RESEARCH REPORT

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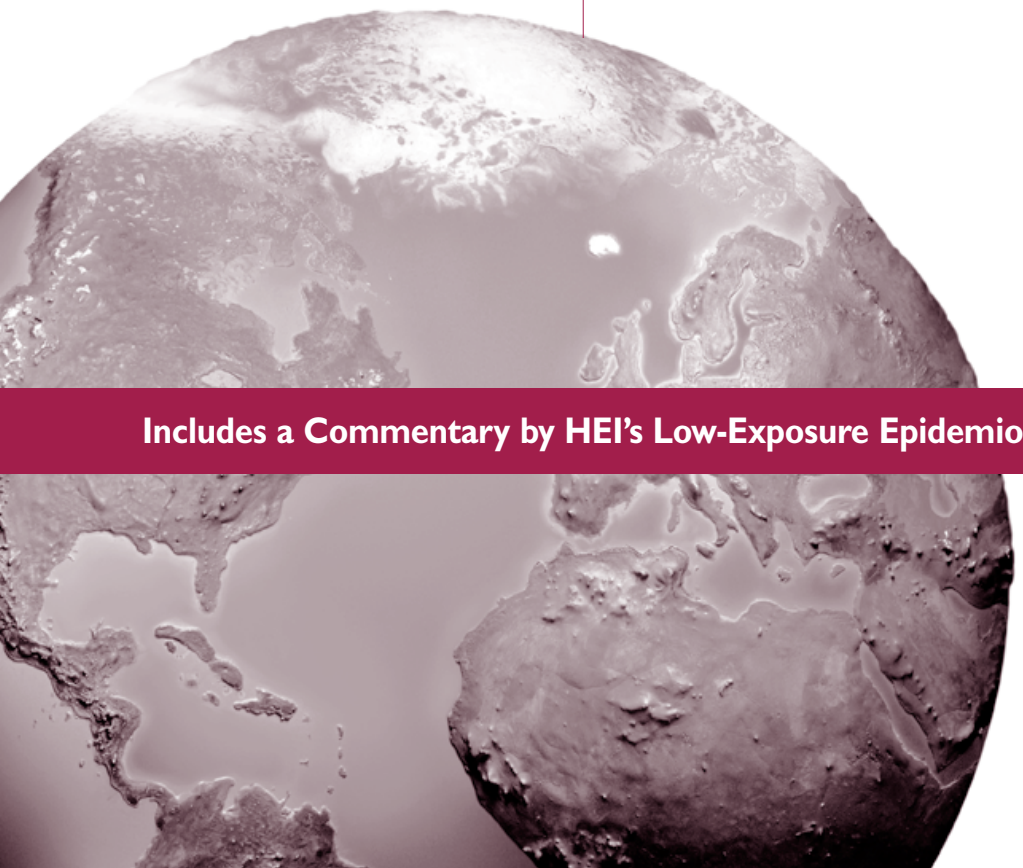
Mortality–Air Pollution Associations in Low-Exposure Environments (MAPLE): Phase 1

Michael Brauer, Jeffrey R. Brook, Tanya Christidis, Yen Chu, Dan L. Crouse, Anders Erickson, Perry Hystad, Chi Li, Randall V. Martin, Jun Meng, Amanda J. Pappin, Lauren L. Pinault, Michael Tjepkema, Aaron van Donkelaar, Scott Weichenthal, and Richard T. Burnett



Includes a Commentary by HEI's Low-Exposure Epidemiology Studies Review Panel

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CONTENTS

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; and
- 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 1,000 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. For this study, a special panel — HEI's Low-Exposure Epidemiology Studies Oversight Panel — has worked with the Research Committee in project selection and oversight. 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. For this study, a special review panel — HEI's Low-Exposure Epidemiology Studies Review Panel — is fulfilling this role.

All project results and accompanying comments by the Review Committee (or, in this case, the Low-Exposure Epidemiology Studies Review Panel) are widely disseminated through HEI's website (*www.healtheffects.org*), printed reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

ABOUT THIS REPORT

Research Report 203, *Mortality–Air Pollution Associations in Low-Exposure Environments (MAPLE): Phase I,* presents a research project funded by the Health Effects Institute and conducted by Dr. Michael Brauer of The University of British Columbia, Vancouver, Canada, and his colleagues. 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 Low-Exposure Epidemiology Studies Review Panel's comments on the study.

The Investigators' Report, prepared by Brauer and colleagues, describes the scientific background, aims, methods, results, and conclusions of the study.

The Commentary, prepared by members of the Low-Exposure Epidemiology Studies Review Panel 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 was first examined by outside technical reviewers and a biostatistician. The report and the reviewers' comments were then evaluated by members of the Low-Exposure Epidemiology Studies Review Panel, an independent panel of distinguished scientists who have no involvement in selecting or overseeing HEI studies. During the review process, the investigators had an opportunity to exchange comments with the Review Panel and, as necessary, to revise their report. The Commentary reflects the information provided in the final version of the report.

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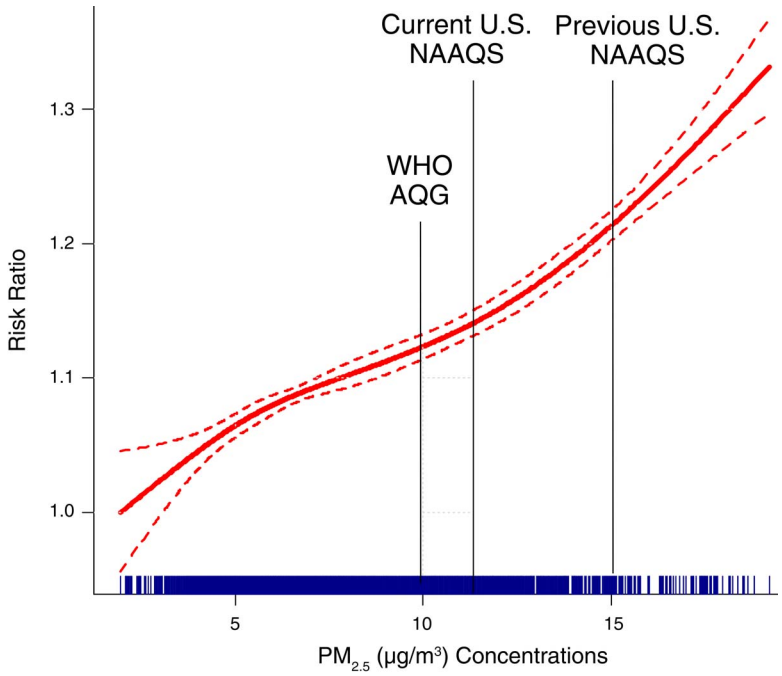
PREFACE

HEI's Program to Assess Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution

INTRODUCTION

Levels of ambient air pollution have declined significantly over the last decades in North America, Europe, and in other developed regions. Despite the decreasing levels of air pollution, recent epidemiological studies report associations between adverse health effects and exposure to air pollution. These studies have found associations between exposure to fine particulate matter, that is, particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$*), and mortality at levels below current ambient air quality standards (e.g., Beelen et al. 2014; Crouse et al. 2012; Hales et al. 2012) (Preface Figure 1). In order to improve the science and inform future regulation, it is important to confirm whether associations with adverse health effects continue to be observed as levels of air pollution have declined. It is also important to better understand the shape of the exposure–response function at those low levels.

The growing scientific evidence for effects at levels below current air quality standards and the large overall estimates of the air pollution-attributable burden of



Preface Figure 1. Shape of the concentration–response function for mortality associated with fine particulate matter in a Canadian Cohort. (Courtesy R. Burnett). NAAQS = National Ambient Air Quality Standard; WHO AQG = World Health Organization Air Quality Guidelines.

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

disease, as well as the interest in reducing greenhouse gases, suggest that more stringent air quality standards and guidelines may be considered in the future. For these reasons, there is a need for additional investigation to improve our understanding of exposure–response function(s) for mortality and morbidity at low levels of $PM_{2.5}$, ozone (O_3), and other ambient air pollutants. Such studies would inform risk assessors and policy makers regarding exposure–response functions at levels of ambient air pollution currently prevalent in North America, Western Europe, and other high-income regions of the world.

In 2014, HEI issued RFA 14-3, *Assessing Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution*, to solicit studies to address these important questions. The main goals of the RFA were to:

1. Fund studies to assess health effects of long-term exposure to low levels of ambient air pollution, including all-cause and cause-specific mortality and morbidity. Such studies should analyze and evaluate exposure–response function(s) for $PM_{2.5}$ and other pollutants at levels currently prevalent in North America, Western Europe, and other high-income regions. The studies may also address related questions about health effects at low levels of ambient air pollution.
2. Develop statistical and other methodology required for, and specifically suited to, conducting such research including, but not limited to, evaluation and correction of exposure measurement error.

Applicants were asked to pay particular attention to having sufficiently large cohorts and statistical power to detect associations should they exist, having the ability to test various potential confounders of any associations, and developing exposure-assessment approaches and statistical methodology that would enable a robust examination of the associations.

Specifically, applicants were asked to propose studies to:

1. Compare and contrast alternative analytic models and accompanying uncertainty. For example, compare threshold against nonthreshold models, linear against nonlinear models, and parametric against nonparametric models, to characterize the exposure–response function(s) at low levels of ambient air pollution.
2. Explore possible variability in estimates of risk at low pollutant concentrations among populations, and identify possible contributing factors. Such factors could include age, smoking, socioeconomic position, health status, and access to medical care, as well as differences in air pollution sources and time–activity patterns.
3. Develop and evaluate exposure-assessment methods suitable to estimate exposure to low levels of air pollution at various spatial and temporal scales in large study populations, including people who reside in areas not covered by routine ground-level monitoring.
4. Develop, evaluate, and apply statistical methods to quantify and correct for exposure measurement error in risk estimates and in characterization of exposure–response relationships.
5. Develop and validate approaches to assess the effects of co-occurring pollutants on any health effect associations at low ambient concentrations.
6. Develop and validate indirect approaches to correct risk estimates for the effects of important potential confounding variables, such as smoking, in the absence of such data at the individual level.
7. Improve techniques for record linkage and methods for disclosure protection for optimal use of large administrative databases in air pollution and health research.

STUDY SELECTION

HEI established an independent Low-Exposure Epidemiology Studies Oversight Panel — consisting of outside experts and HEI Research Committee members — to prepare RFA 14-3 and review all applications submitted in response (see Contributors page). Members of HEI's Research Committees with any conflict of interest were recused from all discussions and from the decision-making process. The HEI Research Committee reviewed the Panel's recommendations and recommended three studies for funding to HEI's Board of Directors, which approved funding in 2015.

Preface

This Preface summarizes the three studies, HEI's oversight process, and the review process for the Phase 1 reports.

