Effect of air quality alerts on human health: a regression discontinuity analysis in Toronto, Canada

Hong Chen, Qiongsi Li, Jay S Kaufman, Jun Wang, Ray Copes, Yushan Su, Tarik Benmarhnia

Summary

Background Ambient air pollution is a major health risk globally. To reduce adverse health effects on days when air pollution is high, government agencies worldwide have implemented air quality alert programmes. Despite their widespread use, little is known about whether these programmes produce any observable public-health benefits. We assessed the effectiveness of such programmes using a quasi-experimental approach.

Methods We assembled a population-based cohort comprising all individuals who resided in the city of Toronto (Ontario, Canada) from 2003 to 2012 (about 2·6 million people). We ascertained seven health outcomes known to be affected by short-term elevation of air pollution, using provincial health administrative databases. These health outcomes were cardiovascular-related mortality, respiratory-related mortality, and hospital admissions or emergency-department visits for acute myocardial infarction, heart failure, stroke, asthma, and chronic obstructive pulmonary disease (COPD). We applied a regression discontinuity design to assess the effectiveness of an intervention (ie, the air quality alert programme). To quantify the effect of the air quality alert programme, we estimated for each outcome both the absolute rate difference and the rate ratio attributable to programme eligibility (by intention-to-treat analysis) and the alerts themselves (by two-stage regression approach), respectively.

Findings Between Jan 1, 2003, and Dec 31, 2012, on average between three and 27 daily cardiovascular or respiratory events were reported in Toronto (depending on the outcome). Alert announcements reduced asthma-related emergency-department visits by 4·73 cases per 1000000 people per day (95% CI 0·55–9·38), or in relative terms by 25% (95% CI 1–47). Programme eligibility also led to 2·05 (95% CI 0·07–4·00) fewer daily emergency-department visits for asthma. We did not detect a significant reduction in any other health outcome as a result of alert announcements or programme eligibility. However, a non-significant trend was noted towards decreased asthma-related and COPD-related admissions.

Interpretation In this population-based cohort, the air quality alert programme was related to some reductions in respiratory morbidity, but not any other health outcome examined. This finding suggests that issuing air quality alerts alone has a limited effect on public health and that implementing enforced public actions to reduce air pollution on high pollution days could be warranted. Together with accumulating evidence of substantial burden from long-term air pollution exposure, this study underscores the need for further strengthening of global efforts that can lead to long-term improvement of overall air quality.

Funding Public Health Ontario, Canadian Institutes for Health Research.

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Introduction

Over past decades, ambient air quality has improved in many regions, particularly in high-income countries, but episodic spikes in air pollution remain common. Short-term increases in air pollution trigger many adverse health events, particularly cardiovascular-related and respiratory-related deaths, admissions, and emergency-department visits. In the USA, about 8000 admissions for heart failure every year are attributable to increases in daily levels of air pollution, yielding US$307 million in medical costs annually.

In response to episodic spikes in air pollution, government agencies worldwide have implemented air quality alert programmes to inform the public (particularly those living with respiratory or cardiovascular conditions) of potential dangers from elevated air pollution. These programmes focus on days with especially elevated levels of air pollution, sometimes referred to as smog days. Smog days have been announced extensively across high-income countries and more recently in developing countries (eg, China, India). These announcements are typically used as a spearhead for addressing air pollution concerns.

Little evidence exists, however, about the effectiveness of air quality alert programmes in reducing the effect of air pollution on health. In many large cities (eg, Beijing, Los Angeles, and Paris), these are among the most prevalent (and highly visible) public programmes to protect the population from air pollution. In view of the central role that air quality alert programmes have had in public responses to air pollution, it is prudent to ask whether these programmes have achieved their intended goals in protecting public health.
Articles

Research in context

Evidence before this study
We searched MEDLINE, Embase, and Scopus for experimental or observational studies that investigated the effectiveness of air quality alert programmes on reducing the health effects of air pollution, with the keywords “air quality”, “air pollution”, “smog”, “alert”, “warning”, “advisory”, “program”, AND “mortality”, “morbidity”, “hospitalization”, “emergency-department visit”, “cardiovascular disease”, “respiratory disease”. Studies published in peer-reviewed literature up to Jan 1, 2017, were included, regardless of the language of publication. We screened bibliographies of these articles and of relevant reviews. Little research has been done on the relation between air quality alert programmes and physical health outcomes. Only one study was identified that investigated the effect of air quality alerts on two selected mortality outcomes, but no study has so far examined the effect of air quality alerts on a wide range of mortality and morbidity outcomes, particularly cardiovascular-related and respiratory-related outcomes that are known to be affected by air pollution. Furthermore, the previous study was undertaken in an economically developing region with severe air pollution.

