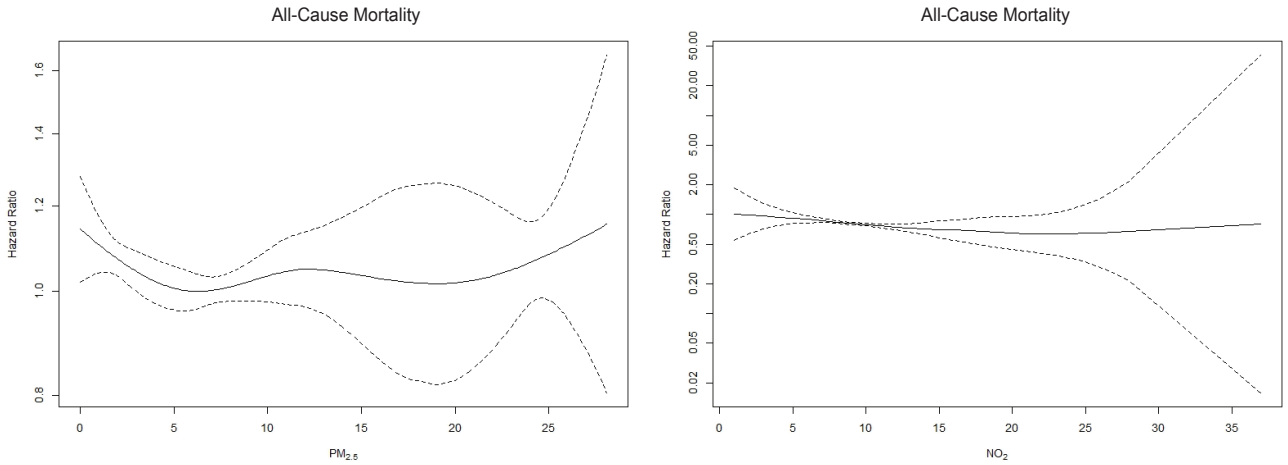

Figure 4. Penalized splines analysis (with four degrees of freedom) examining the relationship between exposure to $PM_{2.5}$ (left) and NO_2 (right) and all-cause mortality for the Community-based Cancer Screening Program (CBCSP) (Model 3).

Subgroup and Sensitivity Analysis

Solid Fuel Use When examining the role of either solid (i.e., firewood or other organic matter) or another polluting (i.e., kerosene) fuel independent of ambient air pollution (i.e., in models without $PM_{2.5}$ or NO_2) we observed that these fuels were positively associated with several mortality outcomes (Appendix Table A19). The use of either a solid fuel or kerosene was associated with an increased likelihood of either all-cause or nonaccidental mortality (HR for solid fuel and all-cause mortality: 1.25, 95% CI: 1.09, 1.44; HR for kerosene: 1.14, 95% CI: 1.08, 1.20). Elevated (and significant) relationships were also observed for kerosene usage and all cancer (HR: 1.26, 95% CI: 1.12, 1.43) and solid fuel use and nonmalignant lung disease (HR: 1.71, 95% CI: 1.03, 2.85). These findings remained when fuel use was paired with $PM_{2.5}$ or NO_2.

Smoking Status Results stratified by smoking status are presented in the Appendix (Tables A20 to A22). When stratifying by smoking status, the generally null results observed within the main analysis persisted, albeit with wider CIs owing to reduced sample sizes across the strata. When specifically examining female nonsmokers, a more strongly positive relationship between all-cancer mortality and both $PM_{2.5}$ (HR: 1.22, 95% CI: 1.04, 1.43) and NO_2 (HR: 2.13, 95% CI: 0.93, 4.89) was observed. With the exception of this observation, the observed HRs for nonsmoking women remained consistent with those observed in the main models.

No Pre-existing Disease at Baseline 32,469 participants had no pre-existing disease at the point of recruitment into the cohort. Among those with no pre-existing disease, the HRs associated with exposure to $PM_{2.5}$ and NO_2 remained consistent with those presented in the main analysis (i.e., generally null findings with nonsignificant confidence intervals, Appendix Table A23).

Urbanicity The degree of urbanicity for the year 2000 was moderately correlated with assigned values of $PM_{2.5}$ (0.51) but more strongly associated with NO_2 (0.78). Mean concentrations of $PM_{2.5}$ were higher for individuals living in urban areas than those living in nonurban areas (35.8 $\mu g/m^3$ vs. 30.1 $\mu g/m^3$), as were concentrations of NO_2 (10.6 ppb vs. 9.3 ppb). After further adjusting models for urbanicity there was no change to the directionality or lack of statistical significance for any findings (Tables 6 and 7, Appendix Tables A24 and A25). For example, the HR for all-cause mortality and $PM_{2.5}$ was 1.00 (95% CI: 0.95, 1.05) when additionally adjusting for urbanicity in 2000. However, when examining exposure to NO_2, there were several outcomes where the association became more positive, albeit without statistical significance. Specifically, the HR for NO_2 exposure and all-cause mortality increased from 1.05 in the main model to 1.26 (95% CI: 0.94, 1.67) after adjusting for urbanicity in 2000, as did the HRs for cardiovascular disease mortality (HR: 1.13, 95% CI: 0.73, 1.74) and nonmalignant lung disease (HR: 1.97, 95% CI: 0.60, 6.55). By contrast, the HR for all cancer decreased from 1.19 (95% CI: 0.70, 2.03) in the main model to 1.06 (95% CI: 0.55, 2.01) after the adjustment.

Penalized Spline and Quartile Analysis Findings for penalized spline analysis for all-cause mortality and $PM_{2.5}$ and NO_2 are presented in Figure 5. All outcomes are presented in the Appendix (Figures A3 and A4). The values for all outcomes were nonsignificant in nonlinear analysis for both $PM_{2.5}$ and NO_2.

Analyses repeated with $PM_{2.5}$ divided into quartiles and NO_2 divided into tertiles (generated owing to a more limited contrast) are presented in Appendix Tables A26 and A27. Consistent with the null findings reported in the main analysis, those exposed to the highest levels of $PM_{2.5}$ (35.6 $\mu g/m^3$) had null findings when compared with those in the lowest exposure group (<29.3 $\mu g/m^3$). The same was observed

Table 6. All-Cause and Cause-Specific Mortality in Relation to Ambient $PM_{2.5}$ Exposure, With and Without Adjustment for Urbanicity in the Golestan Cohort

	Unadjusted for Urbanicity		After Adjustment for Urbanicity [a]	
	N events (total = 49,106)	HR [b] (95% CI)	*N* events (total = 49,106)	HR [b] (95% CI)
All-cause	6,878	0.98 (0.94, 1.03)	6,878	1.00 (0.95, 1.05)
Nonaccidental	5,807	1.00 (0.95, 1.05)	5,807	1.01 (0.96, 1.07)
Cancer	1,366	1.02 (0.92, 1.13)	1,366	0.99 (0.89, 1.12)
Lung cancer	93	0.84 (0.57, 1.25)	93	0.66 (0.40, 1.09)
Cardiovascular disease	2,941	0.98 (0.91, 1.05)	2,941	1.00 (0.92, 1.08)
Nonmalignant lung disease	394	1.10 (0.91, 1.34)	394	1.20 (0.97, 1.49)

[a] Additionally adjusted for degree of urbanicity in the year 2000.

[b] HRs are per 5-μg/m[3] increase in $PM_{2.5}$. Models are adjusted for age (time-axis), sex, recruitment year, smoking status and intensity, body mass index, education, diet, alcohol intake, and domestic fuel use.

Table 7. All-Cause and Cause-Specific Mortality in Relation to Ambient NO_2 Exposure, With and Without Adjustment for Urbanicity in the Golestan Cohort

	Unadjusted for Urbanicity		After Adjustment for Urbanicity [a]	
	N events (total = 49,106)	HR [b] (95% CI)	*N* events (total = 49,106)	HR [b] (95% CI)
All-cause	6,878	1.05 (0.83, 1.33)	6,878	1.26 (0.94, 1.67)
Nonaccidental	5,807	1.05 (0.81, 1.35)	5,807	1.20 (0.88, 1.63)
Cancer	1,366	1.19 (0.70, 2.03)	1,366	1.06 (0.55, 2.01)
Lung cancer	93	0.71 (0.10, 5.33)	93	0.20 (0.01, 2.97)
Cardiovascular disease	2,941	0.93 (0.65, 1.33)	2,941	1.13 (0.73, 1.74)
Nonmalignant lung disease	394	1.22 (0.46, 3.21)	394	1.97 (0.60, 6.55)

[a] Additionally adjusted for degree of urbanicity in the year 2000.

[b] HRs are per 10-ppb increase in NO_2. Models are adjusted for age (time-axis), sex, recruitment year, smoking status and intensity, body mass index, education, diet, alcohol intake, and domestic fuel use.

for NO_2, where those in the highest tertile (>9 ppb) had null findings compared with those in the lowest tertile (<8 ppb).

Evaluation of the Assumption for Proportional Hazards Several variables may have potentially violated the proportional hazards assumption: smoking status, pack-years, sex, and interview year. After removing the continuous variable (pack-years) and stratifying the categorical variables, the repeated analysis yielded no appreciable difference in HRs between pollutants and outcomes (Appendix Table A28).

HEALTH EFFECTS FOR ARSENIC LONGITUDINAL STUDY

The participants of the HEALS consisted of more women than men (59% vs. 41%) with an average age at recruitment of 37. Participants were followed for an average of 10 years after which time 92% (18,458) were still alive. Among those who died, cardiovascular disease was the most common cause of death (*N* = 513) followed by cancer (*N* = 268). Participants tended to be never smokers (67%) with no (44%) or primary (31%) formal education, and an average body mass index of 20. Demographic features are described in Table A29 of the Appendix.

Levels of $PM_{2.5}$ and NO_2 could be predicted for all 19,990 participants of HEALS and NO_2 could be predicted for 19,983. The mean (sd) estimated concentration for $PM_{2.5}$ at recruitment was 57.2 (2.4) μg/m^3 and 6.6 (0.8) ppb for NO_2. $PM_{2.5}$ and NO_2 were moderately correlated with each other (0.46).

After removing participants with missing information on covariates, fully adjusted $PM_{2.5}$ and NO_2 models were generated for 17,361 and 17,355 participants (87% of those with predictions). The findings from unadjusted and partially adjusted models are directionally consistent with the fully adjusted models (Appendix Tables A30 and A31). In the fully adjusted models (Tables 8 and 9), $PM_{2.5}$ showed a negative relationship between exposure and all-cause mortality, but this was nonsignificant and with relatively wide CIs (HR: 0.79, 95% CI: 0.35, 1.80). A similar effect was observed with nonaccidental mortality (HR: 0.84, 95% CI: 0.36, 1.94). Similar effects were observed between $PM_{2.5}$ and individual causes of mortality, none of which reached statistical significance and generally had high levels of uncertainty. For example, a 5-μg/m^3 increase in $PM_{2.5}$ was associated with an HR of 0.38 for deaths from all cancer, with a 95% CI of 0.05 to 2.63.

In contrast to $PM_{2.5}$, a positive and significant relationship between ambient NO_2 and several mortality outcomes was observed. However, as with $PM_{2.5}$, there was considerable uncertainty in the derived estimates. A 10-ppb increase in NO_2 exposure was associated with an HR of 2.80 (95% CI: 1.25, 6.26) for all-cause mortality and 9.47 (95% CI: 2.63, 34.1) for cardiovascular disease mortality.

In two-pollutant models (Appendix Table A32), the directionality of effect for both pollutants (i.e., negative/null for $PM_{2.5}$ and generally positive for NO_2) remained. For example, the HR for NO_2 and all-cause mortality in the single-pollutant model was 2.80 whereas in the two-pollutant model it was 2.76. The positive findings for NO_2 and all-cause and nonaccidental mortality remained statistically significant in two-pollutant models.

Subgroup and Sensitivity Analysis

Smoking Status Results stratified by smoking status are presented in the Appendix (Tables A33 to A35). Owing to limited numbers for individual causes of death, examinations of smoking status were restricted to all-cause and nonaccidental mortality. When stratifying by smoking status, no significant relationship was observed for $PM_{2.5}$. When examining smoking status and NO_2 the positive relationship between NO_2 and mortality observed in the main models was retained among never smokers, albeit still with a wide range of uncertainty (HR: 4.83, 95% CI: 1.29, 18.10). The findings from specifically examining female nonsmokers, were again consistent with those from the main analysis (null for $PM_{2.5}$ and significantly positive for NO_2).

Urbanicity The degree of urbanicity for the year 2000 was weakly negatively correlated with assigned values of $PM_{2.5}$

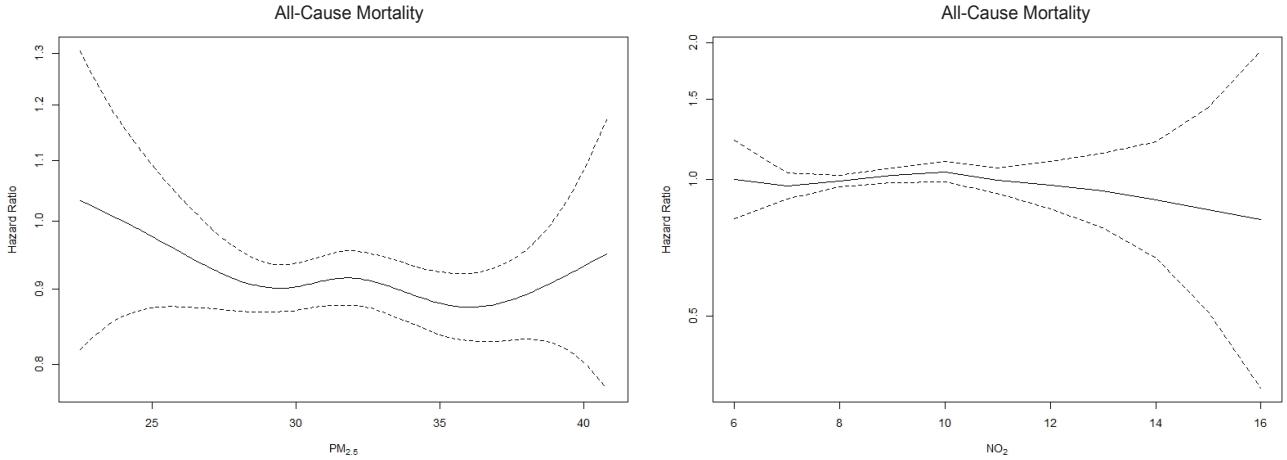

Figure 5. Penalized splines analysis (with four degrees of freedom) examining the relationship between exposure to $PM_{2.5}$ (left) and NO_2 (right) and all-cause mortality for the Golestan cohort (Model 3).