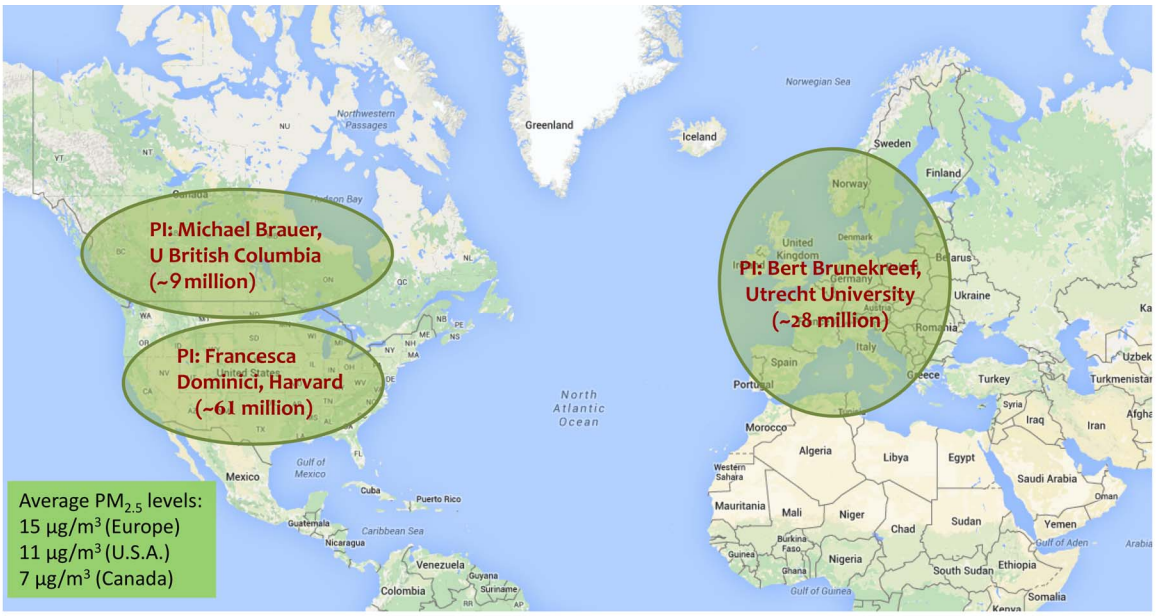
OVERVIEW OF THE HEI LOW-EXPOSURE EPIDEMIOLOGY STUDIES

After a rigorous selection process, HEI funded three teams, led by Michael Brauer at The University of British Columbia, Canada, Francesca Dominici at the Harvard T.H. Chan School of Public Health, United States, and Bert Brunekreef at the University of Utrecht, The Netherlands, to investigate health effects of exposure to low levels of air pollution in very large populations in Canada, the United States, and Europe, respectively (see Preface Table 1 and Preface Figure 2). The studies included large population cohorts (with detailed individual information about potential confounders for all subjects or for subsets of cohorts), as well as large administrative databases with greater statistical power (albeit with less individual information about potential confounders). Additionally, the three teams employed satellite data and ground-level pollutant measurements, used high-quality exposure-assessment models at high spatial resolutions, and set out to develop and apply novel statistical methods.

The three studies are expected to inform the scientific community and the risk assessors and policy makers regarding exposure–response functions at levels of ambient air pollution currently prevalent in North

Preface Table. HEI's Program to Assess Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution

Investigator (Institution)	Study Title	Phase 1 Report	Phase 2 (Final) Report Expected
Brauer, Michael (The University of British Columbia, Canada)	Mortality Air Pollution Associations in Low Exposure Environments (MAPLE)	Brauer M, Brook JR, Christidis T, Chu Y, Crouse DL, Erickson A, et al. 2019. Mortality–Air Pollution Associations in Low-Exposure Environments (MAPLE): Phase 1. Research Report 203. Boston, MA:Health Effects Institute.	Summer 2020
Brunekreef, Bert (Utrecht University, The Netherlands)	Mortality and Morbidity Effects of Long-Term Exposure to Low-Level $PM_{2.5}$, Black Carbon, NO_2 and O_3: An Analysis of European Cohorts	None	Fall 2020
Dominici, Francesca (Harvard University, T.H. Chan School of Public Health, U.S.A.)	Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Pollution	Dominici F, Schwartz J, Di Q, Braun D, Choirat C, Zanobetti A. 2019. Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution: Phase 1. Research Report 200. Boston, MA:Health Effects Institute.	Summer 2020



Preface Figure 2. Geographical areas and populations covered by HEI's research program to assess adverse health effects of long-term exposure to low levels of ambient air pollution.

America, Western Europe, and other developed regions. The full sets of analyses are expected to be completed in 2020, as discussed in the following sections.

CANADIAN STUDY (MICHAEL BRAUER ET AL.)

Brauer and colleagues are assessing the relationship between nonaccidental mortality and long-term exposure to low concentrations of $PM_{2.5}$ in four large population-based cohorts, including a careful characterization of the shape of the exposure–response function. The investigators are using Canadian census data and have access to a nationally representative population of approximately 9 million Canadians (ages 25–90 yr) (Preface Figure 2). The Canadian team is developing hybrid models primarily using satellite data, as well as chemical transport models, land-use variables, and routinely collected monitoring data for $PM_{2.5}$. They are also estimating ambient concentrations for nitrogen dioxide (NO_2) and O_3 for Canada and the United States during the period 1981–2016. Additionally, they will be validating satellite data against ground-based monitors in Canada as part of the SPARTAN network (Snider et al. 2015).

The exposure models are applied to estimate effects of air pollution exposure on all-cause and cause-specific mortality in four Canadian cohorts:

1. About 2.5 million respondents who completed the 1991 census long form of the Canadian Census Health & Environment Cohorts (CanCHEC),
2. About 3 million respondents who completed the 1996 CanCHEC census long-form,
3. About 3 million respondents who completed the 2001 CanCHEC census long-form, and
4. About 540,000 respondents who participated in the Canadian Community Health Survey (CCHS) between 2001 and 2012, and reported individual-level risk factors, including smoking.

EUROPEAN STUDY (BERT BRUNEKREEF ET AL.)

Brunekreef and colleagues are basing their study on the European Study of Cohorts for Air Pollution Effects (ESCAPE), which started about a decade ago; its results have been published widely (e.g., Beelen et al. 2014). In the current HEI-funded study, the investigators are analyzing pooled data from 10 ESCAPE cohorts (instead of

the cohort-specific approach they used previously). In addition, they are using data from six large administrative cohorts to yield a total study population of approximately 28 million Europeans (Preface Figure 2). They are developing hybrid, Europe-wide and location-specific exposure models that utilize land-use information, dispersion modeling, satellite data, ESCAPE monitoring data, and routinely collected monitoring data for $PM_{2.5}$, NO_2, O_3, and black carbon at high spatial resolution (residential address level; such detailed information is very difficult to obtain in the United States).

Brunekreef and colleagues are investigating the following health outcomes: all-cause and cause-specific mortality, incidence of coronary and cerebrovascular events, and lung cancer incidence. The incorporation of ESCAPE cohorts with individual covariate information as well as very large administrative cohorts (albeit with less detailed information) will provide new insights in the merits of both approaches.

UNITED STATES STUDY (FRANCESCA DOMINICI ET AL.)

Dominici and colleagues are evaluating Medicare and Medicaid data for a study population of approximately 61 million Americans (Preface Figure 2). They are developing high spatial resolution (1 km^2-grid) hybrid exposure models that incorporate satellite data, chemical transport models, land-use and weather variables, and routinely collected monitoring data for NO_2, O_3, and $PM_{2.5}$ and its components, for the continental United States during the period 2000–2012. Exposure models will be applied to estimate adverse health effects of air pollution in three cohorts:

1. Medicare enrollees (28.6 million elderly enrollees per year, 2000–2012);
2. Medicaid enrollees (28 million enrollees per year, 2010–2012); and
3. Medicare Current Beneficiary Survey enrollees (nationally representative sample of approximately 15,000 enrollees per year with rich individual-level risk factor information, including smoking).

Dominici and colleagues are analyzing the following health outcomes: time to death, time to hospitalization by cause, and disease progression (time to rehospitalization). They are developing and applying new causal inference methods to estimate exposure–response functions to adjust for confounding and exposure measurement error. Additionally, they are developing tools for reproducible research including approaches for data sharing, record linkage, and statistical software.

STUDY OVERSIGHT

HEI's independent Low-Exposure Epidemiology Studies Oversight Panel continues to provide advice and feedback on the study design, analytical plans, and study progress throughout the duration of the research program.

Given the substantial challenges in conducting a systematic analysis to assess health effects of long-term exposure to low levels of ambient air pollution, HEI has worked actively (and continues to do so) with the study teams to coordinate their efforts and ensure the maximum degree of comparable epidemiological results at the end of this research effort. To this end, HEI has regularly held investigator workshops and site visits, among other activities. In addition, the studies are subject to HEI's special Quality Assurance procedures, which include an audit by an independent audit team (see *www.healtheffects.org/research/quality-assurance).*

REVIEW OF PHASE 1 AND PHASE 2 (FINAL) REPORTS

To inform the ongoing review of the U.S. National Ambient Air Quality Standards (NAAQS) for $PM_{2.5}$ and O_3 starting in 2018, HEI requested Phase 1 reports from the investigators based on the research completed during the first two years of the Canadian and U.S. studies. Thus, the Phase 1 reports by Drs. Brauer and Dominici provide summaries of results to date, including those published in journal articles.

As is common for major research programs, HEI convened a Low-Exposure Epidemiology Studies Review Panel to independently review the Phase 1 reports by Drs. Brauer and Dominici. The Panel consists of seven experts in epidemiology, exposure assessment, and biostatistics (see Contributors page). Commentaries by the Review Panel accompany the Phase 1 reports. The Panel will also review the final reports of the three studies.

The Phase 1 Research Reports provide an opportunity to present the results from the first two years of research in one place and to present the Review Panel's Commentaries, which review the results and evaluate the studies' strengths and weaknesses. The three studies commenced in spring 2016 and are expected to be completed in summer 2020, with final reports published during 2021.

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HEI STATEMENT

Synopsis of Research Report 203

Mortality–Air Pollution Associations in Low-Exposure Environments (MAPLE): Phase 1

INTRODUCTION

The levels of ambient air pollutants have declined significantly over the last few decades in North America, Europe, and in other developed regions. Recent epidemiological studies, however, have suggested an association between exposure to ambient levels of air pollution — even below the U.S. National Ambient Air Quality Standards (NAAQS) — and adverse health effects. In view of the importance of such research findings, in 2014 the Health Effects Institute issued a request for applications (RFA14-3), seeking to fund research to assess the health effects of long-term exposure to low levels of ambient air pollution and to develop statistical methods for conducting such research. HEI funded three studies under this program, each using state-of-the-art exposure methods and very large cohorts, to investigate these questions. The studies are based in

What This Study Adds

- This study addresses important questions regarding associations of air pollution exposure and health outcomes at ambient air pollution levels at or below current national ambient air quality standards.
- The investigators combined state-of-the-art satellite data, ground-level measurements, atmospheric modeling data, and land-use covariates to estimate annual exposure to outdoor $PM_{2.5}$ (particulate matter $\leq$ 2.5 μm in aerodynamic diameter) at high spatial resolution (1 km^2) across the United States and Canada from 1981–2016.
- They analyzed four large, nationally representative Canadian cohorts comprised of approximately 9 million respondents based on census data and a national health survey.
- The study reported associations between nonaccidental mortality and long-term exposure to outdoor $PM_{2.5}$ concentrations, including levels below the current annual U.S. national ambient air quality standard for $PM_{2.5}$ of 12 $\mu g/m^3$.
- The associations were robust to most adjustments for potential confounding by a number of lifestyle and behavioral factors and by exposure to nitrogen dioxide, although effects of ozone exposures on the main $PM_{2.5}$ results need further exploration.
- The HEI Low-Exposure Epidemiology Studies Review Panel noted that several important issues still need to be addressed regarding these results, particularly the degree to which alternative statistical methods affect the exposure–response relationship, as well as possible explanations for the strong influence of ozone on the $PM_{2.5}$ models.
- The Panel concluded that Brauer and colleagues have conducted a thorough and innovative study on a large population-based cohort using advanced methods for both exposure and health assessment, including the derivation of concentration–response functions. While initial conclusions may be drawn from these analyses, the Panel awaits the extensive further analyses underway before reaching full conclusions on the air pollution and public health implications of this important effort.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Michael Brauer at The University of British Columbia, School of Population and Public Health, Vancouver, BC, Canada, and colleagues. Research Report 203 contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Review Committee.

the United States, Canada, and Europe, thus providing a comprehensive cross-section of the industrialized countries where ambient levels are quite low.

The low-exposure-level studies are scheduled to be completed in 2020. In 2018, in order to inform the ongoing review of the NAAQS for fine particles and ozone, HEI requested Phase 1 reports from the U.S. and Canadian investigators. These two Phase 1 reports provided an opportunity for a specially formed Low-Exposure Epidemiology Studies Review Panel to review the methods and results and to evaluate the strengths and weaknesses of the studies. This statement focuses on the study by Dr. Michael Brauer of The University of British Columbia in Vancouver, Canada, titled, "Mortality–Air Pollution Associations in Low-Exposure Environments (MAPLE)."

APPROACH

Brauer and colleagues used a very large (~9 million people) and nationally representative sample of the adult Canadian population to evaluate health effects of air pollution at low ambient concentrations. Data were obtained on approximately 8.5 million participants who responded to the long-form census (ages 25–90) in 1991, 1996, and 2001 (Canadian Census Health and Environment Cohort, or CanCHEC); they also accessed data on ~550,000 respondents to the annual Canadian Community Health Survey between 2001 and 2012 (CCHS), which includes additional lifestyle and behavioral information. To derive exposure estimates at a fine spatial scale (1-km^2 grid) during the period 1981–2016, the research team developed hybrid exposure models using primarily satellite measurements, as well as GEOS-Chem atmospheric modeling data, land-use variables, and routinely collected monitoring data for particulate matter ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) in Canada and the United States. They also estimated exposures to nitrogen dioxide (NO_2) at a 100-m^2 grid and ozone (O_3) at 10- or 21-km^2 grids.