Added value of this study
As far as we know, our study is the first to evaluate comprehensively the effect of an air quality alert programme on a wide array of health outcomes and the first to be undertaken in a region where air pollution levels are in a range relevant to many high-income countries. Moreover, our study is, to our knowledge, the first to apply the regression discontinuity design to evaluate an air pollution intervention. By emulating randomisation through a natural experiment, this approach overcomes the vulnerability of observational studies to bias from unmeasured confounding and, thus, enables valid causal inference about air quality alerts. With population characteristics and the air quality alert programme of this study resembling those of the USA and many European countries, our results will be highly generalisable to many other regions.

Methods

Study setting and design
We undertook this study in Toronto, which is Canada’s most populous city (population about 2.6 million) and is the fourth largest city by population in North America.10 Toronto is among the major Canadian cities that most frequently have air quality alerts.11 With its socio-demographic characteristics—eg, age, sex, and average family income—resembling those of many major cities in North America and Europe, Toronto represents an ideal setting to evaluate an air quality alert programme.12

To assess the population effects of the air quality alert programme in Toronto, we applied the regression discontinuity design, which is a quasi-experimental study design that can overcome the vulnerability of observational studies to bias from unmeasured confounding and, thus, permit valid causal inference about the effectiveness of this programme.13

We did a population-based study to assess the public-health effects of an air quality alert programme in the city of Toronto (Ontario, Canada). We applied the regression discontinuity design, which is a quasi-experimental study design that can overcome the vulnerability of observational studies to bias from unmeasured confounding and, thus, permit valid causal inference about the effectiveness of this programme.10–11

Methods

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We undertook this study in Toronto, which is Canada’s fourth largest city by population in North America.14 With its socio-demographic characteristics—eg, age, sex, and average family income—resembling those of many major cities in North America and Europe, Toronto represents an ideal setting to evaluate an air quality alert programme.14

In the same way as if they were randomised,11–13 the days that fall just on either side of this division can be judged exchangeable in the same way as if they were randomised.11–13

The air quality alert programme covering Toronto has been operated by the Ontario Ministry of the Environment and Climate Change since 2000.16 Similar to programmes in the USA and Europe,17,18 air quality alerts in Toronto communicate the health importance of air pollution to the public by announcing poor air quality through media coverage, to urge behavioural changes related to outdoor activities (appendix). An air quality alert was issued based on—at least partly—a threshold for the air quality index (AQI), a score corresponding to the concentration of any one pollutant with the highest concentration relative to its air quality standards.19 Because of uncertainty in forecasting air quality, whether a day with the AQI close to the threshold would lie above or below the threshold is essentially random, just as in an experimental design.10–11 A discontinuity in health outcomes at this threshold would suggest a causal effect of alerts on modifying health, whereas continuity suggests a null effect.

Implications of all the available evidence

Globally, air quality alert programmes represent one of the most common public responses to protect the population from air pollution. Understanding whether these programmes indeed result in any observable public health benefits has enormous implications. Despite their widespread use over past decades, the findings of our study show that air quality alert programmes offer inadequate protection for public health. This evidence highlights the need for implementing enforced public actions, such as emission control, to reduce air pollution on high pollution days. Together with accumulating evidence of substantial burden from long-term air pollution exposure, our study findings underscore the need for further strengthening of global efforts that will lead to long-term improvement of overall air quality.
The ethics review board of Public Health Ontario approved the study.

Procedures
To capture a wide range of health outcomes that are sensitive to daily increases in air pollution and, thus, might be affected by air quality alerts, we considered seven mortality and morbidity outcomes, comprising deaths from any cardiovascular cause and from any respiratory cause, and hospital admissions or emergency-department visits for acute myocardial infarction, congestive heart failure, stroke, asthma, and chronic obstructive pulmonary disease (COPD; appendix). For every outcome, we created a daily time series during the study period (from Jan 1, 2003, to Dec 31, 2012) using data from the Office of the Registrar General death database, hospital discharge abstracts database, and the National Ambulatory Care Reporting System database from the Canadian Institute for Health Information. All datasets were linked using unique encoded identifiers and analysed at the Institute for Clinical Evaluative Sciences (ICES).