(–0.20) and NO_2 (–0.14). After further adjustment of models for urbanicity there was no change in the directionality or significance for any findings (Tables 8 and 9 and Appendix Tables A36 and A37). For example, the HR for all-cause mortality and $PM_{2.5}$ remained nonsignificant after adjusting for urbanicity (HR after adjusting for urbanicity in 2000: 0.84, 95% CI: 0.33, 2.12). Similarly, the HR for all-cause mortality and NO_2 remained significantly positive after additional adjustment for urbanicity (HR after adjusting for urbanicity in 2000: 2.91, 95% CI: 1.29, 6.54). All participants were considered within an urban space after application of the Global Settlement Layer, so this portion of analysis was not performed.

Penalized Spline and Quartile Analysis The findings for penalized spline analysis for all-cause mortality and $PM_{2.5}$ are presented in Figure 6. Figures for all outcomes are presented in the Appendix (Figure A5). The *P* values for all outcomes were nonsignificant for a nonlinear relationship.

Tables showing analysis repeated with $PM_{2.5}$ divided into quartiles are presented in the Appendix Table A38. Consistent with the null findings reported in the main analysis, those exposed to the highest levels of $PM_{2.5}$ (>60.7 μg/m^3) had null findings when compared to those in the lowest exposure group (<55.9 μg/m^3). There was insufficient variation in NO_2 exposure to allow spline or quartile analysis.

Evaluation of the Assumption for Proportional Hazards The only variable to potentially violate the proportional hazards assumption within the HEALS cohort was that of pack-years. After repeating analysis with this variable removed (Appendix Table A39), the only change of note was that the positive association between NO_2 and nonaccidental mortality decreased somewhat toward the null (2.13) and lost statistical significance (95% CI: 0.96, 4.74). However, the positive association between NO_2 and all-cause mortality remained (HR: 2.33, 95% CI: 1.07, 5.07).

JAPAN PUBLIC HEALTH CENTER-BASED PROSPECTIVE STUDY

The JPHC study population consisted of slightly more women than men (53% versus 47%), with an average age at recruitment of 52 years. Participants were followed for an average of 20 years, after which time 80% (69,722) were still alive. Among those who died, cancer was the most common cause of death (*N* = 7,331, 41% of all deaths) followed by "other" (i.e., not cancer, cardio/cerebrovascular, or lung disease, *N* = 5,236, 29%). Participants tended to be nonsmokers (60%) with a mean body mass index of 23. Demographic details are further described on Appendix Table A40.

Ambient $PM_{2.5}$ was able to be predicted for 87,600 participants (99% of total) and NO_2 was predicted for 85,177 (97%). The mean (sd) estimated concentration for ambient $PM_{2.5}$ at recruitment was 10.9 (3.3) μg/m^3 and 9.4 (7.8) ppb for NO_2. $PM_{2.5}$ and NO_2 were moderately correlated with each other (0.50).

Due to missing information on covariates, fully adjusted $PM_{2.5}$ models were only available for 78,142 participants and fully adjusted NO_2 models for 76,075. However, the findings from unadjusted and partially adjusted models are directionally consistent with the fully adjusted models (Appendix Tables A41 and A42). In the fully adjusted models (Tables 10 and 11) both $PM_{2.5}$ and NO_2 were consistently positively associated with all-cause mortality and several specific causes of mortality. A 5-μg/m^3 increase in $PM_{2.5}$ was associated with an HR of 1.06 (95% CI: 1.03, 1.09) for all-cause mortality and a 10-ppb increase in NO_2 was associated with an HR of 1.16 (95% CI: 1.12, 1.19). $PM_{2.5}$ was significantly associated with increased likelihoods of deaths from cancer (HR: 1.10, 95% CI: 1.06, 1.16), cerebrovascular disease (HR: 1.13, 95% CI: 1.03, 1.24), and "other" causes of death (HR: 1.05, 95% CI: 1.00, 1.10). Combining cardiac diseases with cerebrovascular diseases, to provide a cardiovascular outcome based on ICD

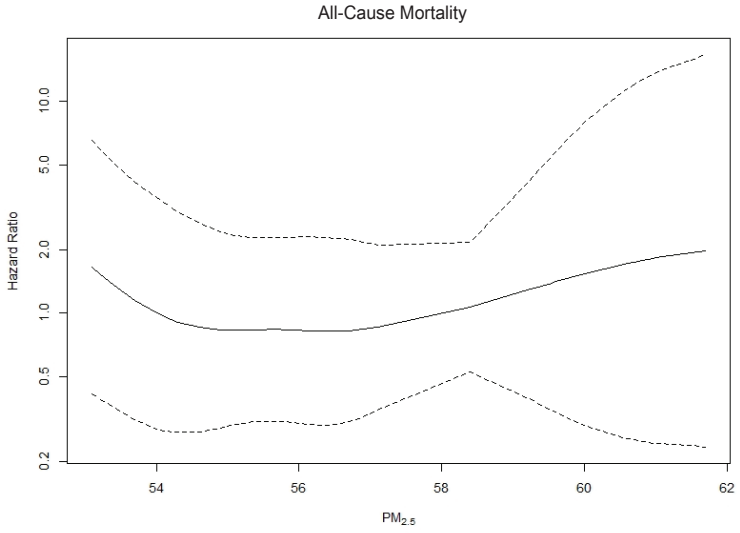

Figure 6. Penalized splines analysis (with four degrees of freedom) examining the relationship between $PM_{2.5}$ exposure and all-cause mortality for the Health Effects for Arsenic Longitudinal Study (HEAL) (Model 3).

Table 8. All-Cause and Cause-Specific Mortality in Relation to Ambient $PM_{2.5}$ Exposure in the Health Effects for Arsenic Longitudinal Study (HEALS)

	Unadjusted for Urbanicity		After Adjustment for Urbanicity [a]	
	N events (total = 17,361)	HR [b] (95% CI)	*N* events (total = 17,361)	HR [b] (95% CI)
All-cause	1,300	0.79 (0.35, 1.80)	1,300	0.84 (0.33, 2.12)
Nonaccidental	1,249	0.84 (0.36, 1.94)	1,249	0.92 (0.36, 2.37)
All cancer	228	0.38 (0.05, 2.63)	228	0.36 (0.04, 3.33)
Lung cancer	51	0.14 (<0.01, 6.57)	51	0.15 (<0.01, 14.0)
Cardiovascular disease	440	0.60 (0.15, 2.43)	440	0.70 (0.14, 3.37)
Nonmalignant lung disease	180	0.80 (0.09, 7.37)	180	1.30 (0.11, 15.5)

[a] Additionally adjusted for degree of urbanicity in the year 2000.

[b] HRs are per 5-μg/m^3 increase in $PM_{2.5}$. Models are adjusted for age (time-axis), sex, recruitment year, smoking status and intensity, body mass index, and education.

Table 9. All-Cause and Cause-Specific Mortality in Relation to Ambient NO_2 Exposure in the Health Effects for Arsenic Longitudinal Study (HEALS)

	Unadjusted for Urbanicity		After Adjustment for Urbanicity [a]	
	N events (total = 17,355)	HR [b] (95% CI)	*N* events (total = 17,355)	HR [b] (95% CI)
All-cause	1,298	2.80 (1.25, 6.26)	1,298	2.91 (1.29, 6.54)
Nonaccidental	1,147	2.70 (1.18, 6.16)	1,147	2.82 (1.23, 6.46)
All cancer	228	0.93 (0.12, 7.40)	228	0.97 (0.12, 7.82)
Lung cancer	51	7.34 (0.19, 291)	51	8.39 (0.21, 340)
Cardiovascular disease	439	9.47 (2.63, 34.1)	439	10.4 (2.86, 37.9)
Nonmalignant lung disease	180	2.16 (0.23, 20.0)	180	2.40 (0.26, 22.5)

[a] Additionally adjusted for degree of urbanicity in the year 2000.

[b] Hazard ratios are per 10-ppb increase in NO_2. Models are adjusted for age (time-axis), sex, recruitment year, smoking status and intensity, body mass index, and education.

codes consistent with the other cohorts in this study, also resulted in a positive relationship between $PM_{2.5}$ and cardiovascular disease (HR: 1.07, 95% CI: 1.01, 1.13). Similarly to $PM_{2.5}$, NO_2 was significantly associated with increased likelihoods of death from cancer (HR: 1.18, 95% CI: 1.13, 1.23), cardiovascular disease (HR: 1.12, 95% CI: 1.03, 1.23), lung cancer (HR: 1.13, 95% CI: 1.01, 1.27), and "other" causes of death (HR: 1.19, 95% CI: 1.13, 1.26). In the combined cardiovascular disease outcome, NO_2 was also positively associated with death from this cause (HR: 1.08, 95% CI: 1.01, 1.16).

In two-pollutant models (Appendix Table A42), the HRs observed for $PM_{2.5}$ tended to increase toward a greater likelihood whereas for NO_2 they tended to regress toward the null point or become nonsignificant. For example, the HR for all-cause mortality and $PM_{2.5}$ increased from 1.06 (95% CI: 1.03, 1.09) in the one-pollutant model to 1.23 (95% CI: 1.19, 1.28) in the two-pollutant model whereas for NO_2, the HR decreased from 1.18 (95% CI: 1.13, 1.23) to 1.06 (95% CI: 1.02, 1.10).

Subgroup and Sensitivity Analysis

Smoking Status Tables with results stratified by smoking status (never/former/current) are presented in Appendix Tables A43 to A45. When stratifying by smoking status, the general directionality observed in the main models generally remained, albeit with greater uncertainty due to the reduced sample sizes across the strata. Included within this observation was the association between $PM_{2.5}$ and all-cause mortality, which remained positive for never smokers (HR: 1.09, 95% CI: 1.05, 1.13), former smokers (HR: 1.04, 95% CI: 0.97, 1.11), and current smokers (HR: 1.04, 95% CI: 0.99, 1.09). Also retained were the positive associations between all cancer, cerebrovascular disease, and combined cardiovascular disease. Similarly to $PM_{2.5}$, the observed positive relationships generally remained for NO_2 across the different smoking status strata. This included the relationship between NO_2 and all-cause mortality, which remained across never smokers (HR: 1.26, 95% CI: 1.20, 1.32), former smokers (HR: 1.14, 95% CI: 1.06, 1.22), and current smokers (HR: 1.06, 95% CI: 1.01, 1.11). An exception to this observation was that the previously observed relationships between NO_2 and cardiac and combined cardiovascular diseases were only retained for never smokers (HR for combined cardiovascular diseases: 1.15, 95% CI: 1.04, 1.28) and former smokers (HR: 1.16, 95% CI: 1.00, 1.35), whereas for current smokers, the relationship became null (HR: 0.95, 95% CI: 0.85, 1.05).

When specifically examining female nonsmokers, the previously observed positive relationships remained, especially for all-cause mortality, cancer mortality, and combined cardiovascular mortality. For nonsmoking women, the HR for $PM_{2.5}$ exposure and all-cause mortality was 1.08 (95% CI: 1.03, 1.14) and for NO_2 it was 1.27 (95% CI: 1.20, 1.33).

No Pre-existing Disease at Baseline 37,352 participants reported having no pre-existing disease at the point of recruitment. Among this group, the previously reported relationships between $PM_{2.5}$ and all-cause and cause-specific mortality generally remained, albeit with reduced certainty — likely resulting from the reduced sample size (Appendix Table A46). This included the relationship between $PM_{2.5}$ and all-cause mortality (HR: 1.07, 95% CI: 1.01, 1.13) and combined cardiovascular mortality (HR: 1.07, 95% CI: 0.94, 1.22). By contrast, the positive relationship observed with NO_2 in the main models did not remain when restricting to those who were disease-free. When examining all deaths, the HR became mildly protective (HR: 0.94, 95% CI: 0.89, 0.99). Additionally, the previously positive relationship between NO_2 and lung cancer became null (HR: 0.98, 95% CI: 0.81, 1.18).

Restriction to Those Alive in 1998 The vast majority (97%) of those within JPHC for whom predictions could be made were still alive in 1998, resulting in 75,855 predictions for $PM_{2.5}$ and 73,789 for NO_2. The overall findings of the models examining $PM_{2.5}$ were generally consistent with those in the main analysis (Appendix Table A47), including the positive relationship between $PM_{2.5}$ and all-cause mortality (HR: 1.04, 95% CI: 1.02, 1.07) and combined cardiovascular mortality (HR: 1.05, 95% CI: 0.99, 1.11). However, the previously observed positive relationships between NO_2 and mortality outcomes reverted toward the null, including the relationship between NO_2 and all-cause mortality (HR: 1.01, 95% CI: 0.97, 1.05) and combined cardiovascular disease (HR: 0.92, 95% CI: 0.84, 1.00).

Urbanicity The degree of urbanicity for the year 2000 was weakly correlated with assigned values of $PM_{2.5}$ (0.36) but more strongly correlated with NO_2 (0.60). Mean concentrations of $PM_{2.5}$ were somewhat higher among those living in urban areas than those not living in urban areas (13.0 μg/m^3 vs. 10.4 μg/m^3) with a more pronounced difference for NO_2 (20.0 ppb vs. 6.8 ppb). After additionally adjusting for urbanicity there was no change in the directionality or significance for any findings (Tables 10 and 11, Appendix Tables A48 and A49). For example, the HR for all-cause mortality and $PM_{2.5}$ remained positive after adjusting for urbanicity (HR after adjusting for urbanicity in 2000: 1.07, 95% CI: 1.04, 1.10). Similarly, the positive associations observed for NO_2 also remained after additional adjustment for urbanicity (HR for all-cause mortality and NO_2: 1.21, 95% CI: 1.17, 1.26).