Data sources for the exposure estimates included the moderate resolution imaging spectroradiometer (MODIS) instrument for the 1-km^2 aerosol optical depth (AOD) data (available since 1998), and ground-monitoring estimates from the Interagency Monitoring of Protected Visual Environments (IMPROVE), Canadian National Air Pollution Surveillance, and United States Air Quality System Data Mart. Aerosol composition information from IMPROVE was used to inform GEOS-Chem parameters to improve the AOD–surface $PM_{2.5}$ relationship. The investigators used the GEOS-Chem chemical transport model to combine remote-sensing-based AOD with simulations of the daily AOD-to-surface-$PM_{2.5}$ relationship to produce annual $PM_{2.5}$ estimates. These surface estimates were further refined through the application of a geographically weighted regression technique that combines monthly mean ground measurements with the surface $PM_{2.5}$ estimates. For application in epidemiological analysis, these resulting hybrid estimates were then projected back (*backcasted*) for the years 1981 through 1999, using GEOS-Chem simulations and historical ground-based measurements of $PM_{2.5}$, PM_{10}, and total suspended particles. Similarly, an NO_2 model was developed at a very fine spatial resolution, obtained through satellite inputs (10 km^2) that were downscaled to 100 m^2 using land-use regression modeling. In contrast, the exposure estimates for O_3 and O_x (combined oxidant capacity of NO_2 and O_3) have a coarser resolution (10- or 21-km^2) compared with the $PM_{2.5}$ model.

For the epidemiological analyses, the annual $PM_{2.5}$ exposure estimates were assigned to respondents in each of the years 1981–2016, based on residential location from geocoded postal codes, taking into account residential mobility. Canadian urban postal codes often correspond to one side of a city block or to a single apartment building and fall within a single 1-km^2 raster of $PM_{2.5}$ concentration, while rural postal codes are often much larger. Since there may be greater potential for exposure misclassification among respondents with rural postal codes, investigators considered models with varying buffers for urban (1 km^2) and rural (10 km^2) residences. The exposure assignment used a constant temporal 3-year moving average.

Investigators linked respondents to vital statistics and tax records through 2016 to assess the relationship of mortality with $PM_{2.5}$ exposure. Next, they fitted Cox proportional hazards models for all individuals based on the year of follow-up for all four cohorts. All survival models were stratified at baseline by age (5-year groups), sex, and immigrant status (yes/no). Hazard ratios (per 10-μg/m^3 $PM_{2.5}$ exposure) were computed for the CCHS cohort and for each of the three CanCHEC cohorts; the latter were also pooled to obtain a single summary hazard ratio using meta-analytic methods. The investigators fit two primary covariate adjustment models (i.e., a model informed by directed acyclic graphs

[DAGs] and a fully adjusted model). Both models adjusted for geographically based covariates, while the full model further adjusted for available individual-based covariates.

The investigators also examined the shape of the association between long-term exposure to ambient concentrations of $PM_{2.5}$ and nonaccidental mortality by first fitting a restricted cubic spline (RCS) function of exposure in the Cox model. They then used predictions from that spline function to fit shape-constrained health impact functions (SCHIFs) in all four cohorts.

Brauer and colleagues further evaluated indirect adjustment for missing behavioral factors (i.e., smoking, alcohol use, exercise, and diet) using the CCHS cohort. They also assessed the sensitivity of $PM_{2.5}$–mortality associations in the Canadian immigrant population and adjusted for ground-level O_3, NO_2, and O_x and the choice of varying temporal (1-, 3-, and 8-year moving average) and spatial (1-, 5-, and 10- km^2) scales.

RESULTS

Assigned mean $PM_{2.5}$ estimates were highest in the 1991 CanCHEC cohort and lowest in the more recent 2001 CanCHEC cohort, with greater declines of $PM_{2.5}$ concentrations in locations with previously higher concentrations. These results reflect the decreasing trend of the overall population-weighted annual average $PM_{2.5}$ concentrations over the past 35 years across North America — from 22 $\mu g/m^3$ in 1981 to 8 $\mu g/m^3$ in 2016.

Brauer and colleagues reported that the exposure prediction model performed well, and $PM_{2.5}$ estimates at 1-km^2 resolution were in good agreement with ground-based monitors across Canada and the northern United States. The historical backcasted $PM_{2.5}$ exposure estimates improved when all ground-based measurement sites (i.e., $PM_{2.5}$, PM_{10}, and total suspended particles) were used for adjustment, compared with $PM_{2.5}$-only ground monitors. When satellite remote sensing information was removed from the models, the performance of estimate prediction decreased.

Brauer and colleagues found that a 10-$\mu g/m^3$ increment in long-term average $PM_{2.5}$ was associated with a 5% increase in the risk of nonaccidental mortality in the main model of pooled estimates across the three CanCHEC cohorts (see Statement Figure). Consistent results, though generally smaller than the full model effect estimates, were also found in the DAG-adjusted models. Generally, the $PM_{2.5}$–mortality risk was slightly lower in the 1991 and 1996 cohorts compared with the 2001 CanCHEC cohort. In their analyses of the CCHS cohort data, with additional potential individual confounders, such as smoking habits, obesity, exercise, alcohol consumption, and diet, they reported an 11% increase in the risk of nonaccidental mortality.

The immigrant subanalyses found larger $PM_{2.5}$ – mortality hazard ratios for nonimmigrants when compared with immigrants in the CCHS and 1991 and 1996 CanCHEC cohorts; however, the reverse was observed in the 2001 CanCHEC cohort, though differences were smaller.

Results from the CCHC cohort analysis and the indirect adjustment suggest that behavioral covariates (e.g., smoking and diet) only slightly confounded the $PM_{2.5}$–mortality association. Based on sensitivity analyses in the 2001 CanCHEC cohort, the investigators concluded that missing data on behavioral covariates were unlikely to significantly confound the $PM_{2.5}$–mortality relationship in the Canadian population.

Overall, both the RCS and the SCHIF analyses show a supralinear association in all four cohorts, with a steep increase in the spline predictions across lower concentrations (i.e., <5 $\mu g/m^3$), followed by a leveling off or a smaller increase after ~10 $\mu g/m^3$. The investigators suggest that there is no evidence of a threshold or sublinear association at very low concentrations. They caution against overinterpretation of the SCHIF results due to wide confidence intervals, and state that these nonlinear hazard risks should not be directly compared with the linear estimates derived from the Cox proportional hazards model.

From their sensitivity analyses using the 2001 CanCHEC cohort, investigators also concluded that (1) the best fitting models were those with longer moving exposure averages (up to 8 years) and smaller spatial scales (1 km^2 vs. 10 km^2), and (2) consistently observed across all cohorts, there was a blunting or elimination of the $PM_{2.5}$ hazard ratios after adjustment for the copollutants O_3 and O_x.

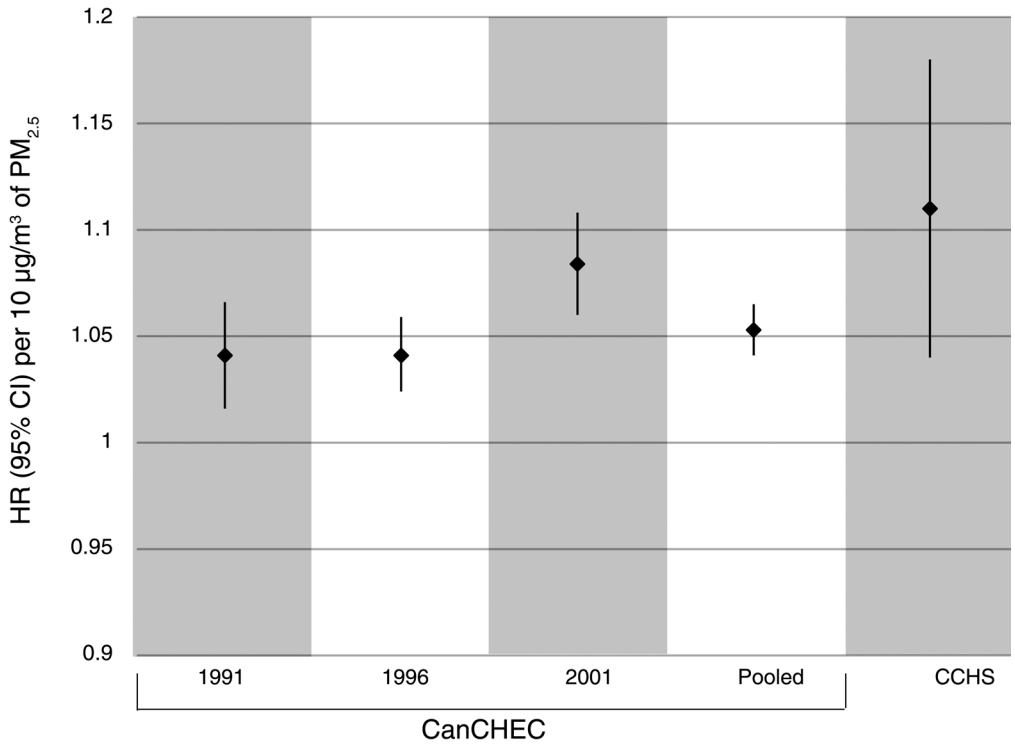
INTERPRETATION AND CONCLUSIONS

In its independent review of the research, HEI's Low-Exposure Epidemiology Studies Review Panel noted that Brauer and colleagues have conducted an

impressive and innovative study on a very large population-based cohort using advanced methods for both exposure and health assessment, including the derivation of concentration–response functions. This research contributes to the growing body of epidemiological evidence regarding associations of air pollution and health at low ambient $PM_{2.5}$ concentrations and advances the science considerably. Across all cohorts, Brauer and colleagues showed evidence of associations between $PM_{2.5}$ and nonaccidental mortality at concentrations below current health standards. Finally, analyses of the rich CCHS data set suggested that adjustment for additional covariates (i.e., smoking and diet) appeared to be largely unnecessary after adjustment for the available covariates in the CanCHEC data. However, the Review Panel notes that important uncertainties still remain in this Phase 1 report that preclude drawing firm conclusions.

The $PM_{2.5}$ exposure model is an impressive undertaking, drawing from state-of-the-art techniques that allow a spatial resolution of 1 km^2 over the entire area of Canada and the United States. The Review Panel notes that, while this high spatial resolution is a commendable improvement from previous research, this model — like others in the literature — inherently cannot fully capture very fine-scale $PM_{2.5}$ spatial gradients near sources such as roadways and local point emission sources, producing some degree of exposure measurement error.

The predicted $PM_{2.5}$ exposure estimates were improved by the inclusion of satellite remote sensing information — which became available in 1998 — and, as expected, the more recent estimates are more stable and accurate. The Review Panel notes that the performance of the predictions over time and associated error are important considerations in the CanCHEC pooled results from this study, as well as in potential application of this methodology in other studies. Another potential source of error could be that the exposure models seem to be highly reliant on data from the United States, where pollution levels and ground monitor density are generally higher than in Canada.



Statement Figure. Association between $PM_{2.5}$ and nonaccidental mortality in the 1991, 1996, 2001, and pooled CanCHEC cohorts and the CCHS cohort. Shown here are estimated hazard ratios and 95% confidence intervals from the main (full) models.

The health analyses were conducted in large nationally representative samples of the adult Canadian population, using rich data sets with individual-level and geographical covariates. Complete annual residential history data for all cohort members based on unique permission for linkage to postal codes in tax records allowed for detailed spatial characterization and time-varying exposures, a particularly useful feature of this study. The Review Panel commends the investigators on their thorough investigation into the sensitivity of their findings to various methodological choices. These sensitivity analyses demonstrated that the results from the DAG-informed and full models are not substantially different, which increases the confidence in the study's findings.