We obtained from the Ontario Ministry of the Environment and Climate Change a detailed history of air quality alerts announcements in Toronto between 2003 and 2012. These alerts were issued according to two criteria: first, if air quality was forecast by the Ontario Ministry of the Environment and Climate Change to be poor (daily maximum AQI ≥50); and second, if persistent and widespread levels of ozone (O₃), fine particulate matter (particles ≤2.5 μm in diameter [PM₂.₅]), or both were expected. The AQI is on a scale from 0 to 100 or more, with 50 reflecting the temperature, relative humidity, 1 h O₃) or a reference level (eg, 46 µg/m³ for 3 h average). Ontario Ambient Air Quality Criteria (eg, 81 ppb for 2003 and 2012. These alerts were issued according to the Canadian Institute for Health Information. All datasets were linked using unique encoded identifiers and analysed at the Institute for Clinical Evaluative Sciences (ICES).

We obtained daily time-series data for PM₂.₅, O₃, nitrogen dioxide (NO₂), temperature, relative humidity, and precipitation from all monitoring stations in Toronto during the study period. We also created categorical variables for calendar year, season, presence of heat warnings, weekend, and holidays.

Statistical analysis
We implemented the regression discontinuity study design as described elsewhere. First, we verified key assumptions of the design by ensuring the presence of a continuous eligibility measure and that outcomes were ascertained universally in this study. Second, we assessed balance among covariates supposed to be unaffected by the air quality alert programme and any potential for manipulation of the assignment variable. Third, we checked visually the presence of discontinuity. Finally, we fitted regression models to estimate the treatment effect, and we did sensitivity analyses.

Because air quality alerts were issued depending partly on the AQI threshold and partly on other considerations (eg, avoiding alert fatigue—ie, a concern that they were being issued too frequently), the assignment of alerts was not deterministic but probabilistic. Thus, it is a close analogy to imperfect compliance in a randomised experiment. To account for the probabilistic nature of alert assignment, we did a fuzzy regression discontinuity design analysis with two regression models (panel).

This fuzzy regression discontinuity design analysis allowed for estimating the effect of alert eligibility and the effect of alerts on health. The effect of alert eligibility is analogous to an intention-to-treat estimate of programme eligibility and can be interpreted as the causal effect of the air quality alert programme on health in the real-world context. We fitted equation 1 (panel) using Poisson regression with identity and log link functions, respectively, to estimate the programme effect on both absolute and relative scales as a rate difference and rate ratio. To estimate air quality alert effect, a second stage was added to also assess the relation between programme eligibility and alert announcements (equation 2; panel), as described previously. This two-stage regression approach allowed us to compare days with alerts with what would have been observed on the same day without

Panel: Regression models

Equation 1
\[ g(E(Y_i)) = \beta_0 + \beta_1 \times (Z_i - c) + \beta_2 \times P_i + \beta_3 \times (Z_i - c) \times P_i + \beta_4 \times X_{ik} \]

Equation 2
\[ g(E(T_i)) = \delta_0 + \delta_1 \times (Z_i - c) + \delta_2 \times X_i + \delta_3 \times (Z_i - c) \times P_i + \delta_4 \times X_{ik} \]

\(g(\cdot)\) is a generic link function. \(i\) denotes day \(i\) between 2003 and 2012. \(Y_i\) is the daily count of selected outcomes. \(Z_i\) is daily air quality index with a threshold at \(c\) (ie, 48). \(P_i\) is an indicator variable that reflects eligibility status (1 for day \(i\) with \(Z_i \geq c\), otherwise 0). \(T_i\) is an indicator variable equal to 1 for day \(i\) with an alert. \(X_{ik}\) are a set of \(k\) covariates including air quality alert programme and any potential for manipulation of the assignment variable.
alerts (ie, estimating a complier average causal effect). Further details of the two-stage analysis are provided in the appendix.

To ensure exchangeability, we restricted data a priori to a small area around the AQI threshold (ie, within 5 units) using a method described elsewhere. To account for the potential delayed effect of alerts, we considered for every health outcome the daily count averaged across the same day of the alert and the 2 days following. We repeated the analyses for each of the seven prespecified health outcomes.

To assess the robustness of our findings, we did various sensitivity analyses. First, we verified that eligibility status was a strong instrumental variable for alert assignment, in view of the analogy between two-stage fuzzy regression discontinuity design analysis and instrumental variable analysis. Second, we considered a non-linear term for the assignment variable using higher order polynomial terms (a quadratic and a cubic) and a natural spline term with five and seven degrees of freedom, but we did not find any evidence of departure from log-linearity for its relation with the outcomes (appendix).