Penalized Spline and Quartile Analysis Findings for penalized spline analysis for all-cause mortality and $PM_{2.5}$ and NO_2 are presented in Figure 7. Figures for all outcomes are presented in Appendix Figures A6 and A7. The *P* values for nonlinear spline analysis were significant for both $PM_{2.5}$ and NO_2 for all outcomes, indicating a potential nonlinear relationship within the data of this cohort. The HR between all-cause mortality and $PM_{2.5}$ (which was paralleled in the "other" causes of death) is below 1 at lower levels of exposure (until approximately 10 μg/m^3) ,and then increased after that point before declining at the upper levels of exposure. For NO_2, the HR appears to sharply increase for approximately the first 10 ppb of exposure before maintaining an elevated but stable HR for higher levels of exposure.

Table 10. All-Cause and Cause-Specific Mortality in Relation to Ambient $PM_{2.5}$ Exposure in the Japan Public Health Center-based Prospective Study (JPHC)

	Unadjusted for Urbanicity		After Adjustment for Urbanicity [a]	
	N events (total =78,142)	HR [b] (95% CI)	*N* events (total = 78,112)	HR [b] (95% CI)
All-cause	15,700	1.06 (1.03, 1.09)	15,689	1.07 (1.04, 1.10)
All cancer	6,417	1.10 (1.06, 1.16)	6,412	1.12 (1.06, 1.17)
Lung cancer	1,246	1.02 (0.92, 1.13)	1,246	1.03 (0.93, 1.15)
Cardiac disease	2,045	1.02 (0.95, 1.10)	2,044	1.04 (0.96, 1.13)
Cerebrovascular disease	1,599	1.13 (1.03, 1.24)	1,599	1.19 (1.08, 1.30)
Combined cardiovascular	3,644	1.07 (1.01, 1.13)	3,643	1.10 (1.04, 1.17)
Nonmalignant lung disease	1,030	0.85 (0.76, 0.94)	1,028	0.85 (0.76, 0.94)
"Other" deaths	4,609	1.05 (1.00, 1.10)	4,606	1.05 (0.99, 1.11)

[a] Additionally adjusted for degree of urbanicity in the year 2000.

[b] HRs are per 5-μg/m^3 increase in $PM_{2.5}$. Models are adjusted for age (time-axis), sex, recruitment year, smoking status and intensity, body mass index, occupation, diet, and alcohol intake.

Table 11. All-Cause and Cause-Specific Mortality in Relation to Ambient NO_2 in the Japan Public Health Center-based Prospective Study (JPHC)

	Unadjusted for Urbanicity		After Adjustment for Urbanicity [a]	
	N events (total = 76,075)	HR [b] (95% CI)	*N* events (total = 76,045)	HR [b] (95% CI)
All-cause	13,597	1.16 (1.12, 1.19)	13,586	1.21 (1.17, 1.26)
All cancer	5,664	1.18 (1.13, 1.23)	5,659	1.22 (1.15, 1.29)
Lung cancer	1,059	1.13 (1.01, 1.27)	1,059	1.15 (1.01, 1.31)
Cardiovascular disease	1,727	1.12 (1.03, 1.23)	1,726	1.19 (1.07, 1.32)
Cerebrovascular disease	1,411	1.03 (0.93, 1.14)	1,411	1.17 (1.04, 1.32)
Combined cardiovascular	3,138	1.08 (1.01, 1.16)	3,137	1.18 (1.10, 1.28)
Nonmalignant lung disease	822	1.11 (0.97, 1.26)	820	1.18 (1.01, 1.37)
"Other" deaths	3,973	1.19 (1.13, 1.26)	3,970	1.23 (1.15, 1.31)

[a] Additionally adjusted for degree of urbanicity in the year 2000.

[b] HRs are per 10-ppb increase in NO_2. Models are adjusted for age (time-axis), sex, recruitment year, smoking status and intensity, body mass index, occupation, diet, and alcohol intake.

When examining quartiles, the HRs for those in the highest exposed quartile (compared to those in the lowest) showed findings generally consistent with those reported in the main models (Appendix Tables A50 and A51). For example, those in the highest quartile of $PM_{2.5}$ exposure (>12.3 μg/m^3) had a significantly higher likelihood of death from any cause than those in the lowest quartile (<7.7 μg/m^3, HR: 1.14, 95% CI: 1.07, 1.20). Similarly, those in the highest quartile of NO_2 exposure (>11 ppb) were significantly more likely to die from any cause than those in the lowest quartile (<5 ppb). Examinations of HRs across different quartiles of exposure showed inconsistent findings in terms of dose–response relationships. However, the HR for all mortality remains relatively stable across all quartiles for both $PM_{2.5}$ and NO_2. Additionally, the highest HRs for combined cardiovascular disease appear to be highest in the third quartile for both $PM_{2.5}$ (HR: 1.33, 95% CI: 1.19, 1.49) and NO_2 (HR: 1.13, 95% CI: 1.02, 1.25).

Evaluation of the Assumption for Proportional Hazards A different series of variables may have potentially violated the proportional hazards assumption for the models related to $PM_{2.5}$ and NO_2. When evaluating the $PM_{2.5}$ models, dietary intake, sex, starting year, body mass index, and occupational status indicated that they may violate the proportional hazards assumption. Repeating analysis with the continuous variable (dietary intake) removed and the remaining categorical variables stratified showed no appreciable change to the previously observed HRs (Appendix Table A52), including that for all-cause mortality (1.07, 95% CI: 1.04, 1.10).

When evaluating the NO_2 models we observed that NO_2 itself may violate the proportional hazards assumption, alongside sex, starting year, and occupation. We therefore repeated analysis by stratifying the categorical variables and adding an interaction by follow-up time function into the NO_2 analysis (Appendix Table A53). The result of this analysis suggests that the effect of NO_2 may diminish during follow-up. For example, the beta coefficient for NO_2 and all-cause mortality was 0.37, with the time interaction indicating a decline of 0.03 per year of follow-up.

KOREAN MULTI-CENTER CANCER COHORT STUDY

The KMCC study population (N = 18,529) consisted of more women than men (60% versus 40%), with an average age of 55 at recruitment. Participants were followed for an average of 13 years, after which time 82% (15,118) were still alive. Among those who died, the most common cause of death was cancer (N = 1,072) followed by cardiovascular disease (N = 666). Participants tended to be never smokers (63%), have at least primary education (51%), and to be employed in some form (76%). The mean body mass index of participants was 24. Demographic information is further described on Appendix Table A54.

Levels of $PM_{2.5}$ were able to be predicted for all 18,529 members of the KMCC study, whereas NO_2 was predicted for 18,517 (99% of total) members. The mean (sd) concentration of $PM_{2.5}$ was 22.8 (3.1) μg/m^3 whereas for NO_2 it was 11.2 (2.7) ppb. There was a moderate level of correlation between NO_2 and $PM_{2.5}$ (0.57).

Due to missing information on covariates, fully adjusted $PM_{2.5}$ models were only available for 12,988 participants and fully adjusted NO_2 models for 12,981. However, the findings from unadjusted and partially adjusted models were directionally consistent with the fully adjusted models (Appendix Tables A55 and A56). In the fully adjusted models (Tables 12 and 13), $PM_{2.5}$ and NO_2 were negatively associated with all mortality outcomes (with the exception of NO_2 and cardiovascular disease). This observed association was statistically significant for $PM_{2.5}$ and all-cause mortality (HR: 0.80, 95% CI: 0.69, 0.93) and nonaccidental (HR: 0.82, 95% CI: 0.69, 0.96) mortality. The remaining relationships were negative but nonsignificant. The observed negative associations were nonstatistically significant for NO_2. For example, the HR for NO_2 and all-cause mortality was 0.84 (95% CI: 0.68, 1.03).

In two-pollutant models (Appendix Table A57), the negative association between $PM_{2.5}$ and mortality outcomes remained. The observed negative associations with NO_2 migrated toward a null finding.

Subgroup and Sensitivity Analysis

Smoking Status Tables with results stratified by smoking status (never, former, and current) are presented in Appendix Tables A58 and A60. When stratifying by smoking status,

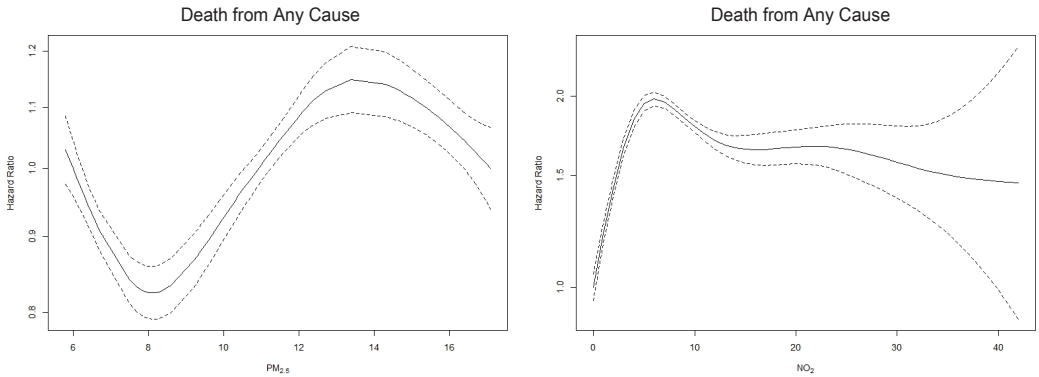

Figure 7. Penalized splines analysis (with four degrees of freedom) examining the relationship between exposure to $PM_{2.5}$ (left) and NO_2 (right) and all-cause mortality for the Japan Public Health Center-based Prospective Study (JPHC) (Model 3).

the negative directionality observed for both $PM_{2.5}$ and NO_2 was retained across the smoking strata, albeit with increased uncertainty owing to reduced numbers. This included the negative HR between $PM_{2.5}$ and all-cause mortality for never smokers (HR: 0.78, 95% CI: 0.63, 0.96), former smokers (HR: 0.86, 95% CI: 0.61, 1.23), and current smokers (HR: 0.72, 95% CI: 0.54, 0.96). The negative but nonsignificant findings for NO_2 generally remained with the exception of all-cause and nonaccidental mortality among current smokers, for whom the negative HR became significant (HR for all-cause: 0.66, 95% CI: 0.46, 0.95; HR for nonaccidental: 0.67, 95% CI: 0.46, 0.99).

When specifically examining female nonsmokers, the previously observed negative relationships for $PM_{2.5}$ and all-cause and nonaccidental mortality remained. For example, the HR between $PM_{2.5}$ and all-cause mortality for female nonsmokers was 0.79 (95% CI: 0.63, 1.00). By contrast, the relationship between NO_2 exposure and all-cause and cause-specific mortality became null. For example, the HR for NO_2 and all-cause mortality among female nonsmokers was 1.08 (95% CI: 0.78, 1.49).

No Pre-existing Disease at Baseline 9,676 participants reported having no pre-existing disease at the point of recruitment and had sufficient covariate information for the generation of prediction models (Appendix Table A61). Within this "healthy" population, the previously observed negative relationships between $PM_{2.5}$ and mortality outcomes remained, as were the generally null relationships with NO_2. This included the relationship between all-cause mortality and $PM_{2.5}$ where, within the "healthy" population, the derived HR was 0.81 (95% CI: 0.66, 0.99).

Restricting to Those Alive in 1998 The vast majority (99%) of those in KMCC for whom predictions could be made were still alive in 1998, resulting in 12,949 predictions for $PM_{2.5}$ and 12,942 predictions for NO_2 (Appendix Table A62). Overall, the findings of the models constructed from this slightly reduced group were identical to those reported in the main findings, including the reduced HR for all-cause mortality and $PM_{2.5}$ (HR: 0.80, 95% CI: 0.69, 0.93).

Urbanicity The degree of urbanicity for the year 2000 was positively correlated with assigned values of $PM_{2.5}$ (0.69) and NO_2 (0.63). Mean concentrations of $PM_{2.5}$ were higher for individuals living in urban areas than those living outside urban areas (28.0 $\mu g/m^3$ vs. 21.8 $\mu g/m^3$) as were concentrations of NO_2 (14.8 ppb vs. 10.5 ppb). No changes to the directionality of the observed HRs were observed following additional adjusting of models for absolute or degree of urbanicity (Tables 12 and 13, Appendix Tables A63 and A64). However, this additional adjustment resulted in the widening of the 95% CIs for each HR, causing the previously significant negative associations to lose their significance. For example, after adjusting for the degree of urbanicity in 2000, the significant and negative association between $PM_{2.5}$ and all-cause mortality remained negative (HR: 0.81) but was no longer statistically significant (95% CI: 0.65, 1.01).

Penalized Spline and Quartile Analysis Findings for penalized spline analysis for all-cause mortality and $PM_{2.5}$ and NO_2 are presented in Figure 8. All outcomes are presented in Appendix Figures A8 and A9. The values for all outcomes were nonsignificant in nonlinear analysis for both $PM_{2.5}$ and NO_2.

The HRs for those in the highest exposed quartile (compared to those in the lowest) showed findings which were generally consistent with those reported in the main models (Appendix Tables A65 and A66). For example, those in the highest quartile of $PM_{2.5}$ exposure (>24.8 $\mu g/m^3$) had a lower HR for all-cause mortality (0.77, 95% CI: 0.60, 0.99) than those in the lowest (<20.2 $\mu g/m^3$). Similarly, the relationship between NO_2 and all-cause and cause-specific outcomes remained generally null and nonsignificant. Examinations of HRs across different $PM_{2.5}$ quartiles showed some suggestion of a negative dose–response relationship between $PM_{2.5}$ and all-cause mortality, where the observed HR decreased from 1.02 in the second quartile to 0.90 in the third and 0.77 in the fourth.

Evaluation of the Assumption for Proportional Hazards Several variables may have violated the assumption for proportional hazards: smoking status, pack-years, sex, and occupation. After repeating analysis after the removal of the continuous variable (pack-years) and stratifying the remaining categorical variables, no appreciable difference in observed HRs between pollutant and outcomes was observed (Appendix Table A67).

MUMBAI COHORT STUDY

The participants in the MCS consisted of more men than women (58% vs. 42%), with an average age of 51. Participants were followed for an average of 5 years, after which time 91% (N = 128,305) were still alive. Specific causes of death were unavailable for 4,245 cases, but among those with known causes cardiovascular disease (N = 3,306) was the most common. Participants were largely nonsmokers (82%) with a mean body mass index of 22 and a primary (28%) or secondary (37%) education (Appendix Table A68).