The evaluation of the concentration–response curve at low exposures was another strength of this study. At this time, the Review Panel finds it difficult to assess the degree to which the SCHIF approach — which has not yet been applied extensively for this kind of analysis — produces results (including uncertainty estimates) that are consistent with what would be obtained by fitting the nonlinear association directly in the Cox model. They appreciated that other more traditional methods to characterize the concentration–response function were explored, such as restricted cubic splines.

Although the main focus of the current study was on $PM_{2.5}$, the investigators used exposure models developed earlier for NO_2, O_3, and O_x to investigate the extent to which those pollutants might influence the $PM_{2.5}$–mortality association. While the estimated hazard ratios showed general consistency of a positive relationship between long-term exposure to low-level $PM_{2.5}$ and nonaccidental mortality across models, a distinct exception was the sensitivity and blunting of the findings to the inclusion of O_3 or O_x as covariates in multipollutant $PM_{2.5}$ models. However, the differing spatial scale of the three-pollutant exposure prediction models (i.e., $PM_{2.5}$ at 1 km^2, NO_2 at 100 m^2, and O_3 at 10 or 21 km^2) hinders drawing conclusions on how these pollutants correlate over space. While the $PM_{2.5}$ models are sensitive to the inclusion of O_3 and O_x, conclusions cannot be drawn at this point about whether the attenuated hazard ratios result from some or all of the following: (1) the confounding effect of O_3; (2) the impacts of O_3 measurement error and the different spatial scales of the pollutant predictions; (3) poorly captured interactions between oxidant pollution and $PM_{2.5}$; and/or (4) the confounding role of O_3 as a measure of urban pollution, more generally, or as a measure of $PM_{2.5}$ characteristics.

It is not clear to the Panel whether the stronger associations in nonimmigrants could be due to exposure misclassification during key time periods, a healthy immigrant effect (given Canadian policies on health status when admitting immigrants into the country), or other reasons.

In summary, Brauer and his colleagues have performed a thorough and state-of-the-art study, and their initial results find that $PM_{2.5}$ exposure at low ambient concentrations — below the U.S. NAAQS — is associated with nonaccidental mortality. However, this Phase 1 report presents work that is still in progress; the investigators' Final Phase 2 report is expected to shed light on the robustness of the association and the concentration–response curve. In the absence of the forthcoming analyses, these initial conclusions on associations and concentration–response relationships should be treated with appropriate caution.

INVESTIGATORS' REPORT

Mortality–Air Pollution Associations in Low-Exposure Environments (MAPLE): Phase 1

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ABSTRACT

Introduction Fine particulate matter (particulate matter ≤2.5 μm in aerodynamic diameter, or $PM_{2.5}$*) is associated with mortality, but the lower range of relevant concentrations is unknown. Novel satellite-derived estimates of outdoor $PM_{2.5}$ concentrations were applied to several large population-based cohorts, and the shape of the relationship with nonaccidental mortality was characterized, with emphasis on the low concentrations (<12 μg/m^3) observed throughout Canada.

Methods Annual satellite-derived estimates of outdoor $PM_{2.5}$ concentrations were developed at 1-km^2 spatial resolution across Canada for 2000–2016 and backcasted to 1981 using remote sensing, chemical transport models, and ground monitoring data. Targeted ground-based measurements were conducted to measure the relationship between columnar aerosol optical depth (AOD) and ground-level $PM_{2.5}$. Both existing and targeted ground-based measurements were analyzed to develop improved exposure data sets for subsequent epidemiological analyses.

Residential histories derived from annual tax records were used to estimate $PM_{2.5}$ exposures for subjects whose ages ranged from 25 to 90 years. About 8.5 million were from three Canadian Census Health and Environment Cohort (CanCHEC) analytic files and another 540,900 were Canadian Community Health Survey (CCHS) participants. Mortality was linked through the year 2016. Hazard ratios (HR) were estimated with Cox Proportional Hazard models using a 3-year moving average exposure with a 1-year lag, with the year of follow-up as the time axis. All models were stratified by 5-year age groups, sex, and immigrant status. Covariates were based on directed acyclical graphs (DAG), and included contextual variables (airshed, community size, neighborhood dependence, neighborhood deprivation, ethnic concentration, neighborhood instability, and urban form). A second model was examined including the DAG-based covariates as well as all subject-level risk factors (income, education, marital status, indigenous identity, employment status, occupational class, and visible minority status) available in each cohort. Additional subject-level behavioral covariates (fruit and vegetable consumption, leisure exercise frequency, alcohol consumption, smoking, and body mass index [BMI]) were included in the CCHS analysis.

This Investigators' Report is one part of Health Effects Institute Research Report 203, which also includes a Commentary by the Low-Exposure Epidemiology Studies Review Panel and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. Michael Brauer, University of British Columbia, School of Population and Public Health, 366A – 2206 East Mall, Vancouver, BC V6T1Z3, Canada; e-mail: *michael.brauer@ubc.ca.*

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

Sensitivity analyses evaluated adjustment for covariates and gaseous copollutants (nitrogen dioxide [NO_2] and ozone [O_3]), as well as exposure time windows and spatial scales. Estimates were evaluated across strata of age, sex, and immigrant status. The shape of the $PM_{2.5}$–mortality association was examined by first fitting restricted cubic splines (RCS) with a large number of knots and then fitting the shape-constrained health impact function (SCHIF) to the RCS predictions and their standard errors (SE). This method provides graphical results indicating the RCS predictions, as a nonparametric means of characterizing the concentration–response relationship in detail and the resulting mean SCHIF and accompanying uncertainty as a parametric summary.

Sensitivity analyses were conducted in the CCHS cohort to evaluate the potential influence of unmeasured covariates on air pollution risk estimates. Specifically, survival models with all available risk factors were fit and compared with models that omitted covariates not available in the CanCHEC cohorts. In addition, the $PM_{2.5}$ risk estimate in the CanCHEC cohort was indirectly adjusted for multiple individual-level risk factors by estimating the association between $PM_{2.5}$ and these covariates within the CCHS.

Results Satellite-derived $PM_{2.5}$ estimates were low and highly correlated with ground monitors. HR estimates (per 10-$\mu g/m^3$ increase in $PM_{2.5}$) were similar for the 1991 (1.041, 95% confidence interval [CI]: 1.016–1.066) and 1996 (1.041, 1.024–1.059) CanCHEC cohorts with a larger estimate observed for the 2001 cohort (1.084, 1.060–1.108). The pooled cohort HR estimate was 1.053 (1.041–1.065). In the CCHS an analogous model indicated a HR of 1.13 (95% CI: 1.06–1.21), which was reduced slightly with the addition of behavioral covariates (1.11, 1.04–1.18). In each of the CanCHEC cohorts, the RCS increased rapidly over lower concentrations, slightly declining between the 25th and 75th percentiles and then increasing beyond the 75th percentile. The steepness of the increase in the RCS over lower concentrations diminished as the cohort start date increased. The SCHIFs displayed a supralinear association in each of the three CanCHEC cohorts and in the CCHS cohort.

In sensitivity analyses conducted with the 2001 CanCHEC, longer moving averages (1, 3, and 8 years) and smaller spatial scales (1 km^2 vs. 10 km^2) of exposure assignment resulted in larger associations between $PM_{2.5}$ and mortality. In both the CCHS and CanCHEC analyses, the relationship between nonaccidental mortality and $PM_{2.5}$ was attenuated when O_3 or a weighted measure of oxidant gases was included in models. In the CCHS analysis, but not in CanCHEC, $PM_{2.5}$ HRs were also attenuated by the inclusion of NO_2. Application of the indirect adjustment and comparisons within the CCHS analysis suggests that missing data on behavioral risk factors for mortality had little impact on the magnitude of $PM_{2.5}$–mortality associations. While immigrants displayed improved overall survival compared with those born in Canada, their sensitivity to $PM_{2.5}$ was similar to or larger than that for nonimmigrants, with differences between immigrants and nonimmigrants decreasing in the more recent cohorts.

Conclusions In several large population-based cohorts exposed to low levels of air pollution, consistent associations were observed between $PM_{2.5}$ and nonaccidental mortality for concentrations as low as 5 $\mu g/m^3$. This relationship was supralinear with no apparent threshold or sublinear association.

INTRODUCTION

Exposure to $PM_{2.5}$ is generally accepted as a causal risk factor for mortality and was estimated to be responsible for 2.9 million deaths and 83 million disability-adjusted life years in 2017 (Global Burden of Disease 2018). Several large epidemiological cohort studies have linked long-term exposure to $PM_{2.5}$ with an increased risk for nonaccidental mortality and chronic diseases such as lung cancer, heart disease, and stroke (Beelen et al. 2014; Burnett et al. 2018; Crouse et al. 2015; Pope et al. 2002; Pun et al. 2017). In the United States, for example, the American Cancer Society cohort study estimated increased relative risks (RR) of nonaccidental mortality (RR = 1.06, 95% CI: 1.02–1.11 per 10-$\mu g/m^3$ increase), as well as cardiopulmonary and lung cancer mortality associated with exposures to $PM_{2.5}$ (Pope et al. 2002). More recently, in an analysis of 60 million Medicare beneficiaries with 12 years of follow-up, nonaccidental mortality was associated with long-term average $PM_{2.5}$ concentrations (HR = 1.073, 95% CI: 1.071–1.075 per 10-$\mu g/m^3$ increase), with associations remaining even when restricted to person-years with exposure less than 12 $\mu g/m^3$ (Di et al. 2017). In an analysis of 22 European cohorts (European Study of Cohorts for Air Pollution Effects), pooled HR for nonaccidental mortality was 1.07 (95% CI: 1.02–1.13) per increase of 5 $\mu g/m^3$ (Beelen et al. 2014). In a study in China of nearly 200,000 men over the age of 40 with 15 years of follow-up, a 10-$\mu g/m^3$ increase in annual average $PM_{2.5}$ was associated with a 9% increase in nonaccidental mortality (95% CI: 1.08–1.09) (Yin et al. 2017), while a study of 13,000 men and women over age 65 in China with 6 years of follow-up estimated a similar magnitude HR for nonaccidental mortality of 1.08 (95% CI: 1.06–1.09 per 10-$\mu g/m^3$ increase in $PM_{2.5}$) (Li et al. 2018).

Positive associations between outdoor $PM_{2.5}$ mass concentrations and mortality have also been repeatedly demonstrated in populations living in areas with low $PM_{2.5}$ levels. For instance, previous studies indicated that exposure to $PM_{2.5}$ was associated with an increased risk of nonaccidental and cardiovascular mortality among Canadians, despite their living in areas where $PM_{2.5}$ mass concentrations were typically below 12 $\mu g/m^3$ (Crouse et al. 2012, 2015; Nasari et al. 2016; Pinault et al. 2016b, 2017; Weichenthal et al. 2017). Crouse and colleagues (2012) used the 1991 CanCHEC to conduct the first nationwide cohort analysis and identified a nonaccidental mortality HR of 1.15 (95% CI: 1.13–1.16) per 10-$\mu g/m^3$ change in $PM_{2.5}$ among nonimmigrant adults. Concentration–response relationships in areas with low $PM_{2.5}$ concentrations are of particular interest as many global regions are approaching these lower levels of exposure (Apte et al. 2015). Canada provides an ideal setting to study these relationships given the availability of large, national cohorts with sufficient sample sizes and detailed exposure information, and that nearly all Canadians live in areas with relatively low $PM_{2.5}$ concentrations.

STUDY RATIONALE

Crouse and colleagues (2012) examined the concentration–response relationship between $PM_{2.5}$ and mortality using the 1991 CanCHEC v1, which followed 2.1 million census respondents over a 10-year period. The Crouse study demonstrated an important impact of low $PM_{2.5}$ concentrations on mortality but was subject to several limitations. First, the $PM_{2.5}$ estimates were available only at a coarse spatial resolution (10 km × 10 km), possibly contributing to exposure misclassification. Second, exposure estimates were assigned only to census enumeration area centroids at baseline, therefore not accounting for residential mobility during follow-up. Third, exposure estimates were based on a 2001–2006 average, and changes in concentrations over time were not considered. Fourth, behavioral covariates such as smoking were not included in the analyses.

Subsequent studies have addressed several of these limitations. For instance, a follow-up study of the same cohort added five additional years of follow-up and used a time-varying 7-year moving average of $PM_{2.5}$ exposures assigned to residential postal codes (which are more precise than enumeration area centroids) to account for annual residential mobility (Crouse et al. 2015). Another study accounted for behavioral covariates such as smoking by using data from the pooled CCHS mortality cohort (mCCHS) in the analysis (Pinault et al. 2016b).