Finally, we applied an alternative assignment variable...
Between Jan 1, 2003, and Dec 31, 2012, 143 days fell within 5 units around the AQI threshold (table 1). Of these, 41 days were above the threshold (AQI ≥48) and, thus, classified as eligible for alerts (eligible days). The days on either side of the threshold showed comparable characteristics on measured factors such as temperatures and humidity, except for holiday or weekend status (table 1). In practice, alerts were issued on 62 days, some of which had an AQI as low as 43.

Figure 1 shows a discernible discontinuity in the probability of an air quality alert at the AQI threshold, with eligible days being around 40% more likely to receive an alert than non-eligible days. This finding provided evidence in support of the feasibility of the regression discontinuity design. Additionally, manipulation of the AQI was verified as unlikely, because its value was continuous with no indication of bunching at the threshold (appendix). This finding was further confirmed by smooth distributions of key covariates around the AQI threshold (appendix).

No evidence was found for an effect of the air quality alert programme on cardiovascular-related or respiratory-related mortality (rate difference 0.29 per 1000000 people per day [95% CI 0.27 to 0.85] for cardiovascular mortality and 0.09 per 1000000 people per day [0.24 to 0.42] for respiratory mortality; table 2). Similar findings were obtained for air quality alert effects, with 4·73 fewer asthma-related emergency-department visits per 1000000 people per day (95% CI 3·80–5·59), or in relative terms a 25% (95% CI 1·36–4·79) reduction by 25% (95% CI 1·36–4·79). A non-significant trend was noted towards decreased asthma-related and COPD-related hospital admissions after the alerts (table 2).

The estimated programme effects on cardiovascular-related and respiratory-related mortality and morbidity were supported by visual checks, which showed a clear

<table>
<thead>
<tr>
<th>Role of the funding source</th>
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<tbody>
<tr>
<td>The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data analysis, data interpretation, or writing of the report.</td>
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<td>Between Jan 1, 2003, and Dec 31, 2012, 143 days fell within 5 units around the AQI threshold (table 1). Of these, 41 days were above the threshold (AQI ≥48) and, thus, classified as eligible for alerts (eligible days). The days on either side of the threshold showed comparable characteristics on measured factors such as temperatures and humidity, except for holiday or weekend status (table 1). In practice, alerts were issued on 62 days, some of which had an AQI as low as 43.</td>
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<tr>
<th>Table 2: Effect of air quality alerts on health outcomes in Toronto, Canada, from 2003 to 2012</th>
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<tr>
<td>Average daily number of events</td>
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<td></td>
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<tr>
<td><strong>Mortality</strong></td>
</tr>
<tr>
<td>Any cardiovascular disease</td>
</tr>
<tr>
<td>Any respiratory disease</td>
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<tr>
<td><strong>Hospital admission</strong></td>
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<tr>
<td>Acute myocardial infarction</td>
</tr>
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<td>Congestive heart failure</td>
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<td><strong>Emergency-department visit</strong></td>
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The model included an indicator variable for eligibility status, daily maximum AQI (centred at the threshold of 48), and an interaction term of eligibility status and daily maximum AQI, with further control for daily maximum temperature (natural spline with three degrees of freedom), daily mean relative humidity, calendar year, season, day of the week, and holiday status. AQI=air quality index.
difference in daily asthma-related emergency-department visits at the AQI threshold (figure 2; appendix). This finding was confirmed by a notable jump in the daily rate of asthma-related emergency-department visits at the AQI threshold, and to a lesser degree, COPD-related morbidity (appendix). No discernible discontinuity was recorded for any other outcome.

Results on programme and alert effect were insensitive to adjustment for air pollutants and consideration of different windows around the AQI threshold (table 3; appendix). Further sensitivity analyses—eg, adjustment for extreme heat warnings and use of an alternative assignment variable—yielded similar results (appendix).

Discussion

The findings of this large population-based cohort study show that the air quality alert programme in Toronto, Canada, yielded inadequate protection of the public from air pollution between 2003 and 2012. Air quality alerts resulted in some reductions in asthma-related emergency-department visits on high pollution days, and to a lesser degree COPD-related morbidity. However, the programme did not prevent any mortality or cardiovascular morbidity.