Ambient $PM_{2.5}$ was able to be predicted for 126,377 (89% of total) individuals and NO_2 for 126,401 (89%) The average (sd) estimated level of ambient $PM_{2.5}$ was 34 (1.3) $\mu g/m^3$ and 23 (2.3) ppb for NO_2. There was no correlation between $PM_{2.5}$ and NO_2 (<0.01).

There was no missing information on covariates. In the fully adjusted models, $PM_{2.5}$ and NO_2 were positively and significantly associated with several mortality outcomes (Table 14). A 5-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with an increased risk of all-cause (HR: 1.15, 95% CI: 1.07, 1.24), nonaccidental (HR: 1.15, 95% CI: 1.05, 1.25), and cardiovascular disease (HR: 1.25, 95% CI: 1.08, 1.46). A 10-ppb increase in NO_2 was associated with an increased likelihood of all-cause (HR: 1.27, 95% CI: 1.17, 1.38), nonaccidental (HR: 1.36, 95% CI: 1.23, 1.51), cancer (HR: 1.51, 95% CI: 1.07, 2.14), and cardiovascular (HR: 1.38, 95% CI: 1.16, 1.65) mortality. These findings were consistent with both the unadjusted and partially adjusted models (Appendix Tables A69 and A70).

Table 12. All-Cause and Cause-Specific Mortality in Relation to Ambient $PM_{2.5}$ Exposure in the Korean Multi-center Cancer Cohort Study (KMCC)

	Unadjusted for Urbanicity		After Adjustment for Urbanicity [a]	
	N events (total = 12,988)	HR [b] (95% CI)	*N* events (total = 12,988)	HR [b] (95% CI)
All-cause	1,857	0.80 (0.69, 0.93)	1,857	0.81 (0.65, 1.01)
Nonaccidental	1,596	0.82 (0.69, 0.96)	1,596	0.82 (0.64, 1.04)
All cancer	608	0.80 (0.61, 1.04)	608	0.83 (0.56, 1.23)
Lung cancer	149	0.66 (0.39, 1.15)	149	0.72 (0.33, 1.60)
Cardiovascular disease	367	0.93 (0.67, 1.31)	367	0.90 (0.55, 1.48)
Nonmalignant lung disease	138	0.83 (0.49, 1.41)	138	0.63 (0.27, 1.47)

[a] Additionally adjusted for degree of urbanicity in the year 2000.

[b] HRs are per 5-μg/m^3 increase in $PM_{2.5}$. Models are adjusted for age (time-axis), sex, recruitment year, smoking status and intensity, body mass index, education, occupation, and alcohol intake.

Table 13. All-Cause and Cause-Specific Mortality in Relation to Ambient NO_2 Exposure in the Korean Multi-center Cancer Cohort Study (KMCC)

	Unadjusted for Urbanicity		After Adjustment for Urbanicity [a]	
	N events (total = 12,981)	HR [b] (95% CI)	*N* events (total = 12,981)	HR [b] (95% CI)
All-cause	1,857	0.84 (0.68, 1.03)	1,857	0.97 (0.86, 1.10)
Nonaccidental	1,596	0.85 (0.68, 1.07)	1,596	0.97 (0.85, 1.10)
All cancer	608	0.88 (0.61, 1.26)	608	1.00 (0.81, 1.24)
Lung cancer	149	0.67 (0.32, 1.38)	149	0.90 (0.59, 1.37)
Cardiovascular disease	367	1.17 (0.74, 1.87)	367	1.13 (0.86, 1.48)
Nonmalignant lung disease	138	0.96 (0.45, 2.06)	138	0.98 (0.62, 1.53)

[a] Additionally adjusted for degree of urbanicity in the year 2000.

[b] HRs are per 10-ppb increase in NO_2. Models are adjusted for age (time-axis), sex, recruitment year, smoking status and intensity, body mass index, education, occupation, and alcohol intake.

In two-pollutant models (Appendix Table A71), the HRs observed in the single-pollutant models generally remained, with only minor alterations to the point estimates. For example, the HR for $PM_{2.5}$ and all-cause mortality in the two-pollutant model was 1.19 (95% CI: 1.11, 1.28) and for NO_2 it was 1.30 (95% CI: 1.20, 1.41).

Subgroup and Sensitivity Analysis

Smoking Status Tables with results stratified by smoking status are presented in Appendix Tables A72 to A74. When stratifying by smoking status, the positive relationships observed in the main models remained, albeit typically with greater uncertainty owing to the reduction in numbers. This included the positive relationship between $PM_{2.5}$ and all-cause mortality for never smokers (HR: 1.08, 05% CI: 0.99, 1.18), former smokers (HR: 1.39, 95% CI: 0.99, 1.94), and current smokers (HR: 1.34, 95% CI: 1.16, 1.55). The same was observed for NO_2, where the positive relationship remained between all-cause mortality and never smokers (HR: 1.22, 95% CI: 1.10, 1.34), former smokers (HR: 1.51, 95% CI: 1.09, 2.09), and current smokers (HR: 1.32, 95% CI: 1.11, 1.56).

These findings generally remained when specifically examining female nonsmokers. For example, the HR for all-cause mortality and $PM_{2.5}$ was 1.10 (95% CI: 0.97, 1.24) and for NO_2 the HR was 1.17 (95% CI: 1.00, 1.36).

Restriction to Those Alive in 1998 In general, the majority of those in the MCS (76%) for whom predictions could be made were still alive in 1998. This resulted in 96,490 $PM_{2.5}$ predictions and 96,509 NO_2 predictions (Appendix Table A75). The findings of the models developed for both $PM_{2.5}$ and NO_2 in this subpopulation were consistent with the main models presented here. This included the overall relationship between $PM_{2.5}$ and all-cause mortality (HR: 1.34, 95% CI: 1.10, 1.63), and NO_2 and all-cause mortality (HR: 1.32, 95% CI: 1.14, 1.53).

Penalized Spline and Quartile Analysis Findings for penalized spline analysis for all-cause mortality and $PM_{2.5}$ and NO_2 are presented in Figure 9. All outcomes are presented in the Appendix Figures A10 and A11. The *P* values for nonlinear spline analysis were significant for both $PM_{2.5}$ and NO_2 for all outcomes except for lung cancer, indicating a potential nonlinear relationship within the data of this cohort. The relationship between all-cause mortality and $PM_{2.5}$ shows a rapid increase in the HR up until exposures of approximately 34 μg/m³ before remaining at an elevated but stable HR for higher levels of exposure. For NO_2, the HR appears to initially decrease at the lower levels of exposure until approximately 20 ppb whereupon the HR increases to a somewhat stable level for the higher levels of exposure, though HRs remained below 1.

When looking at quartiles, the HRs derived for those in the highest exposed quartiles of both $PM_{2.5}$ and NO_2 were generally consistent with those reported in the main models (Appendix Tables A76 and A77). For example, those in the highest quartile of $PM_{2.5}$ exposure (>34.0 μg/m³) had a significantly higher likelihood of death from any cause (HR: 1.11, 95% CI: 1.05, 1.18) than those in the lowest (<33.3 μg/m³). Similarly, those in the highest quartile of NO_2 exposure (>24.8 ppb) had significantly higher likelihoods of death from any cause (HR: 1.18, 95% CI: 1.12, 1.25) than those in the lowest (<21.4 ppb). Examinations of HRs across different quartiles of exposure showed inconsistent findings in terms of dose–response relationships. For example, the HR for all-cause mortality and $PM_{2.5}$ remained relatively stable across the second (1.18), third (1.14), and fourth (1.11) quartiles of exposure.

Evaluation of the Assumption for Proportional Hazards When evaluating the $PM_{2.5}$ models we observed that $PM_{2.5}$ itself may violate the proportional hazard assumption, at least for all-cause and nonaccidental mortality (all other outcomes showed no evidence that $PM_{2.5}$ violated the proportional hazard assumption). Additional variables that may have violated the assumption were sex and smoking status. We therefore repeated analysis by stratifying sex and smoking status and adding a time interaction term to the model. The result of this analysis was that the initial beta estimates observed for $PM_{2.5}$ remained positive with the time interaction indicating

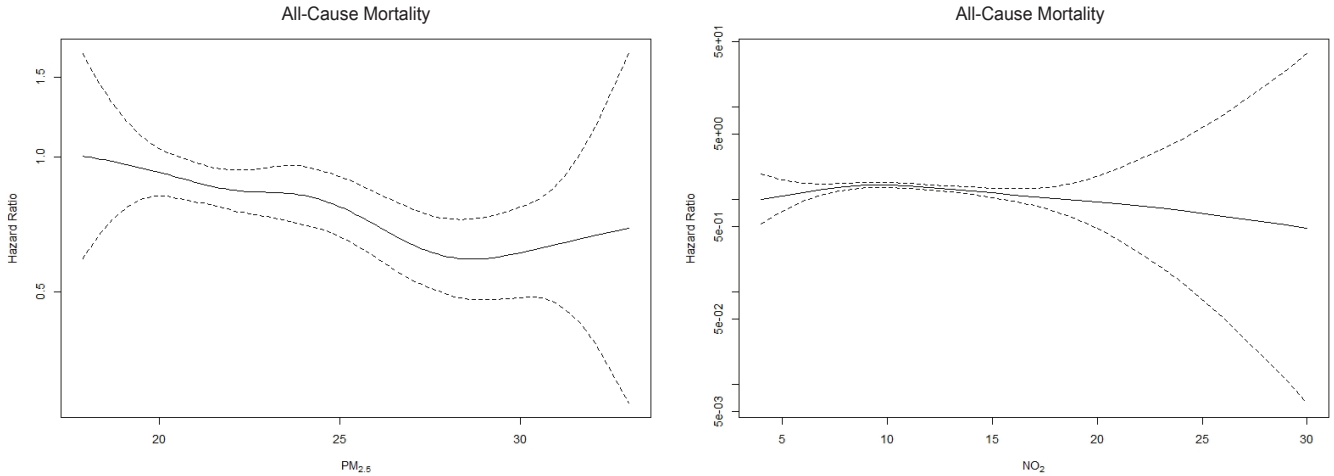

Figure 8. Penalized splines analysis (with four degrees of freedom) examining the relationship between exposure to $PM_{2.5}$ (left) and NO_2 (right) modeled and all-cause mortality for the Korean Multi-center Cancer Cohort Study (KMCC) (Model 3).

Table 14. All-Cause and Cause-Specific Mortality in Relation to Ambient Air Pollution Exposure in the Mumbai Cohort Study (MCS)

	$PM_{2.5}$		NO_2	
	N events (total = 126,377)	HR [a] (95% CI)	*N* events (total = 126,401)	HR [a] (95% CI)
All-cause	11,777	1.15 (1.07, 1.24)	11,779	1.27 (1.17, 1.38)
Nonaccidental	7,881	1.15 (1.05, 1.25)	7,883	1.36 (1.23, 1.51)
All cancer	721	0.95 (0.70, 1.28)	721	1.51 (1.07, 2.14)
Lung cancer	75	1.74 (0.72, 4.21)	75	1.39 (0.47, 4.14)
Cardiovascular disease	2,976	1.25 (1.08, 1.46)	2,977	1.38 (1.16, 1.65)
Nonmalignant lung disease	1,168	1.11 (0.89, 1.38)	1,168	1.22 (0.95, 1.58)

[a] HRs are per 5-μg/m³ increase in $PM_{2.5}$ and 10-ppb increase in NO_2. Models are adjusted for age (time-axis), sex, recruitment year, smoking status and intensity, body mass index, and education.

a declining relationship during follow-up. For example, the beta coefficient for $PM_{2.5}$ and all-cause mortality was 0.15, with the time interaction indicating a decline of 0.03 per year of follow-up (Appendix Table A78).

When examining NO_2 models we observed that sex and smoking status may violate the proportional hazards assumption. Therefore, we repeated analysis with these variables stratified and observed no change of note within the observed hazard ratios (Appendix Table A79).

DISCUSSION AND CONCLUSIONS

Ambient air pollution represents a significant source of death and disability. Within the current project, we have applied global maps of ambient $PM_{2.5}$ and NO_2 to the residential coordinates of people living across various Asian countries in an effort to examine the relationship between ambient air pollution and mortality outcomes in several populations for whom conventional measurements and LURs are not available.

One of our main findings was a positive, borderline non-significant relationship between ambient $PM_{2.5}$ and cardiovascular disease, as observed in the meta-analysis of contributing cohorts (pooled estimate: 1.05, 95% CI: 0.99, 1.12) for a 5-μg/m³ increase in $PM_{2.5}$. This is consistent with a recent systematic review and meta-analysis, in which Chen and Hoek (2020) reported that, in meta-analysis, a 10-μg/m³ increase in $PM_{2.5}$ was associated with a pooled relative risk (RR) of 1.11 (95% CI: 1.09, 1.14) for circulatory mortality. This corresponds to an approximate RR of 1.05 when adjusted to the 5-μg/m³ increase used in the current analysis. This is also reflected in the findings of the recently published PURE study where, through the use of the same global LUR maps used in the current project, ambient $PM_{2.5}$ was generated for a number of sites across the world (Hystad et al. 2020). The authors reported that a 10-μg/m³ increase in $PM_{2.5}$ was associated with a HR for cardiovascular disease mortality of 1.03 (95% CI: 1.00, 1.06).

However, in both the current project and elsewhere, considerable heterogeneity in effect estimates across different study centers was observed, which is reflected in the markers of heterogeneity when pooling individual cohorts in this project via random-effect meta-analysis (I^2 ranged from 0 to 95.8%). We observed HRs for $PM_{2.5}$ and cardiovascular disease ranging from 0.60 (HEALS) to 1.25 (MCS). Similarly, when examining cardiovascular mortality in relation to $PM_{2.5}$ across Europe, Beelen and colleagues (2014b) reported a combination of effect estimates ranging from negative (HR: 0.47, 95% CI: 0.20, 1.10 for SIDRIA-Rome) to strongly positive (2.43, 95% CI: 0.31, 18.92 for SAPALDIA), though the I^2 was 0. This heterogeneity in effect size and direction is likely a reflection of the complex interaction between the ambient environment and human health as opposed to suggesting a protective effect of ambient pollution, which runs counter to the established evidence base. $PM_{2.5}$ is a heterogeneous material, with its constitutional makeup being highly dependent on local sources (e.g., waste burning versus industrial activities). Given the heterogeneity in constituents, it follows that variability in effect sizes and the impact of various covariates may be observed. For example, when examining the elemental constituents of $PM_{2.5}$ and mortality, Chen and colleagues (2021) reported an HR of 1.03 (95% CI: 1.02, 1.05) for a 2-ng/m³ increase in vanadium, and Hvidtfeldt and colleagues (2021) reported increased risks of lung cancer in relation to exposure to several trace elements.