The aim of this ongoing project, Mortality–Air Pollution associations in Low-Exposure environments (MAPLE), is to provide updated analyses using larger and more recent cohorts than the 1991 CanCHEC. This project includes the 1991, 1996, and 2001 CanCHEC cohorts and the cohort of CCHS respondents from 2001–2012, with follow-up to 2016 for all cohorts. We deterministically linked participants to mortality records using individual identifiers (social insurance number), whereas prior analyses used probabilistic linkage. In the current report we address many of the remaining limitations of the previous studies including:

1. **Refining spatial resolution:** MAPLE assigned exposures based on a fine-scale $PM_{2.5}$ model of ~1 km × 1 km resolution that incorporated both remote-sensing-based estimates and ground-level observations (Pinault et al. 2017).
2. **Residential mobility at follow-up:** MAPLE used a complete annual residential history generated for all cohort members based on a linkage to postal codes in tax records (as in Crouse et al. 2015). Missing postal codes in residential histories were imputed with a probabilistic algorithm (Finès et al. 2017).
3. **Year-adjusted exposure estimates:** As in Crouse and colleagues (2015), MAPLE used time-varying exposures based on year-adjusted estimates from 1981 onward. In the case of MAPLE, a new and more sophisticated backcasting approach was used in estimating historical exposures.
4. **Behavioral covariates:** Parallel analyses were conducted in a new, larger mCCHS cohort, and indirect adjustment for missing behavioral risk factors was evaluated for application to the CanCHEC cohorts.
5. **Immigrants**: Most prior analyses excluded all immigrants outright or limited their inclusion based on their time in Canada (e.g., minimum 20 years). In MAPLE we included all immigrant respondents who have been in Canada for at least 10 years prior to the cohort index year.

STUDY OBJECTIVES

The primary aim of MAPLE is to provide a detailed characterization of the relationship between mortality and exposure to low concentrations of $PM_{2.5}$ in Canada. This work addresses many of the limitations listed above and extends previous work in a number of important ways. In this report, we focus specifically on nonaccidental mortality for the main analyses, although specific causes of death have been included in exposure sensitivity and immigrant subanalyses to provide a more in-depth understanding of different exposure metrics and the impacts of

including different immigrant groups. Detailed analyses of cause-specific mortality will be included in the final report, along with analyses where we restrict exposures below selected concentrations (i.e., 12, 10, 8, and 6 $\mu g/m^3$).

Exposure Assignment

We applied satellite-based $PM_{2.5}$ exposure estimates at a 1 km × 1 km spatial resolution across North America for each year from 1981–2016. These annual estimates were based on a combination of remote-sensing-based AOD, a chemical transport model (GEOS-Chem), land-use information, and ground monitoring data.

Specifically, we:

1. Developed and applied annual average satellite-based estimates of $PM_{2.5}$ across North America at 1 km 1 km spatial resolution;
2. Evaluated $PM_{2.5}$ estimates using insight gained from comparisons of colocated measurements of $PM_{2.5}$ and AOD with GEOS-Chem simulations of that relationship;
3. Employed a combination of geophysical and statistical methods, together with land-use information, to further refine the above $PM_{2.5}$ estimates;
4. Created annual estimates of $PM_{2.5}$ based on a combination of remote sensing, GEOS-Chem, land-use information, and ground data for 1981–2016;
5. Made the above refined $PM_{2.5}$ estimates available to other HEI-funded studies that cover Canada and the United States for incorporation into their analyses;
6. Used available $PM_{2.5}$ and total suspended PM (TSP) monitoring data in Canada from 1981–1999, to scale the 1 km^2 2004–2008 surface back in time annually over the 1981 to 1999 period, maintaining the 1 km × 1 km grid detail over the 1981–2016 period.

Epidemiological Analysis

We examined the shape of the association between long-term exposure to ambient concentrations of $PM_{2.5}$ and nonaccidental mortality in four large, population-based Canadian cohorts.

Specifically, we:

1. Linked the following four cohorts to mortality, vital statistics, and tax records up to December 31, 2016:
   - 1991 CanCHEC — data from 2.5 million participants (after exclusions) who completed the 1991 long-form census (before exclusions);
   - 1996 CanCHEC — data from 3 million participants (after exclusions) who completed the 1996 long-form census (before exclusions);
   - 2001 CanCHEC — data from 3 million participants (after exclusions) who completed the 2001 long-form census (before exclusions);
   - CCHS — data from 540,900 participants who completed the 2001, 2003, 2005, 2007, 2008, 2009, 2010, 2011, or 2012 survey panels.
2. Examined the shape of the association between long-term exposure to ambient concentrations of $PM_{2.5}$ and nonaccidental mortality using RCS and SCHIF in all four cohorts.
3. Conducted subanalyses in the 2001 CanCHEC cohort that:
   - Evaluated the indirect adjustment for missing behavioral risk factors such as smoking habits and diet;
   - Evaluated the impact of adjustment for ground level O_3, NO_2, or their combined oxidant capacity (O_x);
   - Evaluated the sensitivity of $PM_{2.5}$–mortality associations to the choice of exposure time window (1, 3, or 8 years);
   - Evaluated the sensitivity of $PM_{2.5}$–mortality associations to the choice of spatial scale used for exposure assessment (1, 5, or 10 km^2).
4. Examined risk estimates across strata of age, sex, and immigrant status.

METHODS

EXPOSURE ASSESSMENT

Overview

Figure 1 provides an overview of the development of satellite-derived $PM_{2.5}$ for MAPLE. Daily satellite retrievals of AOD at 1 km × 1 km resolution were combined with simulations of the daily AOD to $PM_{2.5}$ relationship using GEOS-Chem (chemical transport model) at a 0.5° × 0.67° resolution to produce geophysical $PM_{2.5}$ estimates following the methods described in van Donkelaar and colleagues (2015). The GEOS-Chem simulation accounts for the relationship between available daily satellite observations and monthly mean concentrations. Geographically weighted regression (GWR) is applied to statistically fuse monthly mean measurements from $PM_{2.5}$ monitors with the geophysical $PM_{2.5}$ estimates to produce refined hybrid $PM_{2.5}$ estimates. These hybrid estimates are backcasted using GEOS-Chem simulations and $PM_{2.5}$, PM_{10}, and TSP measurements to produce estimates for the period 1981–1999 as described below and in more detail by Meng and colleagues (2019). Targeted colocated measurements of $PM_{2.5}$ and AOD were conducted at five measurement sites in

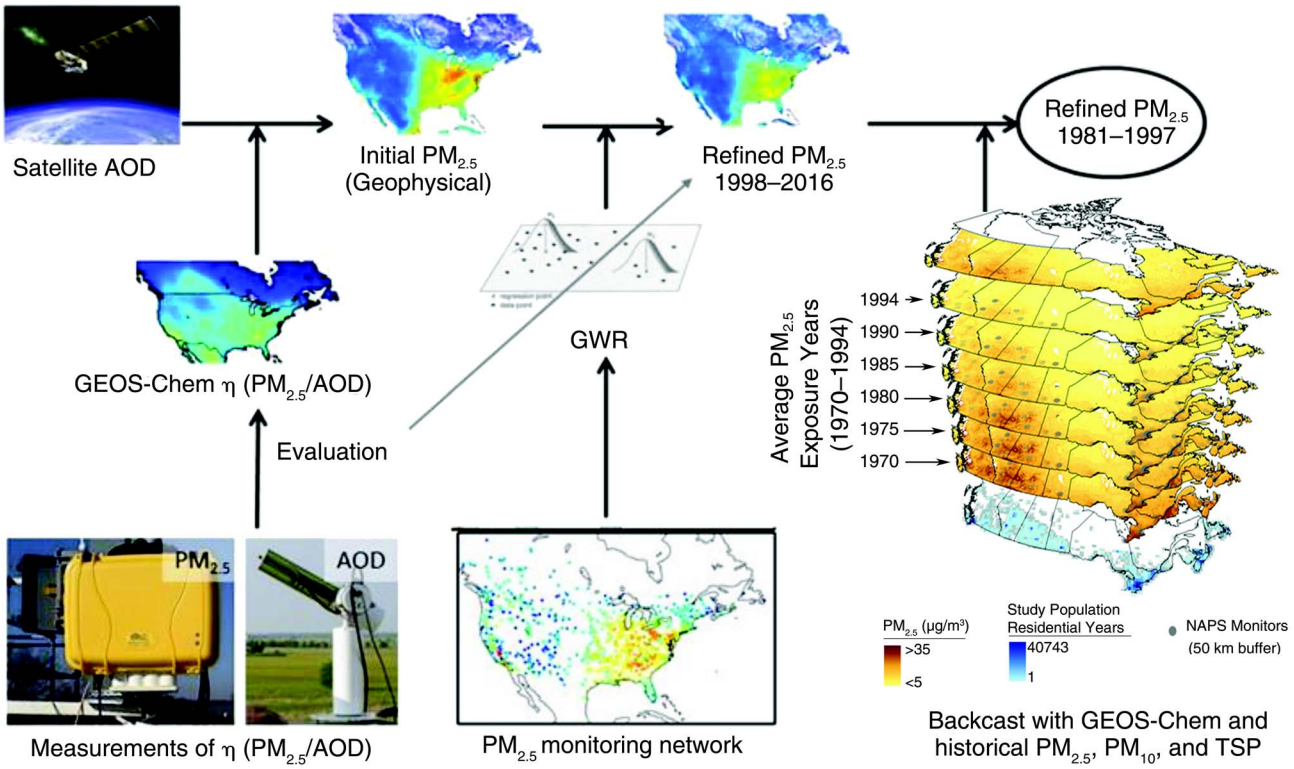

Figure 1. Schematic of the exposure development process for $PM_{2.5}$.

Canada and applied to evaluate the simulation of AOD-to-$PM_{2.5}$ as discussed in the next section.

Collection of Measurements

We expanded the Surface PARTiculate mAtter Network (SPARTAN) (Snider et al. 2015) to routinely collect colocated measurements of $PM_{2.5}$, aerosol scatter, and AOD at five sites across Canada. This collection allows us to evaluate and potentially improve simulations of the $PM_{2.5}$ to AOD ratio in regions of low $PM_{2.5}$ mass concentrations.

Measurements include an impaction filter sampler for analysis of mass and composition, as well as a nephelometer that provides high temporal resolution to relate observations during cloud-free conditions at satellite overpass time to 24-hour averages. The combination of scatter and mass measurements allows for an assessment of the relationship between satellite measurements of backscattered sunlight and the $PM_{2.5}$ mass concentrations of relevance for health. These measurements are compared with GEOS-Chem simulations of the AOD to $PM_{2.5}$ relationship to better understand the geophysical processes affecting the relationship, and in turn to improve the ability of chemical transport models to predict this quantity. For example, while sampling sites were established and collection and chemical analysis of collected filters was ongoing, we utilized data from the Interagency Monitoring of PRotected Visual Environments (IMPROVE) network to evaluate the representation of aerosol mass scattering efficiency in the GEOS-Chem model (IMPROVE 2019). Mass scattering efficiency is fundamental to the measurement of AOD and influences the accuracy of $PM_{2.5}$ estimates as GEOS-Chem simulates the columnar AOD to surface $PM_{2.5}$ relationship. We evaluated the representation of mass scattering efficiency in

GEOS-Chem using colocated measurements of aerosol scatter and mass from IMPROVE network sites between 2000 and 2015.