Many cities worldwide have implemented air quality alert programmes to reduce the negative effects of short-term increases in air pollution. However, whether these programmes have indeed met their goals is largely unknown. To date, only one other study (set in Santiago, Chile) has assessed the effectiveness of air quality alerts, in this case the effect on total and respiratory-related mortality.10 In Santiago, daily PM₁₀ regularly exceeds 300 µg/m³.1 By comparing days with air quality alerts (PM₁₀ ≥240 µg/m³) with similar days before implementation of the programme, around 20 deaths per 100000 people per day were estimated to be reduced by the programme.10 By contrast, the alert programme in Toronto, with much lower levels of air pollution, did not prevent mortality.

The air quality alert announcements in Santiago triggered a string of enforced government actions, including restriction of driving, shutdown of major stationary emitters (eg, factories), and prohibition of biomass combustion, in conjunction with public announcements to encourage avoidance behaviours.10 These measures led to an immediate decline in air pollution on alert days (by about 20%) compared with similar days without alerts.10 Conversely, the air quality alert programme in Toronto used information campaigns such as web notifications and media coverage to advise the public to avoid outdoor physical activities.15 These announcements also encouraged industries to reduce emissions and individuals to restrict activities producing smog (eg, driving), but these measures were voluntary in nature. Although differences in pollution levels or population characteristics might contribute to the different findings about air quality alerts between Toronto and Santiago, it is also likely that interventions relying on information campaigns alone to encourage exposure avoidance and voluntary emission control could yield little benefit if not accompanied by mandatory actions.
Many countries including Canada, the UK, and the USA use information-based campaigns to alert the public and promote behavioural changes on high pollution days. However, existing evidence as to whether these campaigns resulted in precautionary activities remains unclear. In two US studies, decreased attendance to parks (particularly by children and people exercising) was reported after smog alerts in Los Angeles and Atlanta, but findings of several other US studies failed to link air quality alerts to adverse health effects. This possibility could, at least partly, account for why the air quality alerts modified asthma-related hospitalisation, but not mortality or cardiovascular morbidity in young subpopulations (e.g., physically active individuals). This possibility could not be tested with health administrative data. Furthermore, central to the efficacy of air quality alerts is the presumption that public announcements reduce outdoor activities of sensitive individuals. Considering that the most vulnerable people are those who are ill and already spend most time indoors (e.g., those with chronic diseases), it is possible that these alerts benefit specific subpopulations (e.g., physically active individuals) more than others. This possibility could, at least partly, account for why the air quality alerts modified asthma-related outcomes, but not mortality or cardiovascular morbidity in this study. An important implication of this noted deficiency of air quality alerts is that further enforced public actions to reduce air pollution levels (either short-term or long-term) would be warranted.

As far as we know, our study is the first to assess the effectiveness of air quality alert programmes in reducing a range of health outcomes in a region where air pollution levels are relatively low but episodic spikes in air pollution remain common. Another novel aspect of our study is the application of the regression discontinuity design, a powerful quasi-experimental study design. By emulating randomisation, the regression discontinuity design approach circumvents the limitations of observational studies attributable to unmeasured confounding factors and, thus, enables valid causal inference about the air quality alert programme. The regression discontinuity design approach also allows for assessment of both the programme effect (analogous to an intention-to-treat analysis) and the effect of the alerts themselves. With population characteristics and the air quality alert programme of Toronto resembling those of major cities in the USA and Europe, our results could be generalisable to many other regions.

Our study, however, is not without limitations. First, our analysis was restricted to outcomes ascertained from inpatient and outpatient settings. Thus, we were unable to identify undiagnosed cases that were not severe enough for health-care services. Nonetheless, in view of universal health care in Ontario, it is unlikely that incomplete diagnosis would have biased our results because it would have similarly affected eligible and non-eligible days. Second, the success of alert programmes depends on a series of factors (e.g., increasing awareness, reducing exposure). We did not have direct measures of these factors and, thus, were unable to further dissect the links that elucidated our findings. Third, responses to these alerts might differ by socioeconomic status, but this possibility could not be tested with health administrative data.