In addition to the findings described for $PM_{2.5}$, we also observed that NO_2 was positively associated with both all cancer (pooled estimate for a 10-ppb increase: 1.18, 95% CI: 1.13, 1.23) and lung cancer (pooled estimate for a 10-ppb increase: 1.13, 95% CI: 1.01, 1.26) mortality. In a systematic review

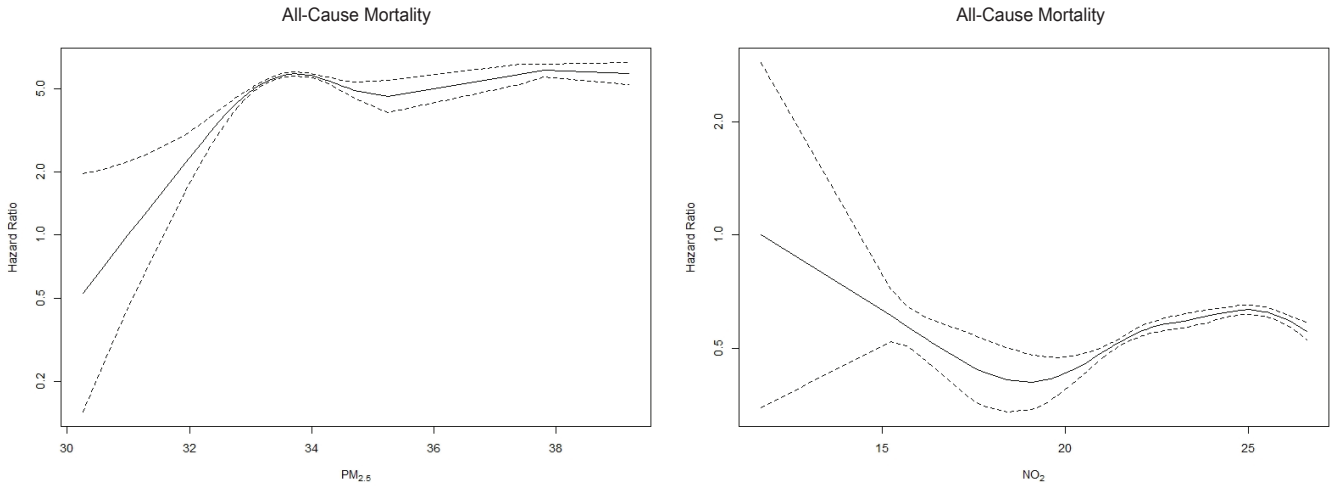

Figure 9. Penalized splines analysis (with four degrees of freedom) examining the relationship between exposure to $PM_{2.5}$ (left) and NO_2 (right) and all-cause mortality for the Mumbai Cohort Study (MCS) (Model 3).

and meta-analysis, Stieb and colleagues (2021) reported that a 10-ppb increase in NO_2 exposure was related to a pooled lung cancer HR of 1.08 (95% CI: 1.04, 1.13). However, they also observed positive relationships with all-cause, cardiovascular disease, and lung disease, which is counter to the findings observed in the current project, where mixed findings were observed. An additional feature to consider is that of contrast. Several of the cohorts examined, especially HEALS and MCS, experienced very high levels of exposure to $PM_{2.5}$ throughout. This means that the analysis was performed examining "high" versus "very high" exposures and that therefore the true health impact of those higher exposures may be lessened by this lack of contrast. There is some suggestion of this in the spline analyses performed for JPHC and MCS where "flatter" associations (i.e. the exposure–response relationship did not continually rise upward but instead remained static) were observed at higher levels of exposure, although this finding was not consistent across cohorts and warrants further examination.

Similarly to $PM_{2.5}$, notable variation in absolute exposures and effect estimates for NO_2 was observed. This again may likely represent a heterogeneity in sources. In particular, a very strong positive association between NO_2 exposure and mortality outcomes was observed for the HEALS cohort, despite there being relatively low levels and limited ranges in exposure (NO_2 exposure ranged from 6 to 10 ppb). Given the very larger confidence intervals indicating high levels of uncertainty and relatively limited confounder analysis, care needs to be taken when examining and interpreting such narrow ranges of exposure. NO_2 is primarily derived from traffic, with high levels in urban centers. In fact, both the JPHC and MCS represent populations from primarily urban centers, and both report positive relationships between NO_2 and mortality outcomes.

An additional observation of note when regarding the heterogeneity of findings was that the socioeconomic status of the underlying nation did not appear to contribute directly to the degree of effect between air pollution and recorded outcomes. The strongest positive relationships observed in the current study were for Japan and India, which represent high and low-middle income countries, respectively (World Bank 2021). Further, null or negative findings were observed for both high-, middle-, and low-income countries with no discernible pattern. Although we note that the number of available countries to properly evaluate this relationship is low, this may again reflect several factors, including differential constituents and sources of pollutants. An additional consideration is that of healthcare access. Previous research has reported that, especially in LMICs, physical restrictions in access to healthcare can have detrimental health effects (Aoun et al. 2015; Joseph et al. 2020). Therefore, individuals living in rural centers or with limited access to healthcare services may have worse health outcomes resulting from reduced healthcare access than those in urban areas where, despite having higher levels of pollution, healthcare services are more accessible. To evaluate this, as well as the impact of other features of the urban environment we additionally adjusted our models for markers of urbanicity. We found that additional adjustment for urbanicity had little impact on the HEALS, JPHC, or KMCC cohorts. However, adjusting for urbanicity in the CBCSCP cohort resulted in elevated (and significant) HRs between $PM_{2.5}$ and nonaccidental mortality and all-cancer mortality. Additionally, in the Golestan cohort, the HR related to NO_2 increased for several outcomes (all-cause mortality, cardiovascular mortality, and nonmalignant lung disease), albeit with nonsignificant CIs. It is worth noting however, there is a danger of co-linearity between pollutant and urban features, which must be considered as many features of urbanicity (e.g., road density) also contribute to levels of ambient air pollution. This is well evidenced by the consistently positive and moderate-to-strong correlations between predicted

pollutants and levels of urbanicity reported here. For example, in the JPHC, the correlation between NO_2 and urbanicity is 0.60.

STRENGTHS AND LIMITATIONS

The current project represents a large-scale examination of the health effects of air pollution across multiple diverse populations. The use of the ACC represents one of the project's major strengths as its centralized data system and data harmonization process provide an avenue through which data from multiple diverse cohorts can be combined to allow easier comparison across otherwise disparate groups. The ability to apply LUR models represents another major strength. The described models have previously been generated using robust measures with an explicit goal of generating a dataset that can be applied to a variety of settings, including the application to areas lacking routine monitoring or their own LUR models to rely on. Many LMIC countries around the world currently lack widespread routine monitoring, providing a valuable role for the future application of these models. This is especially the case within Asia and even more so in Africa where routine monitoring is frequently lacking and, with few exceptions, there are no conventional LUR models to rely upon. Despite their strengths, some limitations of the satellite models must be considered when evaluating their overall use. One important consideration is that of local accuracy. When applied and verified globally, the models reported overall good performance (e.g., an R^2 of 0.81 for the $PM_{2.5}$ models). However, as these models relied on ground-based data for validation, poorer model performance can be expected, and has been observed, in these regions with lower availability of pollution monitoring. This is especially the case for $PM_{2.5}$ where much higher levels of bias and variation were observed in Asia compared to North America and Central and Western Europe. This poorer model performance will likely lead to the introduction of more random "noise" to its predictions, likely directing findings toward the null. Therefore, further refinement through additional ground-based monitoring will be required to better apply these models in the future. A related limitation is that each cohort geocoded residential information following their own internal procedures and/or data availability. While this was performed to protect the privacy of individual participants, this has the potential to increase uncertainty in the relative geo-location of participants and thus their related environmental exposure.

A limitation of the current project relates to the recruitment period for various cohorts. Only two of the cohorts (Golestan and HEALS) recruited participants solely within the time period in which satellite models of ambient pollution were available. For the remaining cohorts, participants who were recruited outside of the range in which satellite models were available were instead assigned the closest available year (1998 for $PM_{2.5}$ and 1997 for NO_2). This may result in considerable exposure misclassification, especially among those who may have died in the period between recruitment and the assigned year of pollution. Additionally, any reductions in air pollution between the period of recruitment and assigned pollution year will result in further misclassification. To evaluate any impact of this, we repeated analysis after including only those participants who were alive from 1998 onward. This analysis produced findings similar to those in the main models reducing, but not eliminating, those concerns.

An additional limitation of the current project is that the overall number of contributing cohorts is relatively low. Out of the more than 20 cohorts participating in the ACC at the start of the project, only six ultimately consented to participate and provide data for use. This reduced number of cohorts limits our ability to fully leverage the full strength of the ACC, including the ability to perform detailed comparisons of low-, middle-, and high-income countries and more fully examine social, cultural, and economic differences between cohorts and countries. This limitation also impacts the generalizability of the findings to the broader community as while there does appear to be evidence of positive associations between air pollutants and mortality outcomes, the variation in those outcomes limits how much we can definitively say about the remaining sites in ACC and Asia in general.

One challenge when only examining ambient air pollution is that household air pollution is not included in the analysis. Household air pollution is typically generated through the combustion of solid (or other polluting) fuels such as wood, coal, and animal waste. This practice is carried out by approximately half of the world's population, primarily from LMIC, and contributes to approximately half of the overall deaths attributed to air pollution (approximately 3 to 4 million deaths). The absolute exposures recorded within these households can be tens, or even hundreds of times higher than those recorded in outdoor spaces (Hu et al. 2014, 2020), meaning that "additional" exposure derived from outdoor sources may be proportionately so small compared to indoor exposures that any effect on health is negligible. This is reflected in the Golestan cohort, which is the only cohort in this project to report on domestic fuel use. Within this group 66% of the population used some form of polluting fuel (wood, kerosene, or "other" organic fuel). When examining the effect of this on health, we observed that, people burning solid fuel or kerosene had a higher likelihood of death from any cause (HR for solid fuel: 1.24, 95% CI: 1.09, 1.44; HR for kerosene: 1.14, 95% CI: 1.08, 1.20) than those not using either of these fuels. Similarly, in the multicountry PURE study (Hystad et al. 2019), solid fuel use was associated with mortality HRs of 1.12 (95% CI: 1.04, 1.21) when compared to electricity or gas users. In India and Bangladesh, as many as 60% and 80% of people also burn solid fuels, respectively, (World Bank 2016) meaning that for the MCS and HEALS cohorts, the observed risk estimates may be biased by the absence of this potentially important covariate information. Future (and ongoing) work should consider the interplay between household and ambient air pollution with human health (Hosgood et al. 2019).

IMPLICATIONS OF FINDINGS

In this study of ambient air pollution and noncommunicable mortality within several Asian cohorts we observed a positive relationship between ambient $PM_{2.5}$ and cardiovascular mortality and ambient NO_2 and cancer and lung cancer mortality. These findings, consistent with those reported elsewhere in the literature, indicate the utility of applying global land use models to examine the health effects of ambient air pollution in regions with limited routine monitoring or exposure models.

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HEI QUALITY ASSURANCE STATEMENT

The conduct of this study was subjected to independent audits by RTI International staff members Drs. Linda Brown, Prakash Doraiswamy, and David Wilson. These staff members are experienced in quality assurance (QA) oversight for air quality monitoring, modeling and exposure assessment, epidemiological methods, and statistical modeling.

The QA oversight program consisted of a remote audit of the final report and the data processing steps. Key details of the dates of the audit and the reviews performed are listed below.

Audit 1: Final Remote Audit, November 2022 – January 2023

The final remote audit consisted of two parts: (1) review of the final project report, and (2) audit of data processing steps. The review of the final report focused on ensuring that the methods are well documented, and the report is easy to understand. The review also examined if the report highlighted key study findings and limitations. The data audit included (1) a remote live demonstration of selected data processing codes, and (2) the review of the codes for data reduction, processing and analysis, and model development. This specific portion of the audit was restricted to the key components of the study and associated findings. Selected codes for exposure assessment and epidemiological model development were sent to RTI. No raw data were sent to RTI due to data confidentiality restrictions.

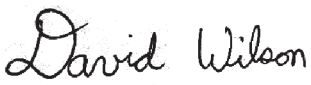
The codes were reviewed at RTI to verify, to the extent feasible, linkages between the various scripts, confirmation of the models reported, and verification of key tables. The codes appear to be largely consistent with the models described in the report and followed the overall model development procedure described. The values themselves could not be generated at RTI due to unavailability of the input data.

The remote live demonstration included a real-time execution of selected codes generating key tables and figures in the report. Values generated by the codes during the real-time demonstration matched the values in the report. Except for a few discrepancies, no major quality-related issues were identified from the review of the codes and the report. Recommendations were made to address noted discrepancies and typographical errors, add clarifying statements for some findings, and make general edits for improved clarity.

A written report was provided to HEI. The QA oversight audit demonstrated that the study was conducted according to the study protocol. The final report, except as noted in the comments and recommended corrections, appears to be representative of the study conducted.

Linda Morris Brown, MPH, DrPH, Epidemiologist, Quality Assurance Auditor

Prakash Doraiswamy, PhD, Air Quality Specialist, Quality Assurance Auditor



David Wilson, PhD, Statistician, Quality Assurance Auditor

January 31, 2023

MATERIALS AVAILABLE ON THE HEI WEBSITE

The Appendix contains supplemental tables and figures not included in the main report. It is available on the HEI website at *www.healtheffects.org/publications*.