Creating Refined $PM_{2.5}$ Exposure Estimates

We developed satellite-based $PM_{2.5}$ exposure estimates at a 1 km × 1 km spatial resolution for each year from 1981–2016 across Canada. This represents a 100-fold higher resolution than the 10 km × 10 km resolution used previously. These estimates were based on a combination of remote-sensing-based AOD, translation of AOD to surface $PM_{2.5}$ concentrations using GEOS-Chem, and the integration of these concentrations with land use and ground monitoring data. The 1-km^2 AOD data source for this estimate was from the MODIS (Moderate Resolution Imaging Spectroradiometer) instrument and was based on an optimal estimation extended to a 1-km^2 resolution (van Donkelaar et al. 2015). We developed a spatiotemporally varying factor η that describes the AOD to $PM_{2.5}$ ratio within the GEOS-Chem model. GEOS-Chem solves for the temporal and spatial evolution of aerosol (sulfate, nitrate, ammonium, carbonaceous, mineral dust, and sea salt) and gaseous compounds using meteorological data sets, emission inventories, and equations that represent the physics and chemistry of atmospheric constituents (GEOS-Chem 2019). We used the recently available improved spatial resolution of GEOS-Forward Processing meteorological data to increase the spatial resolution of η by a factor of 20 to 0.5° × 0.67°. The combination of improved resolution in η and in AOD results in $PM_{2.5}$ estimates for North America at a 1 km × 1 km resolution.

These estimates are available for incorporation into other HEI-supported studies in North America and have been made publicly available (data set version VA.NA.01; Dalhousie University Atmospheric Composition Analysis Group) (Meng et al. 2019; van Donkelaar et al. 2015). As measurement collection and analysis of particle composition is currently ongoing, we will continue to make further refinements with new information on the relationship between $PM_{2.5}$ and AOD provided by the colocated ground measurement data for inclusion in the final report. With additional effort, this approach could also be extended to other regions of the world to support HEI-funded studies elsewhere.

Backcasting

We used available historical ground measurements of $PM_{2.5}$ (beginning in 1984), PM_{10}, and TSP (beginning in 1975) to extend the remote-sensing-based estimates backwards in time for an application to epidemiological analysis (Figure 2). Canadian PM data were obtained from the National Air Pollution Surveillance (Environment Canada 2013). Daily PM data for the United States were obtained from the United States Air Quality System Data Mart for $PM_{2.5}$ and PM_{10} (U.S. Environmental Protection Agency 2018). Using these historical measurements, we developed a consistent $PM_{2.5}$ data set to calibrate the satellite-based estimates and GEOS-Chem simulations historically to estimate annual average concentrations for each year between 1981 and 1999 (Hystad et al. 2011; Meng et al. 2019). Due to the small number of $PM_{2.5}$ measurements available, and the lack of any measurements made prior to 1984, a random effects model was used to estimate $PM_{2.5}$ based on TSP measurements and metropolitan indicator variables. We applied a GWR model for years 1989–2016 using available $PM_{2.5}$ observations and $PM_{2.5}$ concentrations inferred from PM_{10} observations (Meng et al. 2019). Predictors for this model included urban land cover, subgrid elevation difference, and GEOS-Chem simulated aerosol composition. As reliable emission inventories were not available for GEOS-Chem simulations for 1981–1988, we used information on interannual variation from ground-based measurements to backcast gridded $PM_{2.5}$ concentrations. For ground-based measurements, we included TSP, PM_{10}, and $PM_{2.5}$. Since fewer than 200 PM_{10} sites existed before 1986, with even fewer $PM_{2.5}$ sites, we used ground-based $PM_{2.5}$ concentrations inferred from TSP measurements for this period. The ratio between annual mean $PM_{2.5}$ of the year of interest and the 3-year mean $PM_{2.5}$ of the following 3 years over each ground-based monitoring site was calculated for each year. We required 75% completeness coverage to ensure representativeness of the annual mean over each site. We used the ratios from TSP sites as the basis, which were first overwritten by the ratios from PM_{10} sites, and then by the ratios from $PM_{2.5}$ sites. This ratio field from ground-based measurements was then interpolated to other grids using inverse-distance-weighted interpolation. Finally, we applied this ratio field to the 3-year mean $PM_{2.5}$ (of the following 3 years' estimates) to estimate $PM_{2.5}$ for the specific year of interest.

Assigning Exposure Estimates to Cohorts

We applied the North American $PM_{2.5}$ estimates with ground-monitor-based adjustment (data set version VA.NA.01; Dalhousie University Atmospheric Composition Analysis Group) (Meng et al. 2019; van Donkelaar et al. 2015) to the epidemiological analyses. Based on residential location from postal codes, all respondents in each cohort were assigned an exposure estimate, for each year from 1981 through 2016, from the closest 1 km × 1 km grid cell of $PM_{2.5}$ derived above. Postal codes were geocoded

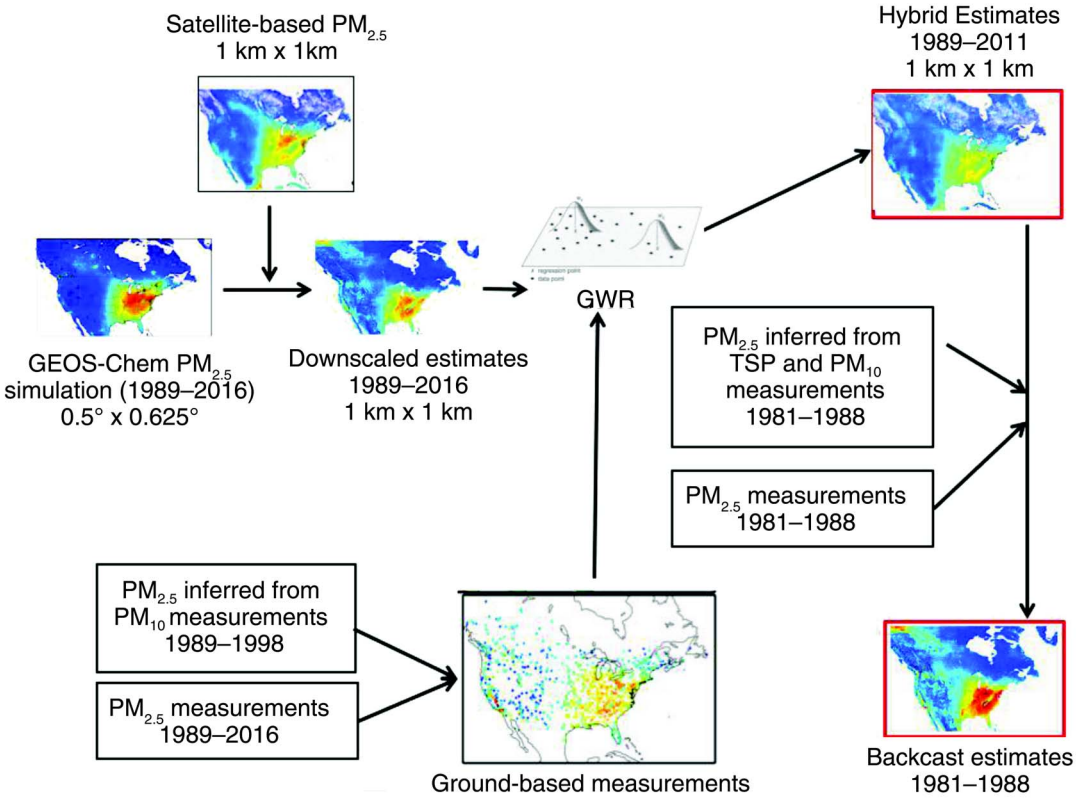

Figure 2. Overview of the $PM_{2.5}$ backcasting estimation methodology. (Reprinted from Meng et al. 2019 [doi:10.1021/acs.est.8b06875] with permission from American Chemical Society (ACS). Further permission related to this article should be directed to ACS.)

using the Statistics Canada Postal Code Conversion File Plus (PCCF+) containing the June 2017 postal code release with additional postal codes from the May 2011 and August 2015 releases (Statistics Canada 2017a). The PCCF+ contains representative coordinates for current and retired postal codes based on the centroid of a block face, dissemination block, or dissemination area. Missing postal codes were imputed based on those reported in adjacent years, using a method where the probability of imputation varies depending on the number of adjacent years missing (Finès et al. 2017). We departed from imputation methods that were implemented in previous publications (e.g., Crouse et al. 2015; Pinault et al. 2017). Postal codes available prior to and after the missing code were required have least two digits in common. Exposure was then assigned based on a population-weighted average of the geographic area covered by these two digits. Previously, in cases where this criterion was not met, we had assigned exposure based on the national population-weighted average for that year.

EPIDEMIOLOGICAL ANALYSIS

The Research Ethics Board of The University of British Columbia determined this study in humans was exempt from ethical review.

Cohort Creation

MAPLE incorporates four longitudinal cohorts:

1. **1991 CanCHEC** — 2.5 million subjects (after exclusions) over the age of 25 years who completed the 1991 long-form census linked to vital statistics, tax records, and cause-of-death from census day (June 4, 1991) to

December 31, 2016, using the methodology previously described in Wilkins and colleagues (2008) and in Peters and colleagues (2013). The long-form census includes content related to family status, education, income, ethnicity, occupation, and employment status.

2. **1996 CanCHEC** — 3 million subjects (after exclusions) over the age of 25 years who completed the 1996 long-form census linked to vital statistics, tax records, and cause-of-death from census day (May 14, 1996) to December 31, 2016 (Christidis et al. 2018).
3. **2001 CanCHEC** — 3 million subjects (after exclusions) over the age of 25 years who completed the 2001 long-form census linked to vital statistics, tax records, and cause-of-death from census day (May 15, 2001) to December 31, 2016 (Pinault et al. 2017).
4. **CCHS** — 540,900 subjects over the age of 25 years who completed one of the survey panels (2001, 2003, 2005, 2007, 2008, 2009, 2010, 2011, or 2012), which are linked to vital statistics, tax records, and cause-of-death from the day of survey completion to December 31, 2016. The CCHS is an annual nationally representative interview survey (Statistics Canada 2005). In addition to basic sociodemographic content, the CCHS also includes individual-level information on self-reported health status, such as BMI, and health behaviors, including diet, physical activity, smoking, and alcohol consumption.

Noninstitutionalized respondents that lived in Canada were considered in scope for linkage (Pinault et al. 2016a). To create the cohorts, respondents who agreed to record linkage and data sharing were linked to death records and residential history through the Statistics Canada Social Data Linkage Environment (Statistics Canada 2017b), which creates linked population data files for social analysis. Linkage was approved by Statistics Canada and is governed by the Directive on Microdata Linkage. The process starts with linkage to the Derived Record Depository, a highly secure linkage environment comprised of a national dynamic relational database of basic personal identifiers. Survey and administrative data are linked to the Derived Record Depository using G-Link, an SAS-based generalized record linkage software that supports deterministic and probabilistic linkage techniques developed at Statistics Canada (Fellegi and Sunter 1969). A list of linked unique individuals is created through linkages that are deterministic (matching records based on unique identifiers) and probabilistic (matching records based on non-unique identifiers such as names, sex, date of birth, and postal code and estimating the likelihood that records are referring to the same entity). Through this linkage, we obtained each respondent's annual mailing address postal code (to account for residential mobility in analysis) and social insurance number on their tax form. Respondents with no postal code history were excluded from the analysis.

Postal code history was not available for each person in every year of follow-up, either because they did not file a tax return or because there were gaps in administrative data. For any gaps in postal code information in a given year, if the person in question had the same postal code postal code the year before and the year after, they were assigned that postal code for the missing year. After this imputation across all CanCHEC cohorts, 87.8% of person-years had an available postal code. We imputed an additional 2.1% of person-years of missing postal codes if that shared the first two characters (Finès et al. 2017; Pinault et al. 2017), totaling 89.9% of person-years with a postal code. Person-years were then excluded if they did not have an assigned postal code. Further exclusions of person-years occurred for the following reasons: immigrated to Canada less than 10 years before survey date (9,364,400 person-years); age during follow-up period exceeded 89 years (7,357,200); could not be linked to air pollution values (17,814,400); could not be linked to Canadian Marginalization Index (Can-MARG) values (25,973,900); could not be linked to census metropolitan area (CMA)/census agglomeration (CA) size (25,613,100); could not be linked to airshed (25,545,500); the 3-year moving average was informed by only one year of exposure (20,056,400); the person-year was after the year of the subject's death (17,936,100). The above exclusion numbers may overlap. The total available person-years for analyses were 150,996,500 after all exclusions (Additional Materials 1, Figure C1; available on the HEI website).