Table 3: Effect of air quality alerts on health outcomes in Toronto, Canada, from 2003 to 2012, with further adjustment for daily air pollution levels

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Programme effect</th>
<th>Alert effect</th>
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<tbody>
<tr>
<td>Any cardiovascular disease</td>
<td>0.21 (-0.26 to 0.87)</td>
<td>1.06 (0.92 to 1.20)</td>
</tr>
<tr>
<td>Any respiratory disease</td>
<td>0.20 (-0.24 to 0.42)</td>
<td>1.08 (0.84 to 1.38)</td>
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<tr>
<th>Hospital admission</th>
<th>Programme effect</th>
<th>Alert effect</th>
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<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>0.20 (-0.37 to 0.79)</td>
<td>1.05 (0.91 to 1.21)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>-0.05 (-0.64 to 0.55)</td>
<td>0.98 (0.84 to 1.13)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.18 (-0.38 to 0.74)</td>
<td>1.06 (0.91 to 1.22)</td>
</tr>
<tr>
<td>Asthma</td>
<td>-0.21 (-0.58 to 0.18)</td>
<td>0.72 (0.50 to 1.05)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>-0.46 (-1.00 to 0.10)</td>
<td>0.86 (0.72 to 1.03)</td>
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<table>
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<tr>
<th>Emergency-department visit</th>
<th>Programme effect</th>
<th>Alert effect</th>
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<tbody>
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<td>Acute myocardial infarction</td>
<td>0.13 (-0.22 to 0.50)</td>
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<tr>
<td>Congestive heart failure</td>
<td>-0.33 (-0.97 to 0.31)</td>
<td>0.93 (0.82 to 1.05)</td>
</tr>
<tr>
<td>Stroke</td>
<td>-0.15 (-0.63 to 0.33)</td>
<td>0.96 (0.84 to 1.10)</td>
</tr>
<tr>
<td>Asthma</td>
<td>-2.20 (-4.16 to -0.21)</td>
<td>0.80 (0.64 to 0.98)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>-0.40 (-1.22 to 0.41)</td>
<td>0.94 (0.82 to 1.07)</td>
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The model included an indicator variable for eligibility status, daily maximum AQI (centred at the threshold of 48), and an interaction term of eligibility status and daily maximum AQI, with further control for daily maximum temperature (natural spline with three degrees of freedom), daily mean relative humidity, calendar year, season, day of the week, holiday status, and daily mean levels of PM$_2.5$, NO$_2$, and O$_3$. AQI=air quality index. NO$_2$=nitrogen dioxide. O$_3$=ozone. PM$_2.5$=particles ≤2.5 µm in diameter.
databases. Moreover, we made many comparisons and reported significant results for one health outcome. We cannot rule out the possibility that this finding might be attributable to chance. Finally, although our results are pertinent to many countries with low-to-moderate air pollution levels, whether they can be generalised to specific regions with severe air pollution (eg, China) is unclear and merits further investigation.

Our results suggest that issuing air quality alerts to encourage avoidance behaviours alone has a limited effect on public health, and that implementing enforced public actions to reduce air pollution levels on high pollution days may be warranted. Together with accumulating evidence of substantial burden from long-term air pollution exposure, this study underscores the need for further strengthening global efforts that can lead to long-term improvement of overall air quality. We hope our findings will aid these future research efforts.

Contributors
HC had the idea for the study. HC, TB, and JSK contributed to study design. HC, QL, and JW prepared and cleaned the data. HC, YS, and QL contributed to the exposure assessment. TB and JSK provided substantial scientific input into statistical methods and interpretation of data. HC, TB, QL, JW, and JSK contributed to data analyses. HC and TB took the lead in drafting the manuscript. All authors contributed to interpretation of data, provided important revisions to the manuscript, and approved the final draft.

Declaration of interests
We declare no competing interests.

Acknowledgments
Richard T Burnett (Health Canada, Ottawa) for valuable advice and supported by the Canada Research Chairs Program. We thank Canadian Institutes for Health Research (MOP-133463). JSK was funded for this study is provided by PHO (2015-16-PIF-011) and the Ontario Ministry of the Environment and Climate Change. This study was supported by Public Health Ontario (PHO) and the Ministry of the Environment and Climate Change (Ontario). This research was conducted using data from the Ontario Ministry of Health and Long-Term Care. The Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). Parts of this material are based on data and information compiled and provided by the Canadian Information Health Institute (CIHI). The opinions, results, and conclusions reported in this Article do not necessarily represent the views of ICES, PHO, MOHLTC, CIHI or the Ontario Ministry of the Environment and Climate Change. Funding for this study is provided by PHO (2015-16-P1F-011) and the Canadian Institutes for Health Research (MOP-113463). JSK was supported by the Canada Research Chairs Program. We thank Richard T Burnett (Health Canada, Ottawa) for valuable advice and suggestions in the preparation of this report.

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