Appendix: Supplementary Tables and Figures

Community-based Cancer Screening Program

Golestan Cohort Study

Health Effects for Arsenic Longitudinal Study

Japan Public Health Center-based Prospective Study

Korean Multi-center Cancer Cohort Study

Mumbai Cohort Study

ABOUT THE AUTHORS

George S. Downward received his Ph.D. in environmental epidemiology from Utrecht University and is currently an assistant professor of global health at the Julius Centre for Global Health, University Medical Centre Utrecht. His research interests are the combination of global and environmental health to examine risk factors in resource limited settings.

Roel Vermeulen received his Ph.D. in environmental epidemiology from Utrecht University and is currently a professor of environmental epidemiology and exposome science at Utrecht University and the director of the Institute for Risk Assessment Sciences. His research interests are in examining environmental risk factors for noncommunicable diseases with a strong emphasis on integrating epidemiology, high quality exposure assessment, and molecular biology into multidisciplinary investigations.

Research Report 213, *Ambient Air Pollution and All-Cause and Cause-Specific Mortality in an Analysis of Asian Cohorts*, G. S. Downward and R. Vermeulen

INTRODUCTION

Air pollution is a major global public health risk factor. There is now broad expert consensus that exposure to air pollution causes an array of adverse health effects based on evidence from a large body of scientific literature that has grown exponentially since the mid-1990s (IARC 2016; Thurston et al. 2017; U.S. EPA 2016, 2019; WHO 2021).

Based on that evidence, the Global Burden of Disease (GBD*) project estimated that in 2019 air pollution ranked as the leading environmental risk factor for global mortality, surpassed only by high blood pressure, tobacco use, and poor diet (HEI 2020). The air pollution burden varies widely around the globe, and is highest in countries in Asia and Africa, partly due to the typically high exposure levels in those regions.

Much of what is currently known about the adverse effects of ambient air pollution comes from studies conducted in high-income regions, especially North America and Europe, with relatively low air pollution levels. Studies of long-term exposure and morbidity and mortality in low- and middle-income countries have emerged more recently. Hence, an integrated exposure–response (IER) function was developed to estimate mortality relative risks across the global exposure range and has been used by the GBD collaboration and the World Health Organization (WHO) to estimate the burden of disease attributable to particulate matter ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$). The IER function combines relative risk estimates from various $PM_{2.5}$ sources, including active and passive smoking, to fill in the knowledge gap of air pollution studies in high exposure settings (Burnett et al. 2014). In the most recent GBD estimates (GBD 2019 Risk Factors Collaborators 2020), active smoking studies were excluded from the IER function to characterize risks at high exposure, because the few new studies of high air pollution conditions in Asia provided enough information so that evidence from active smoking data is no longer necessary to use. The number of studies of long-term air pollution and health in Asia, however, remains limited to date, and there is a clear research gap with respect to the true size of the ambient air pollution and mortality associations in that region.

Dr. Vermeulen's study was funded through a special invitation based on several scientific and strategic considerations. At Utrecht University, the Netherlands, Dr. Vermeulen proposed to evaluate the association between long-term exposure to ambient air pollution and all-cause and cause-specific mortality in a pooled analysis of 23 Asian cohorts from the Asia Cohort Consortium (Aim 1). Moreover, he proposed to explore the heterogeneity in mortality risks among cohorts in the context of cultural, social, economic, or infrastructural differences between countries (Aim 2). Although the application came outside of a specific Request for Applications, it was reviewed using the same two-stage process: external reviewers evaluated the technical quality of the proposed work, followed by a discussion of strengths and limitations by the Research Committee. The HEI Research Committee recommended Dr. Vermeulen's application for funding because of the strong design features, the large number of participating cohorts, and the availability of individual-level covariate information. In addition, they appreciated that the cohorts were already harmonized, making it a cost-efficient and low-risk proposal. Dr. Vermeulen recruited Dr. George S. Downward as the analytical project lead.

During the course of the work, there were several unforeseen setbacks regarding cohort participation for various reasons, and only six of the original 23 cohorts that had expressed interest in participating were eventually included in the analyses. Therefore, the current report is focused solely on Aim 1. Aim 2 was not further pursued due to the small number of cohorts included in the final analyses.

This Commentary provides the HEI Review Committee's evaluation of the study. It is intended to aid the sponsors of HEI and the public by highlighting both the strengths and limitations of the study and by placing the Investigators' Report into a broader scientific perspective.

Dr. Roel Vermeulen's (principal investigator) 2-year study, "Long-Term Outdoor Air Pollution and Cause-Specific Mortality in a Pooled Analysis of 23 Asian Cohorts," began in July 2018. Total expenditures were $236,000. The draft Investigators' Report from Downward (first author) and Vermeulen was received for review in September 2021. A revised report, received in August 2022, was accepted for publication in September 2022. During the review process, the HEI Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Review Committee's Commentary.

* A list of abbreviations and other terms appears at the end of this volume.

SCIENTIFIC BACKGROUND

The study by Downward and Vermeulen assessed the association between long-term exposure to ambient air pollution and all-cause and cause-specific mortality in an analysis of six Asian cohorts, with more than 340,000 participants (see Commentary Table 1 and Commentary Figure 1). The investigators estimated exposure to $PM_{2.5}$ and nitrogen dioxide (NO_2) at the residence of the participants for the year of recruitment using global satellite-based models. They applied single-pollutant Cox proportional hazard models to assess the association between air pollution exposure and all-cause and cause-specific mortality adjusted for important confounders, as described in more detail below.

STUDY POPULATION

The current study leverages the *Asia Cohort Consortium,* a multicenter collaborative effort since 2008 that consists of more than one million people to date from several dozen cohorts from 10 Asian countries. The Consortium seeks to understand the relation between genetics, environmental exposures, and the etiology of disease. To be eligible, cohorts must have information on mortality outcomes and important confounding variables, such as smoking and body mass index. Data on those variables were harmonized before entering the Consortium to ensure comparability.

The final analyses included six cohorts from the Asia Cohort Consortium and represented more than 340,000 adult participants in six countries (Commentary Figure 1, which includes the study name abbreviations). The study included three high-income countries (Japan, Taiwan, and Republic of Korea), one lower-middle country (Iran), and two low-income countries (Bangladesh, and India); designations are based on 2006 World Bank classifications. The cohorts were general population studies and varied widely in size, study period, recruitment method, geographical scope, exposure assignment, and outcome assessment (Commentary Table 1). The Indian MCS and the Japanese JPHC studies were the largest cohorts by far. Participants were recruited from 1991 to 2008 and followed-up between 5 and 23 years. Some cohorts were conducted in a single city or district (e.g., the Indian MCS and Bangladeshi HEALS), and others included much larger areas in a country (e.g., the Japanese JPHC). Mean exposures varied from 8 to 58 $\mu g/m^3$ for $PM_{2.5}$ and 7 to 23 ppb for NO_2. Correlations between $PM_{2.5}$ and NO_2 exposures varied from <0.01 to 0.57 (Commentary Table 1).

EXPOSURE ASSESSMENT

The investigators estimated exposure at the residence of the participants for $PM_{2.5}$ and NO_2 by using existing global satellite-based models and building on the exposure methods that were also used in the GBD project (Larkin et al. 2017; van Donkelaar et al. 2015, 2016). The global models provided high resolution (1 km^2 for $PM_{2.5}$, 100 m^2 for NO_2) annual average concentrations for 1998 (or 1997 in case of NO_2) to 2008. The method is a sophisticated integration of primarily satellite data, with a chemical transport model, land-use information, and ground-monitoring data included as well. The models were validated against ground-based monitor data, with an overall R^2 of 0.81 and 0.54 for $PM_{2.5}$ and NO_2, respectively. The estimates were assigned to study participants based on geocoded residential location data, but for the year of recruitment only. The 1998 exposure estimate was assigned for the participants that were recruited from 1991 to 1997 (i.e., before the global model estimates became available). Note that in four cohorts, exact address data were available for the year of recruitment; for the remaining cohorts (Indian MCS and Iranian Golestan) aggregated address data were used (e.g., postal codes).

OUTCOME ASSESSMENT

The study included both all-cause mortality and cause-specific mortality outcomes: nonaccidental, all cancer, lung cancer, cardiovascular disease, and noncancer lung disease mortality. The outcome assessment was performed by each individual cohort, typically through active follow-up or linkage to death registries. The same International Classification of Diseases (ICD) 9 or 10 coding was used for the different outcome categories across the cohorts except for the Japanese JPHC cohort. The JPHC cohort used slightly different ICD codes, particularly for cardiovascular disease. The JPHC cohort also did not have information on nonaccidental deaths.

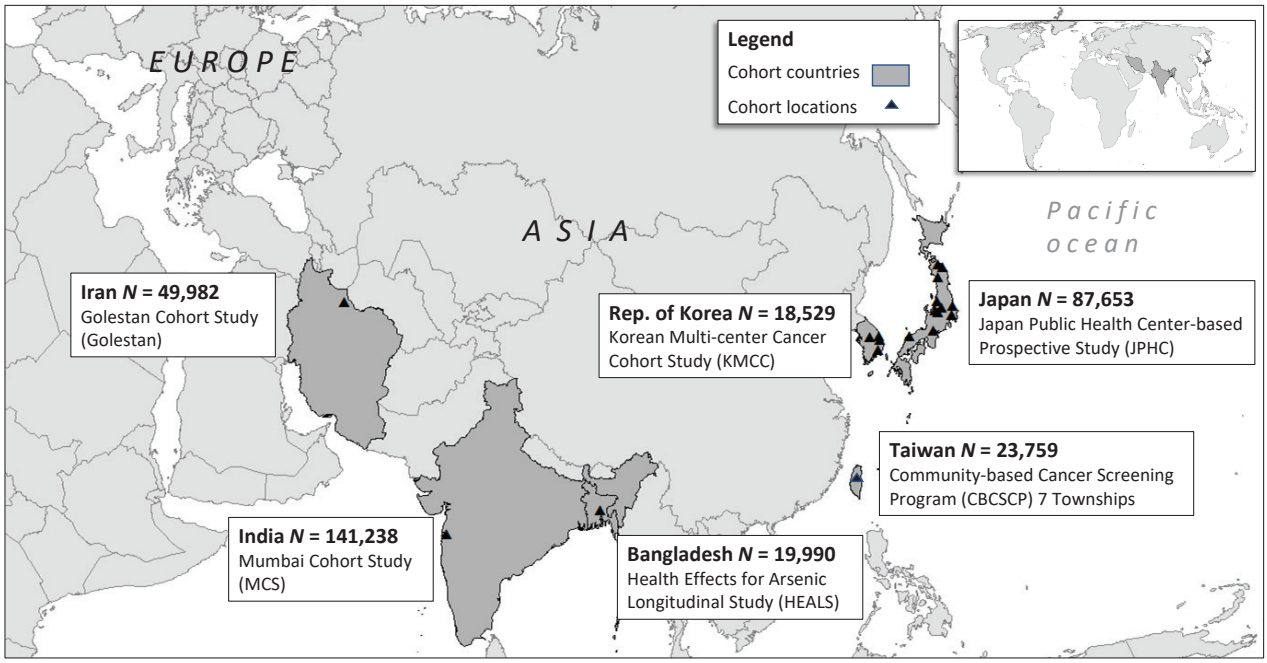
ANALYSES

The investigators applied single-pollutant Cox proportional hazard models to assess the association between air pollution exposure and all-cause and cause-specific mortality. Models were adjusted for age (time axis), sex, recruitment year, smoking status, pack-years, body mass index, and a measure of socioeconomic status (education or employment). In addition, models adjusted for alcohol intake or diet for all cohorts except the Indian MCS and Bangladeshi HEALS cohorts. Models from one cohort (Iranian Golestan) were also adjusted for domestic fuel use — an indicator of household air pollution. That indicator was missing for the other cohorts.

The investigators calculated hazard ratios for each cohort separately and then combined using random effects meta-analysis. Associations were reported per 5- and 10-ppb increment in $PM_{2.5}$ and NO_2, respectively. For each cohort, the investigators tested assumptions for the Cox proportional hazard models, ran two-pollutant models, and characterized the exposure–response function using splines and exposures by quartiles. Furthermore, they assessed the robustness of the associations by conducting several sensitivity and subgroup analyses. Notably, they conducted a sensitivity analysis in which associations were adjusted for urbanicity. Moreover, they reran analyses for the subcohorts of participants alive in 1998 when global model estimates became available. Note that no meta-analyses were conducted on any of the sensitivity analysis results.

Commentary Table 1. Key Characteristics of the Six Asian Cohorts at Recruitment (ordered by sample size)

Study Name	Location	Recruitment Years	Average Years of Follow-up	Sample Size	Mean Age	Mean Exposure $PM_{2.5}$ ($\mu g/m^3$)	Mean Exposure NO_2 (ppb)	Correlation $PM_{2.5}$ and NO_2	Exposure Assignment	Outcome Assessment
MCS	Mumbai, India	1991–1997	5	141,238	51	34	23	<0.01	Postal code	Active follow-up at regular intervals
JPHC	11 regions in Japan	1990–1995	20	87,653	52	11	9	0.50	Residential address	Death registries
Golestan	Gonbad city and surrounding rural area in Iran	2004–2008	11	49,982	52	32	9	0.54	Community level	Active follow-up at 1-year intervals
CBCSCP	7 townships in Taiwan	1991–1992	23	23,759	47	8	9	0.14	Residential address	Health examinations, medical records, and cancer and death registries
HEALS	Araihazar in Bangladesh	2000–2008	10	19,990	37	58	7	0.46	Residential address	Active follow-up at 1-year intervals
KMCC	4 areas in the Republic of Korea	1993–2005	13	18,529	55	23	11	0.57	Residential address	Health insurance, cancer, and death registries
TOTAL	6 countries	1991–2008	5–23	341,151	37–55	8–58	7–23	<0.01–0.57		



Commentary Figure 1. Geographical location of the six Asian cohorts.

SUMMARY OF RESULTS ACROSS COHORTS

- The meta-analytical summary effect estimates documented no association between long-term exposure to ambient $PM_{2.5}$ and all-cause mortality and cause-specific mortality, except for a positive association with cardiovascular mortality (Commentary Figure 2). The combined estimate for cardiovascular mortality was 1.05 per 5-μg/m^3 increment and was borderline significant (95% confidence interval 0.99–1.12).
- For ambient NO_2, the combined estimates showed positive associations for all mortality outcomes, in particular the cancer outcomes. The combined estimate for all-cancer and lung cancer mortality were 1.18 and 1.13 per 10-ppb increment, respectively; both estimates were statistically significant. Combined estimates were heavily driven by positive associations from a single cohort (see below).