For the CCHS cohort, response rates varied by cycle (2000/2001 [Cycle 1.1], 84.7%; 2003 [Cycle 2.1], 80.7%; 2005 [Cycle 3.1], 78.9%; 2007/2008, 76.4%; 2009/2010, 72.3%; 2011/2012, 68.4%), as did the numbers of respondents who agreed to data linkage (2000/2001 [Cycle 1.1], n = 117,800 respondents; 2003 [Cycle 2.1], n = 112,900 respondents; 2005 [Cycle 3.1], n = 113,900 respondents; 2007/2008, n = 112,700 respondents; 2009/2010, n = 104,700 respondents; 2011/2012, n = 104,100 respondents). Of those who agreed to linkage, 95.2% were successfully linked to the Social Data Linkage Environment, with 99.8% of relevant deaths linked. There were 540,900 respondents in the cohort who all had up to 36 years of residential history occurring both before and after survey date, which was transposed to a file of 19,472,400 person-years (540,900 36). Of these, a number of person-years were excluded for various reasons (note that totals will exceed number of deleted person-years, given that more than one exclusion criteria may apply to a single person-year), as

follows: immigrated to Canada less than 10 years before survey date (n = 541,600 person-years); age during follow-up period exceeded 89 years (n = 161,000); had no postal code (n = 5,009,900); could not be linked to air pollution values (n = 5,711,600); could not be linked to Can-MARG values (n = 7,668,000); could not be linked to CMA/CA size (n = 4,800,600); could not be linked to airshed (n = 3,500); the 3-year moving average was informed by only one year of exposure (n = 4,321,500); the person-year after subject death (n = 343,600), the person-year before the survey interview date (n = 13,570,300). The total available person-years for analyses was 4,452,700 after all exclusions (Additional Materials 1, Figure C2).

Description of Covariates

We employed a defined strategy for covariate inclusion and focused our core analyses on two primary models. All models were stratified by age (5-year age group), sex, and immigrant status. The first model was based on a DAG outlining the conceptual relationship between outdoor $PM_{2.5}$ concentrations and mortality (Figure 3). This model included covariates that could conceivably be causes of both outdoor $PM_{2.5}$ concentrations and mortality; as a result, the DAG-based model included ecological variables (airshed, community size, neighborhood dependence, neighborhood deprivation, ethnic concentration, neighborhood instability, and urban form) as individual-level factors and not a priori causes of outdoor $PM_{2.5}$ concentrations (e.g., increasing individual-level education is not a cause of residential outdoor $PM_{2.5}$ concentration). However, given the observational nature of our study, there could be an imbalance of subject-level mortality risk factors across the distribution of outdoor $PM_{2.5}$ concentrations by chance, and this could bias $PM_{2.5}$–mortality associations. To address this possibility, a second model was examined including all of the DAG-based covariates as well as all of the subject-level risk factors available in each cohort. These parameters are described below. As the CCHS included additional subject-level behavioral covariates, we included several additional intermediate models to allow for comparisons with CanCHEC and to help inform the sensitivity to inclusion of behavioral risk factors not present in CanCHEC.

Subject-Level Risk Factors Available subject level covariates included income, education, marital status, indigenous identity, employment status, occupational class, visible minority status, and years since immigrating to Canada. Income quintiles were derived by summing total pre-tax income from all sources for all economic family members or unattached individuals for the year prior to the census and then calculating the ratio of this total income to the Statistics Canada low income cut-off for the applicable family size, community size group, and year. Weighted quintiles were derived based on this ratio for each CMA, CA area, or provincial residual for each cohort (Statistics Canada 2016). Employment status was defined as employed, unemployed, or not in the labor force (i.e., persons who left on disability, had retired, or had never worked) in the week prior to the census day (Statistics Canada 2003). Visible minority status was defined in the Employment Equity Act as "persons, other than Aboriginal persons, who were not white in race or color" (Statistics Canada 2003). Years-since-immigration was categorized as nonimmigrants (0 years, reference category), 11 to 20 years, 21 to 30 years, and >30 years). Respondents who immigrated to Canada 10 or fewer years prior to the index census year were excluded from the analysis, as they had spent most of their lives outside of Canada with unknown exposure. For example, for the 1991 cohort the minimum immigration year was 1980, for the 2001 cohort the minimum immigration year was 1990. Additionally, in the CCHS analyses covariates describing fruit and vegetable consumption, leisure exercise frequency, alcohol consumption behavior, smoking behavior, and BMI were evaluated.

Area-Level Contextual Risk Factors We use the CAN-Marg index (Matheson et al. 2012) to describe socioeconomic characteristics of an individual's home community. CAN-Marg is based on census data and geography; it is used to describe differences in marginalization among areas and to characterize inequalities in various predictors of health and social wellbeing. Derived from principal component analysis, it contains four dimensions of marginalization: material deprivation (e.g., proportion of population with low education, low income), residential instability (e.g., proportion of dwellings that are not owned, proportion of multi-unit housing), dependency (e.g., ratio of seniors and youth to working-age population), and ethnic concentration (e.g., proportion of recent immigrants and self-reported visible minorities). We defined CAN-Marg based on census tracts (i.e., neighborhoods) in cities and census subdivisions (i.e., municipalities) outside of larger metropolitan areas. All missing person-years for CAN-Marg were removed from the analysis.

Geographic Identifiers This category includes covariates such as community size, urbanization, and airshed. Urbanization is a further designation for communities with a population size over 100,000, based on a combination of population density and mode of transit (Gordon

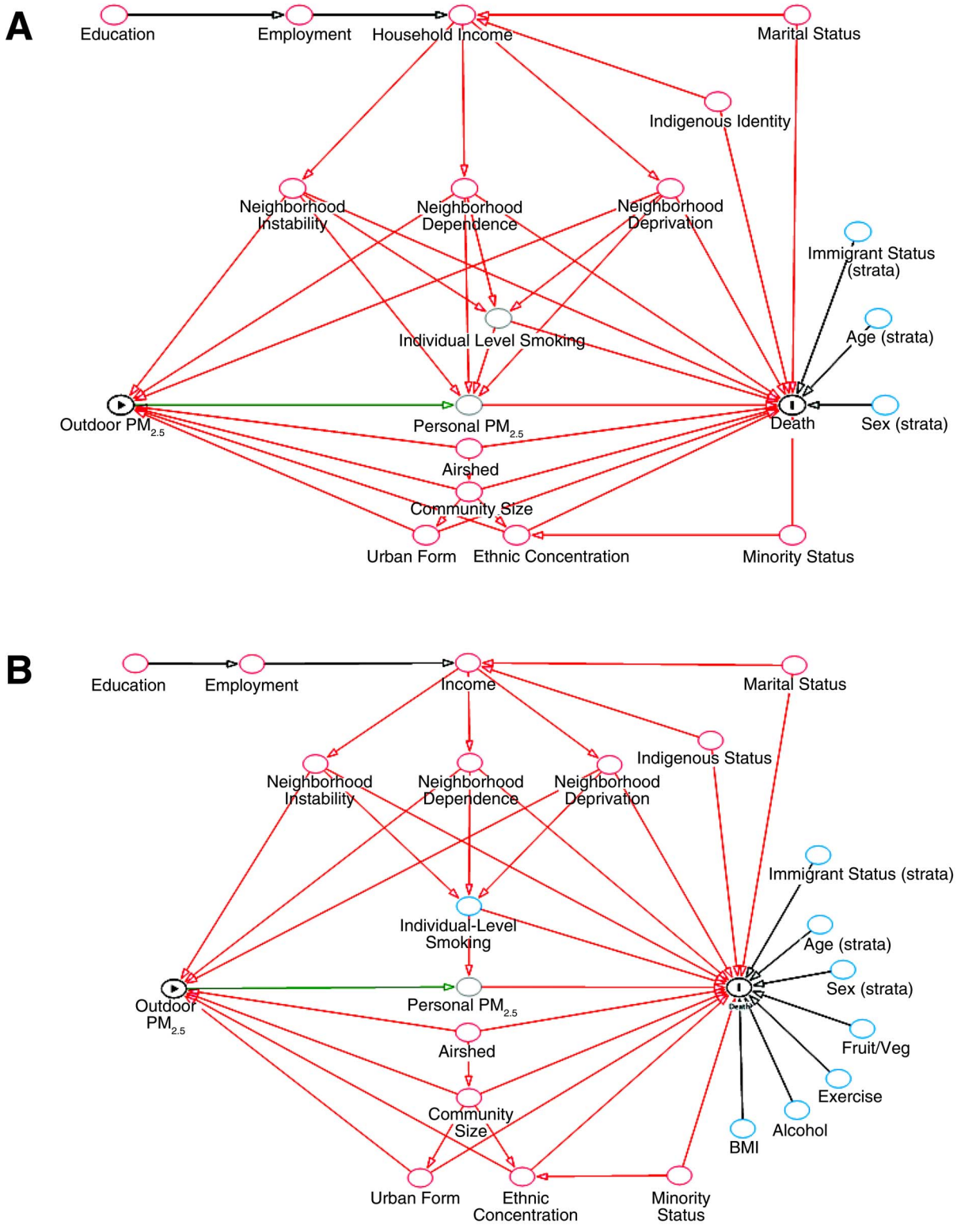

Figure 3. DAGs for the CanCHEC (A) and CCHS cohorts (B). Unmeasured parameters are shown in gray. The following covariates were included in the DAG-based model for both CanCHEC and CCHS: airshed, community size, urban form, neighborhood dependence, neighborhood deprivation, neighborhood ethnic concentration, and neighborhood instability. A second model (the full model, which added all subject-level covariates available in each cohort), was also examined. (From Pappin et al. 2019, Supplemental Material.)

and Janzen 2013). We designated communities as one of the following:

- *active urban core* (active transportation modes used to commute to work at greater than 150% of the metro average and greater than 50% of the national average),
- *transit-reliant suburb* (transit use to commute to work greater than 150% of the metro average and greater than 50% of the national average, active transit use less than 150% of the metro average),
- *car-reliant suburb* (gross population density greater than 150 people per square kilometer and transit use and active transportation use less than 150% of the metro average), and
- *exurban* (gross population density less than 150 people per square kilometer and more than 50% of workers commuting into the metropolitan area).

Airshed was defined by the Canadian Air Quality Management System on the basis of similar air-quality characteristics or dispersion patterns (Crouse et al. 2016). It subdivides the country into six large geographic areas and adjusts for broad-scale spatial variation in mortality rates not captured by other risk factors.

All missing person-years for geographic identifiers were removed from the analysis. Further, person-years were excluded from the analysis if postal code information was inadequate and could not be linked to air pollution and ecological covariates, or if the air pollution and ecological covariate file did not have an input for postal code.

Analysis Approach

Our primary statistical model relating exposure to mortality was the Cox proportional hazards model. Participants were at least 25 years of age at the beginning of each cohort, and the time axis was the year of follow-up until 2016. Person-years before census year and after a subject's death year were excluded from the analysis. Events were determined by year-of-death for nonaccidental causes. Cause-specific mortality (i.e., all cardiovascular causes, ischemic heart disease, stroke, all respiratory causes, chronic obstructive pulmonary disease, pneumonia, diabetes, lung cancer) for the main analyses (all CanCHEC cycles and CCHS) will be included in the final report. The Cox model baseline hazard function was stratified by age (5-year groups), and sex. Each subject was censored at 89 years of age, either at the start of each cohort or during follow-up, due to evidence from the 2011 Household Survey of an increased mismatch with increasing age between home address and the tax return mailing address (Bérard-Chagnon 2017). We postulate that relatives of elderly people were completing their tax returns. Each of the three CanCHEC cohorts (1991, 1996, and 2001) were examined separately. The three HRs were then pooled to form a single summary HR. A test for differences in the HRs among cohorts was also conducted.

As described above, we fit two covariate adjustment models for each cohort. The first was based on the DAG and consisted of all the geographically based predictors: CAN-Marg (four dimensions), airshed, urban form, and community size. The second model, denoted as *Full*, also included the subject level predictors (income, education, occupational class, indigenous status, visible minority status, employment status, and marital status) as there may be an imbalance in these subject-level mortality predictors over the $PM_{2.5}$ distribution. All models were stratified by age (5-year age groups), sex, and immigrant status (yes or no).

We also conducted analysis by categories of immigrant status (yes or no), sex (male or female), age during follow-up (<65, 65–74, or ≥75 years) for each cohort separately, again pooling the cohort-specific HR estimates among the three CanCHEC cohorts. In addition, we examined the $PM_{2.5}$ association adjusting for O_3, NO_2, or O_x by cohort.