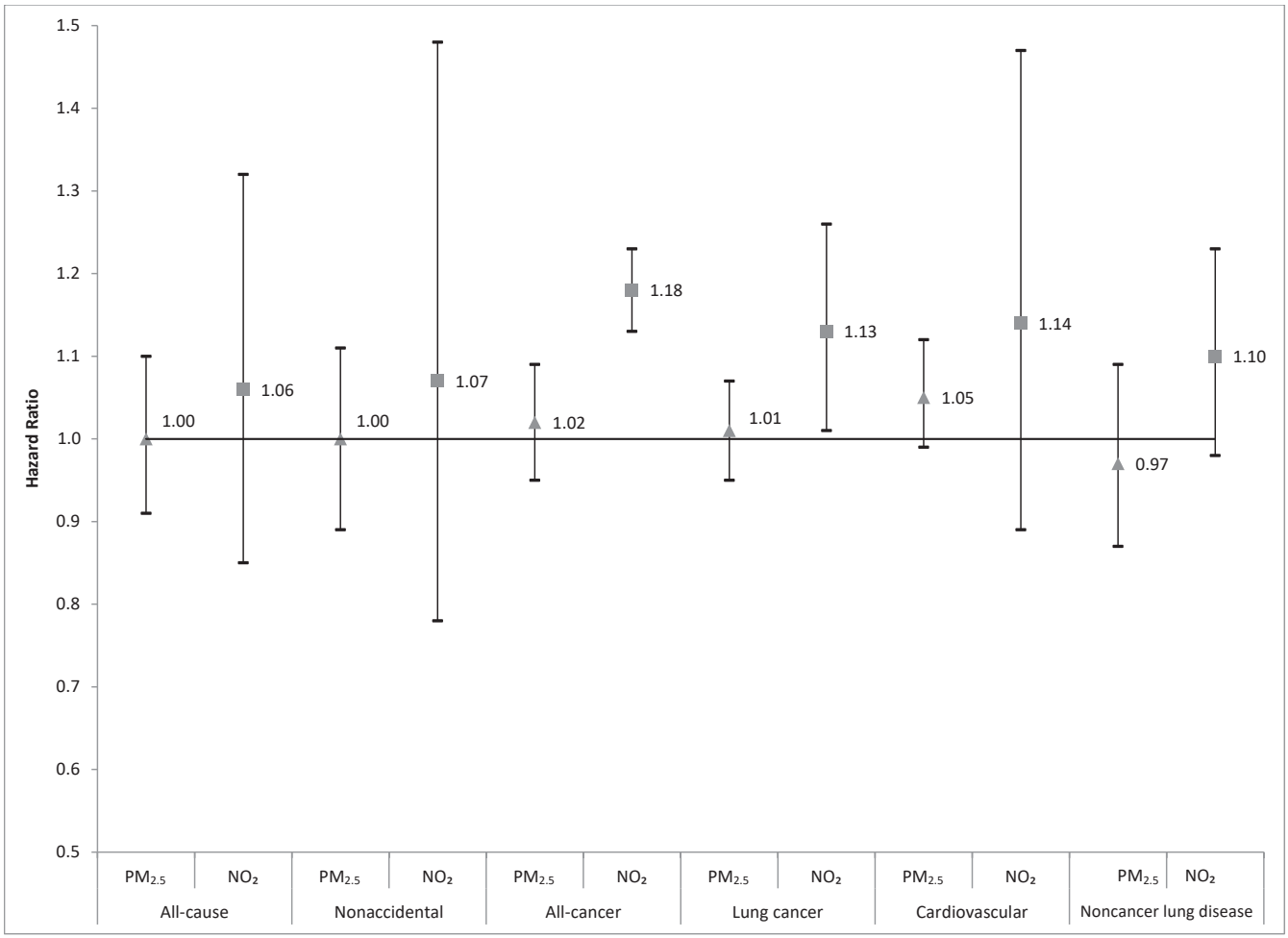
SUMMARY OF RESULTS WITHIN COHORTS

- The two largest cohorts — the Indian MCS and the Japanese JPHC — and the smaller Taiwanese CBCSCP cohort reported positive associations between ambient $PM_{2.5}$ and cardiovascular mortality (Commentary Table 2). Those associations were statistically significant and fairly robust to further adjustment for urbanicity. The other three cohorts did not find an association with cardiovascular mortality.
- For ambient NO_2, the combined estimates for cancer outcomes were heavily influenced by the positive association in the Japanese JPHC cohort. This cohort carried greater than 90% of the weight in meta-analyses. Most other cohorts documented no association with cancer outcomes.
- Large heterogeneity of the findings was reported across the cohorts, with null, negative, or positive findings, with sometimes no apparent pattern (Commentary Table 2). The Iranian Golestan and Korean KMCC cohorts consistently reported null findings. Findings from the Bangladeshi HEALS cohort were uninformative, due partly to the large confidence intervals and minimal exposure contrast. Hence, this cohort carried the lowest weight in the meta-analyses (often below 1%).

HEI REVIEW COMMITTEE'S EVALUATION

In its independent review of the study, the HEI Review Committee thought the research was well motivated and addressed a clear research gap. There are few long-term air pollution and health studies in Asia, and additional studies are urgently needed. This report adds to the overall knowledge base on health outcomes associated with air pollution in Asia. Although the number of cohorts participating was lower than anticipated when the study was funded, the inclusion of six harmonized cohorts ensured a large sample size.

In summary, the study documented large heterogeneity of the findings across the individual cohorts, with no association between long-term exposure to ambient $PM_{2.5}$ and all-cause mortality and cause-specific mortality in meta-analyses of all cohorts combined, except for a borderline significant positive association with cardiovascular mortality. Several individual



Commentary Figure 2. Meta-analysis for the association between exposure to $PM_{2.5}$ (per 5 µg/m³) and NO_2 (per 10 ppb) and mortality in the six Asian cohorts combined. Associations were from single-pollutant models and adjusted for important potential confounders, such as smoking, body mass index, and socioeconomic status.

cohorts (i.e., Indian MCS, Japanese JPHC, and Taiwanese CBCSCP), however, did display positive significant associations between ambient $PM_{2.5}$ and cardiovascular mortality. For ambient NO_2, the combined estimates showed positive associations for all mortality outcomes, in particular the cancer outcomes, although estimates were heavily driven by positive associations from the Japanese JPHC cohort.

The Committee noted several strengths of the research. First, it recognized the benefits of leveraging the Asia Cohort Consortium to study health effects of ambient air pollution. The study included data from six cohorts, representing more than 340,000 adult participants, which is a large sample size. The data were already harmonized and included both all-cause mortality and cause-specific mortality outcomes. There were also data available for several individual-level lifestyle factors, such as smoking status and intensity, body mass index, and diet, and the analyses were adjusted accordingly. As such, the study provides a useful model for future applications of harmonized cohort data to study the effects of air pollution on human health.

Second, the Committee appreciated the uniform assessment of long-term $PM_{2.5}$ and NO_2 using state-of-the-art exposure estimation methods. Exposures to $PM_{2.5}$ and NO_2 were estimated at a reasonably high spatial resolution — residential address level for most of the cohorts — and took advantage of global satellite-based models. The existing monitoring networks have limited spatial coverage with typically few stations in suburban and rural locations, particularly in low- and middle-income countries. According to the 2022 WHO Air Quality database, 40% of countries have no ground-level PM monitors. Ground-based monitor data are even sparser for NO_2, with 62% of countries with no monitors (WHO 2022). In addition, most existing monitoring networks have insufficient density to capture small-scale (within-city) variation of air pollution, which can be substantial for certain pollutants, such as NO_2.

Commentary Table 2. Summary of Null, Negative, or Positive Findings in the Six Asian Cohorts

	$PM_{2.5}$						NO_2					
	MCS	JPHC	Golestan	CBCSCP	HEALS	KMCC	MCS	JPHC	Golestan	CBCSCP	HEALS	KMCC
	India	Japan	Iran	Taiwan	Bangladesh	Korea	India	Japan	Iran	Taiwan	Bangladesh	Korea
All-cause	+	+	0	0	0	– (0)	+	+	0	–	+	0
Nonaccidental	+	NR	0	0 (+)	0	– (0)	+	NR	0	–	+	0
All-cancer	0	+	0	0 (+)	0	0	+	+	0	0	0	0
Lung cancer	0	0	0	0	0	0	0	+	0	0	0	0
Cardiovascular	+	+	0	+	0	0	+	+	0	0	+	0
Noncancer lung disease	0	–	0	0	0	0	0	0 (+)	0	– (0)	0	0

0 = null findings; – = negative association; + = positive association; NR = not reported. In parentheses, the summary of findings after additional adjustment for urbanicity when those findings differed from the main analysis. Note that in the Indian MCS cohort it was assumed that this cohort was fully urban, and no further adjustment was conducted.

Recent developments in satellite-based remote sensing and other exposure methods and models offer new ways to provide air pollution estimates that cover large areas in a country, whole countries, or even multiple countries, with a sufficiently high degree of spatial resolution. The global satellite-based models applied in this study allowed exposure to be estimated for a large urban and rural population in six Asian countries. The Committee also thought the analyses were generally straightforward and clearly presented in the report. For example, the Committee appreciated the various sensitivity and subgroup analyses, including the additional adjustment for urbanicity in a sensitivity analysis.

Although the Review Committee broadly agreed with the investigators' conclusions, it identified limitations detailed below that should be considered when interpreting the results.

INADEQUATE ADJUSTMENT LIKELY FOR CHARACTERISTICS THAT CORRELATE WITH AIR POLLUTION AND MORTALITY

The Committee was concerned that residual confounding was likely in the main analyses due to inadequate adjustment for characteristics that correlate with air pollution and mortality, most notably socioeconomic status and urbanicity. These characteristics are likely related to both exposure and health, and difficult to fully capture based on the available indicators. Findings sometimes differed for models that adjusted for urbanicity as compared to those that did not (see Commentary Table 2). The Committee thought the authors should have adjusted for urbanicity in their main models instead of adjusting for urbanicity in a sensitivity analysis, even if there was some modest collinearity between air pollution estimates and urbanicity in some cohorts, as documented by the investigators. The Committee does appreciate the tables in the main text that compare the results with and without the urbanicity variable, additions made in response to earlier Committee comments.

The need for adjustment for urbanicity was also shown in the recent Prospective Urban and Rural Epidemiology (PURE) study (Hystad et al. 2020). The primary analyses adjusted for an indicator variable (urban or rural location). Models that further adjusted for "unmeasured differences between urban and rural areas within centers, as well as differences across centres" resulted in notable different results, especially for mortality. For example, the negative association between $PM_{2.5}$ and all-cause mortality flipped to a positive association.

In the PURE study a notable negative association was also observed between markers of healthcare (hospital admissions or medication use) and deaths; this result suggests that poorer access to healthcare could be responsible, at least partly, for the higher mortality rates in low- and middle-income countries. Socioeconomic status and access to healthcare are closely related in many settings (Dagenais et al. 2020).

Since socioeconomic status influences where people live and is related to both exposure and health, this is often considered to be one of the most important confounders in air pollution epidemiology (Clark et al. 2014; Hajat et al. 2015; O'Neill et al. 2003). Additionally, there is evidence of differing correlations between socioeconomic status and air pollution exposure by location, highlighting the importance of adjusting for socioeconomic status based on the specific setting (Cesaroni et al. 2010; Hajat et al. 2013; Wang et al. 2022).

The current study adjusted for socioeconomic status in a fairly basic way with the use of an individual socioeconomic status indicator (i.e., education or employment) as a fixed covariate effect in the health model of the individual cohorts. The Committee thought that more effort to capture individual

or area-level socioeconomic status in the study would have been beneficial.

HETEROGENEITY IN EFFECT ESTIMATES

The Committee noted that although the same exposure assessment and statistical methods were used, large heterogeneity of the findings was reported across the cohorts, with null, negative, or positive findings, with sometimes no apparent pattern. Some heterogeneity of the findings is expected, given the wide diversity of the six Asian cohorts. Heterogeneity is likely due, for example, to differences in populations, with different exposure levels, pollution sources and mixtures, time periods, age structure and follow-up times, socioeconomic status, urban–rural status, health status, access to healthcare, and outcome misclassification. Some specific differences across the cohorts were particularly striking, such as the low exposure contrast (Indian MCS and Bangladeshi HEALS), the low correlation between $PM_{2.5}$ and NO_2 (Indian MCS and Taiwan CBCSCP), the large percentage of illiterate population (Iranian Golestan), the short follow-up time (Indian MCS), the young study population (Bangladeshi HEALS), the rural location (Bangladeshi HEALS), particularly urban location (Indian MCS), and the low percentage of number of deaths, in particular for cancer (Indian MCS). Those and other differences could have contributed to the large heterogeneity of the findings observed in the current study.

In the systematic reviews underpinning the 2021 WHO Air Quality Guidelines for long-term exposure to $PM_{2.5}$ and NO_2, a high degree of heterogeneity of the findings was also observed; this result was expected given that studies were included from across the globe (Chen and Hoek 2020; Huangfu and Atkinson 2020). Most of the heterogeneity in those studies, however, was due to heterogeneity in the magnitude of the positive association, not in the direction of the association (negative or positive). In particular, the negative associations in the current study are puzzling and run counter to the evidence base that documents clear evidence that long-term exposure to ambient air pollution is associated with increased mortality.

In the current study, a thorough evaluation of heterogeneity in mortality risks between cohorts in the context of cultural, social, economic, or infrastructural differences between countries was originally planned but was not pursued due to the small number of cohorts included in the final analyses. Although that decision is understandable given the data available to the investigators, the Committee would have been interested in better understanding potential sources of heterogeneity in the findings and noted that many questions have been unresolved.

Although the analyses were straightforward and clearly presented in the report, the study could have benefitted from a more detailed discussion and interpretation of all results, including the various sensitivity and subgroup analyses. For example, the added exposure–response function analysis was not tied together with the predetermined categorical analysis. Also, the Cox proportional hazards assumptions were violated for $PM_{2.5}$ (Indian MCS) and NO_2 (Japanese JPHC) for some mortality outcomes; the implications of which were not thoroughly addressed by the investigators. Also, an evaluation of potential selection bias due to the loss of several key cohorts from their original plans would have been useful. These and other issues limit what can be inferred from this study.

SUBSTANTIAL TEMPORAL AND SPATIAL MISALIGNMENT OF THE EXPOSURE DATA

The Committee had concerns about the exposure assessment approach because of the substantial temporal and spatial misalignment of the data. The study relies on an historical exposure assessment at recruitment that can be temporally misaligned with the health data by 5 to 23 years, depending on the cohort. Several issues of concern with the exposure assessment were noted by the Committee. First, the back extrapolations used for the participants before 1998 when the global model estimates became available to match the exact period of interest could introduce additional exposure error. The two largest cohorts (Indian MCS and Japanese JPHC) might be particularly affected by this misalignment, because those were also among the oldest cohorts. A sensitivity analysis in the subcohorts of participants alive in 1998 when global model estimates became available were generally consistent with the findings from the full cohorts, which was reassuring. Second, information on residential addresses after recruitment (i.e., moving history) was not available. Hence, residential mobility was not incorporated in the exposure assessment. Residential mobility can be substantial, especially in some low-and middle-income regions that are undergoing rapid urbanization in recent decades with population migration from rural to urban regions. Third, for a few cohorts (Indian MCS and Iranian Golestan) aggregated residential address data were used since individual address data were unavailable. That might be a particular issue for a pollutant such as NO_2, which is characterized by greater spatial variability than $PM_{2.5}$ and is influenced heavily by local emission sources. $PM_{2.5}$, in contrast, has long-range and secondary components and thus varies primarily at a regional level (Cyrys et al. 2012; Eeftens et al. 2012). More broadly, although the study applied state-of-the art exposure estimation methods with validated models, model performance differed regionally, with poorer $PM_{2.5}$ performance in Asia compared to the global evaluation, as described by van Donkelaar and colleagues (2015, 2016). For NO_2, the model performance in Asia approximately matched the global evaluation estimate (Larkin et al. 2017). Nonetheless, in a later GBD application, NO_2 adjustments were made to correct the Larkin estimates for a "high bias in rural areas" (Anenberg et al. 2022). It should be noted that in model evaluations, estimates are compared to ground-based monitor data, but such evaluations are hampered by the paucity of ground-based monitors, with most of them located in urban areas of North America and Europe, as discussed in an earlier section. Although the Committee understands that Drs. Downward and Vermeulen made best use of the global exposure models available, the substantial temporal and spa-

tial misalignment of the exposure data might have influenced the analysis of mortality outcomes in unpredictable ways.

HOUSEHOLD AIR POLLUTION WAS NOT EXAMINED

Like most other ambient air pollution and health studies, household air pollution was not examined in the current study. The Committee thought household air pollution might be a potential confounder or effect modifier. The investigators also alluded to that issue in the discussion of the findings. Household air pollution results from the burning of various fuels (coal, charcoal, wood, agricultural residue, animal dung, and kerosene, among others) for heating or for cooking using open fires or cookstoves with limited ventilation. Burning those fuels produces an array of pollutants that could harm human health, including $PM_{2.5}$, black carbon, and carbon monoxide. This practice is carried out by about half of the world's population, primarily from low- and middle-income countries. According to the most recent estimates from the GBD project, household air pollution contributes to about one third of the overall deaths linked to air pollution in 2019 (HEI 2020).

Only one cohort (Iranian Golestan) adjusted for domestic fuel use — an indicator of household air pollution. That indicator was missing for the other cohorts, unfortunately. The investigators reported consistent null findings between ambient air pollution and mortality for the Golestan cohort but found positive associations between some polluting fuel use (i.e., wood, kerosene, or "other" organic fuel) and mortality, that remained after adjusting for ambient $PM_{2.5}$. Similarly, in the PURE study, associations with solid fuel use for cooking and all-cause and cardiovascular mortality and morbidity were much more pronounced than the ambient $PM_{2.5}$ associations (Hystad et al. 2019, 2020).

Investigating the complex interplay between household and ambient air pollution with health is difficult because household air pollution is typically not measured for large populations over long periods of time. Hence, most studies rely on use of fuel types as an indicator of household air pollution. The Committee welcomes the investigators' future work on this topic using the Asian Cohort Consortium as described by Hosgood and colleagues (2019).

BROADER CONTEXT OF AIR POLLUTION AND HEALTH IN ASIA

The current study adds to a small evidence base in Asia, where the levels of air pollution are often high, and the types and sources of air pollution markedly differ from those in high-income settings. Although cross-sectional or short-term health studies are increasingly available in Asia, there are few studies focused on long-term exposure to ambient air pollution (Baumgartner et al. 2020). The evidence base documenting clear evidence that long-term exposure to ambient air pollution is associated with increased mortality from all causes, cardiovascular disease, respiratory disease, and lung cancer continues to be dominated by studies from North America and Europe. The recent systematic reviews underpinning the 2021 WHO Air Quality Guidelines for $PM_{2.5}$ and NO_2 identified only a few long-term studies in Asia, and no single study from Africa, Central America, or South America (Chen and Hoek 2020; Huangfu and Atkinson 2020). For example, only three studies from Asia entered the $PM_{2.5}$ meta-analysis for all-cause and cardiovascular mortality (Tsjeng et al. 2015; Yang et al. 2018; Yin et al. 2017). Some studies of long-term exposure and morbidity and mortality in Asia emerged more recently (Commentary Table 3). Most of the studies from Asia documented a positive association between long-term exposure to $PM_{2.5}$ and mortality outcomes, but there remains uncertainty about the true size of the $PM_{2.5}$ mortality relative risks. A recent study particularly relevant for the current study is the PURE study, which also used similar satellite-based global models (Hystad et al. 2020). The PURE study investigated the association between long-term exposure to $PM_{2.5}$ and all-cause and cardiovascular mortality and morbidity in a large, pooled cohort of adults from 21 countries, with most of the study population residing in low- and middle-income countries. The PURE study reported that long-term exposure to $PM_{2.5}$ was associated with increased risk for cardiovascular mortality and morbidity and adjusted for many important confounders, such as smoking, physical activity, socioeconomic status, urban or rural location and fuel use for cooking. No consistent association was observed for all-cause mortality and noncardiovascular mortality, and models were sensitive to adjustment for urbanicity, similar to the current study.

Given the paucity of studies in high air pollution settings, an IER function was developed for the GBD study to estimate mortality relative risks across the global exposure range for burden assessments. The function integrated four types of $PM_{2.5}$ exposures (outdoor $PM_{2.5}$, household air pollution, active smoking, and second-hand smoking) associated with cause-specific mortality (Burnett et al. 2014). In the most recent GBD estimates (GBD 2019 Risk Factors Collaborators 2020), active smoking studies were excluded from the IER function to characterize risks at high exposure, because the few new studies of high air pollution conditions in Asia provided enough information so that evidence from active smoking data is no longer necessary to use. This led to substantial increases in the relative risk curve for ischemic heart disease and stroke at the high end of the curve compared to the integrated curve that included active smoking studies. Notable increases in the relative risk curve were also reported in a $PM_{2.5}$ exposure–response function (global exposure mortality model [GEMM]), which was solely based on ambient $PM_{2.5}$ studies (Burnett et al. 2018). The use of GEMM resulted in burden estimates that were two to three times higher than those from the IER function. For the GEMM they included data from 41 cohorts in 16 different countries, including three studies from Asia (Tseng et al. 2015; Wong et al. 2015; Yin et al. 2017).

The differences in burden estimates reflect current uncertainty about key assumptions underlying the IER and GEMM models and therefore about the true size of the $PM_{2.5}$ mortality

Commentary Table 3. Summary of Selected Studies on Long-Term Exposure to $PM_{2.5}$ and Mortality in Asia (in order of publication year)

Reference	Study Name	Location	Study Period	Sample Size	Mean $PM_{2.5}$	Mortality Outcome	Hazard Ratio per 5 μg/m^{3a}
Tseng et al. 2015	Civil servants' cohort	Greater Taipei, Taiwan	1989–2008	43,227	~29	All-cause	0.96 (0.85–1.08)
						Cardiovascular	0.89 (0.65–1.22)
Yin et al. 2017	Chinese men	45 districts in China	1990–2005	189,793	43.7	All-cause	1.04 (1.04–1.05)
						Cardiovascular	1.04 (1.04–1.05)
						Lung cancer	1.06 (1.04–1.08)
Yang et al. 2018	Hong Kong elderly	Hong Kong	1998–2011	66,820	42.2	All-cause	1.03 (1.01–1.05)
						Cardiovascular	1.05 (1.02–1.09)
						Respiratory	1.01 (0.97–1.06)
Li et al. 2018	CLHLS	China	2008–2014	13,344	50.7	All-cause	1.04 (1.03–1.05)
Yorifuji et al. 2019	Okayama City	Okayama City, Japan	2006–2016	75,569	14.0	All-cause	1.29 (1.18–1.41)
						Cardiovascular	1.06 (0.90–1.26)
						Lung cancer	1.63 (1.13–2.34)
Hystad et al. 2020	PURE	17 low- and middle-income countries	2003–2018	140,020	47.5 (all 21 countries)	All-cause	0.99 (0.98–1.00)
						Cardiovascular	1.02 (1.00–1.03)
						Noncardiovascular mortality	0.98 (0.96–0.99)
						Cardiovascular event (fatal + nonfatal)	1.03 (1.01–1.04)
Kim et al. 2020	NHIS-NSC	Republic of Korea	2002–2013	436,933	18.8	All-cause	1.02 (1.01–1.02)
						Cardiovascular	1.03 (1.02–1.03)
Brown et al. 2022	MDS	India	2004–2013	6.8 million	24.3	All-cause	1.01 (1.01–1.02)
						Ischemic heart disease	1.00 (0.99–1.02)
						Stroke	1.04 (1.02–1.07)
						Respiratory	1.01 (0.98–1.03)

CLHLS = Chinese Longitudinal Healthy Longevity Survey; MDS = Million Death Study; NHIS-NSC = National Health Insurance Service-National Sample Cohort; PURE = Prospective Urban and Rural Epidemiology (PURE).

[a]Findings are converted to 5-μg/m^3 increase in $PM_{2.5}$ to allow comparison with the current study.

relative risks, particularly at the low- and high-end of the global exposure range (Burnett and Cohen 2020). The study by Downward and Vermeulen highlights the urgent need for future studies that could prove to be useful in reducing this uncertainty. At some point in the near future with sufficient studies, it might be possible to develop separate risk curves for outdoor air pollution, second-hand smoking, and household air pollution in the GBD study. Having those separate risk curves would remove an important source of uncertainty related to equitoxicity of particles (assuming no differences in health impact by PM source, size, and chemical composition) as well as uncertainties related to some other aspects of exposure to those distinct sources of PM.

SUMMARY AND CONCLUSION

Drs. Downward and Vermeulen have assessed the association between long-term exposure to ambient air pollution and all-cause and cause-specific mortality in an analysis of six Asian cohorts. The research was well motivated and addressed a clear research gap. The large sample size and leverage of harmonized data from the Asia Cohort Consortium were considered to be strengths of the study. Furthermore, data were available for several individual-level lifestyle factors, such as smoking status and intensity, body mass index, and diet, and the analyses were adjusted accordingly. Application of existing global satellite-based models allowed for a uniform estimation of exposure at a reasonably high

spatial resolution for a large urban and rural population in six Asian countries. Such a study would otherwise not have been possible given the paucity of ground-based monitors, particularly in low- and middle-income countries.

The study documented no association between long-term exposure to ambient $PM_{2.5}$ and all-cause mortality and cause-specific mortality in meta-analyses, except for a borderline significant positive association with cardiovascular mortality. Several individual cohorts (i.e., Indian MCS, Japanese JPHC, and Taiwanese CBCSCP), however, did display positive significant associations between ambient $PM_{2.5}$ and cardiovascular mortality. For ambient NO_2, the combined estimates showed positive associations for all mortality outcomes, in particular the cancer outcomes, although estimates were heavily driven by positive associations from the Japanese JPHC cohort. The cohorts were very diverse and large heterogeneity of the findings was reported across the individual cohorts, with null, negative, or positive findings, with sometimes no apparent pattern. Although the Review Committee broadly agreed with the investigators' conclusions, it identified limitations that should be considered when interpreting the results.

Importantly, the Committee was concerned that residual confounding was likely in the main analyses due to inadequate adjustment for characteristics that correlate with air pollution and mortality, most notably socioeconomic status and urbanicity. Findings sometimes differed for models that adjusted for urbanicity as compared to those that did not. The Committee would have been interested in better understanding potential sources of heterogeneity in the findings. There were also concerns about the exposure assessment approach because of the substantial temporal and spatial misalignment of the data, which might have influenced the analysis of mortality outcomes in unpredictable ways.

Overall, there remains uncertainty about the true size of the ambient air pollution and mortality associations in Asia, where the levels of air pollution are often high, and the types and sources of air pollution, including household air pollution, markedly differ from those in high-income settings. The study by Downward and Vermeulen highlights the urgent need for future studies that could prove to be useful in reducing this uncertainty. At the same time, these populations are experiencing very high levels of air pollution, meriting attention and action to reduce ambient air pollution regardless of the uncertainties.

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ABBREVIATIONS AND OTHER TERMS

AERONET	AErosol RObotic NETwork
ACC	Asia Cohort Consortium
CBCSCP	Community-based Cancer Screening Program
CI	confidence interval
DALYs	disability adjusted life years
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
ESCAPE	European Study of Cohorts for Air Pollution Effects
GBD	Global Burden of Disease
GEMM	Global Exposure Mortality Model
HEALS	Health Effects for Arsenic Longitudinal Study
HIC	high-income country
HR	hazard ratio
ICD	International Classification of Diseases
IER	integrated exposure–response
JPHC	Japan Public Health Center-based Prospective Study
KMCC	Korean Multi-center Cancer Cohort Study
LMIC	low-and-middle-income countries
LUR	land use regression
MCS	Mumbai Cohort Study
NO_2	nitrogen dioxide
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
ppb	parts per billion
PURE	Prospective Urban and Rural Epidemiology
R^2	coefficient of determination
RR	relative risk
sd	standard deviation
WHO	World Health Organization

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