Although a number of known and important risk factors for mortality were reported on the long-form census, many risk factors were not recorded, such as smoking habits, BMI, or diet. We addressed the influence on the air pollution risk estimate of not having direct information on these risk factors in two ways. First, using the CCHS cohort where several of these major risk factors were reported, we conducted a sensitivity analysis by fitting survival models with all risk factors and omitting those risk factors not reported on the long form. Second, we applied and formally evaluated a newly developed method of indirect adjustment for multiple individual-level risk factors (Shin et al. 2014) to the 2001 CanCHEC by estimating the association between air pollution and the missing risk factors available in the CCHS, and then using this information to indirectly adjust the risk estimate in the census cohorts.

Exposure Time Windows The primary exposure time window was a 3-year moving average assigned to the year prior to a given person-year to ensure that exposures precede follow-up. Annual exposures were assigned by converting postal codes to geographic locations (i.e., latitudes and longitudes). However, some postal codes were missing as not all subjects filed a tax return each year. These missing postal codes were imputed based on available postal codes prior to and after missing years. Some postal codes cannot be adequately imputed and were set to missing. In order to estimate exposures, 2 years out of each 3-year period must have had available postal codes to

calculate 3-year moving averages. We flagged missing person-years in the analytical file based on this requirement, and missing person-years were removed from the analysis.

As a sensitivity analysis, we also examined a 10-year moving average in a subanalysis of one of the CanCHEC cohorts (2001 CanCHEC). In this case we required 7 of 10 years to be nonmissing in order to calculate an exposure. We flagged missing person-years based on this requirement. We required subjects to have filed tax returns 10 years prior to the cohort starting year (i.e., 1981 for the 1991 cohort, 1986 for the 1996 cohort, and 1991 for the 2001 cohort). An implication of this exposure assignment protocol is that subjects must be living in Canada 10 years prior to start of their respective cohort. We thus excluded all subjects who immigrated to Canada within 10 years of their cohort enrollment. In our analysis comparing the 10-year to the 3-year moving average, missing person-years were removed from both to ensure that they have the exact same person-years.

Shape of the Association Between $PM_{2.5}$ Exposure and Mortality We originally planned to use the SCHIF (Nasari et al. 2016) to examine the shape of the association between $PM_{2.5}$ and mortality. A major advantage of the SCHIF over nonparametric smoothing functions are the resulting specific parameter estimates that can be applied in related analyses, for example in cost–benefit evaluations. Further, SCHIFs are constrained to produce functions that increase monotonically with concentration and in forms that are biologically plausible, for example, not allowing multiple upward and downward inflections. SCHIFs construct a family of transformations of concentration based on variations on sigmoidal functions. We suggest that such a family can characterize a wide variety of shapes, including near-linear, supralinear, and sublinear. Sublinear shapes approximate a threshold concentration–response pattern well. However, due to computing limitations, we were not able to fit all the desired transformations. Hence, we were concerned that we could not fully characterize the shape of the $PM_{2.5}$–mortality association. We had also planned to fit RCS as an alternative method of shape characterization. Therefore, we subsequently developed a method that is computationally feasible by first fitting an RCS with a very large number of knots and then fitting the SCHIF to the RCS predictions and their SEs. In this manner we required only a single Cox model run on the raw survival data.

The parametric SCHIF and nonparametric spline are two very different approaches to characterizing the shape of the concentration–response function. In general, splines are designed to provide a series of smooth(er) estimates of defined segments of the underlying data, while the SCHIF is a smoothed estimate of the full range of the data that is constrained by functions that can be useful for policy analyses, such as benefits assessment. While splines will, by design, provide a better approximation of the underlying data, the SCHIF provides parameters allowing for external use of the function (e.g., in benefits assessments), a feature not provided by splines.

Our method involved two steps. The first step was a data reduction step where we fit an RCS with a very large number of knots in order to characterize the shape of the concentration–response relationship in sufficient detail. In our case we selected 15. From this first step we obtained estimates of the logarithm of the RCS HR (logRCS) and the associated SE at 500 equally spaced concentrations between the minimum and the 99th percentile of the exposure distribution. We did not include predictions above the 99th percentile since RCS are linear beyond the highest knot concentration. This algebraic form can have some influence on the shape of the SCHIF throughout the concentration range since the SCHIF is a single algebraic function. We thus reduced the data complexity from millions of person-years in the cohorts to a few hundred observations. We also fixed the logRCS to zero at the minimum concentration; its associated standard error, $SE_{RCS}(z)$, was also set to zero. Note that the RCS SEs vary by concentration z. The second step is the fitting of the SCHIF to the RCS predictions. The resulting SCHIFs for each individual CanCHEC cohort are then pooled in a meta-analytic summary. Specifically, the SCHIF has the mathematical form:

$$\log \mathrm{SCHIF}(z) = \theta \log\left(z/\alpha + 1\right) l(z), \tag{1}$$

with unknown parameter θ to be estimated from the data. Here, α controls the curvature of the logarithmic function with larger values producing less curvature; μ is the inflection point or highest derivative of the logistic function

$$l(z) = \frac{1}{1 + \exp\left(-(z-\mu)/\tau r\right)}, \tag{2}$$

and τ controls the curvature in $l(z)$, with larger values representing less curvature, and r representing the range in concentration z.

The main purpose of the SCHIF is to produce an algebraic function of the association that we suggest is suitable for risk and benefits analyses. That is, the SCHIF not only

is monotonically increasing, but also only allows shapes within the sigmoidal family. It does not allow a shape, for example, that increases at low concentrations, remains nearly flat at mid concentrations, and then increases again at higher concentrations. Furthermore, the SCHIF controls the amount of curvature in the function. For example, if the function is purely supralinear, the SCHIF cannot have more curvature than a logarithmic function. We do this by restriction: $1 \le \alpha \le \max(z)$. By restricting $\alpha \ge 1$, we are assuming the SCHIF cannot have more curvature at the origin than a standard logarithmic function. The function $\log(z/\max(z) + 1)$ is nearly linear, and thus values of $\alpha \ge \max(z)$ do not change the shape. If the shape is sublinear and approximates a threshold function, the transition from no change in risk to an increase in risk is smoother in the SCHIF than a pure threshold function would predict. We do this by the restriction $0.1 \le \tau \le 1$. Values $\tau < 0.1$ produce a sigmodal shape with extreme curvature, while $\tau > 1$ yields a near linear shape. We model sublinear associations throughout the concentration range by the restriction $\min(z) \le \mu \le \max(z)$.

We obtain values of the SCHIF parameters by first creating a series of transformations of concentration

$$T(z) = \frac{\log(z/a + 1)}{1 + \exp\left(-(z - \mu)/\tau r\right)} \tag{3}$$

based on combinations of the parameters $\alpha = 1, \ldots, r$ by 1, $\mu = 0, \ldots, r$ by 1, and $\tau = 0.1, \ldots, 1$ by 0.1. We then fit a linear model with the response defined by the logRCS predictions at the 500 concentrations and the model as $\theta\ T(z)$. For each transformation, the linear regression model yields an estimate of θ with the corresponding log-likelihood value. We select the transformation, and thus the values of (α, μ, τ), and the corresponding value of θ that minimizes the log-likelihood.

We use the SE of the RCS predictions to form 95% CIs on the SCHIF predictions. We do this by considering a model of the $SE_{RCS}(z)$, in the RCS predictions. However, unlike the log-linear model, RCS SEs can vary in a nonlinear manner with concentration. We thus consider a model for the $SE_{RCS}(z)$, as a function of concentration of the form:

$$SE_{RCS}(z) = g_\sigma(z) \times T(z) \tag{4}$$

where $T(z) = \log(z/\alpha + 1)l(z)$ and σ is a vector of unknown parameters. We define $g_\sigma(z)$ as a cubic polynomial $g_\sigma(z) = \sigma_0 + \sigma_1 z + \sigma_2 z^2 + \sigma_3 z^3$ to describe the relationship between the RCS SEs and the SCHIF transformation. In effect, we are assigning all the uncertainty in the SCHIF predictions to the parameter θ, in a manner similar to the linear model. We estimate the unknown parameters of $g_\sigma(z)$ by linear regression. We selected a cubic polynomial since it appears to be sufficient to describe the association between the SEs of the RCS and $T(z)$. A major advantage of the SCHIF over nonparametric smoothing functions is the resulting specific parameter estimates, which can be applied in related analyses — for example, in cost–benefit evaluations. The parameter estimates are given in Table 1. We provide graphical results indicating the RCS predictions and their corresponding 95% CIs as a nonparametric means of characterizing the concentration–response relationship in detail. We also present the SCHIF predictions with two sets of 95% CIs given by

$$\exp\left(\theta \pm 1.96 \times g_\sigma\ (z)\right) \times \log(z/\alpha + 1)l(z). \tag{5}$$

In our approach we have captured the uncertainty in the RCS predictions at each concentration and then applied this uncertainty to the SCHIF model predictions.

Table 1. SCHIF Parameter Estimates by CanCHEC

Cohort	θ	α	μ	τ	γ	σ_0	σ_1	σ_2	σ_3
1991	0.1103	1	0	0.1	16.8	0.0552	−0.00669	0.000442	−0.0000103
1996	0.0942	1	0	0.1	14.6	0.0574	−0.00717	0.000491	−0.0000118
2001	0.0771	1	0	0.1	11.9	0.0629	−0.00616	0.000244	−0.0000016
Pooled	0.0997	1.0138	−0.0485	0.0877	16.8	0.0357	−0.00401	0.000226	−0.0000035

For benefits analysis, we calculate the change in the logHR between any two concentrations, for example, z and z'. For the RCS this can be represented mathematically as:

$$\begin{aligned}&\log\mathrm{RCS}(z)-\log\mathrm{RCS}(z')=\sum_{l=1}^{L}\hat{\gamma}_l\left(s_l(z)-s_l(z')\right)\\&=\hat{\gamma}'\left(s(z)-s(z')\right)\end{aligned}\qquad(6)$$

where $\hat{\gamma}_l$, $l=1,\ldots L$ are the L RCS parameter estimates and $s_l(z)$, $l=1,\ldots,L$ are the L RCS transformations of concentration with $\hat{\gamma}$ and $s(z,z')=s(z)-s(z')$, the corresponding vector notation. The SE of $\log\mathrm{RCS}(z)-\log\mathrm{RCS}(z')$ is:

$$\mathrm{SE}_{\mathrm{RCS}}(z,z')=\sqrt{s'(z,z')\mathrm{COV}\left(\hat{\gamma}\right)s(z,z')},\qquad(7)$$

where $\mathrm{COV}\left(\hat{\gamma}\right)$ is the L by L covariance matrix of the RCS parameter estimates.

For the SCHIF, the change in logHR is given by $\hat{\theta}\left(T(z)-T(z')\right)$, and we suggest an appropriate ad hoc approximation to the SE as:

$$\mathrm{SE}_{\mathrm{SCHIF}}(z,z')=g_\sigma\left(\overline{z,z'}\right)\left(T(z)-T(z')\right)\qquad(8)$$

where $g_\sigma\left(\overline{z,z'}\right)$ is the average of g_σ between z and z'. Future work will focus on evaluating the quality of using $\mathrm{SE}_{\mathrm{SCHIF}}(z,z')$ instead of $\mathrm{SE}_{\mathrm{RCS}}(z,z')$ for the specific cases examined in the final report.

Finally, we construct pooled SCHIF models among the three cohorts in the following manner: Let $v_c(z)$ be the variance of the logarithm of the SCHIF prediction $\log\mathrm{SCHIF}_c(z)$ at concentration z for cohort $c=1,2,3$. We construct a meta-analytic summary of the SCHIF predictions among the three cohorts as:

$$\log\mathrm{SCHIF}_{\mathrm{Pooled}}(z)=\sum_{c=1}^{3}w_c\log\mathrm{SCHIF}_c(z),\qquad(9)$$

where $w_c(z)=\left(1/v_c(z)\right)/\sum_{c=1}^{3}1/v_c(z)$. For the variance of $\log\mathrm{SCHIF}_{\mathrm{Pooled}}(z)$ we include the variation in predictions among the cohorts in addition to the sampling uncertainty for each cohort as:

$$\begin{aligned}&\sum_{c=1}^{3}w_c^2(z)\left(v_c(z)+\left(\log\mathrm{SCHIF}_c(z)\right.\right.\\&\left.\left.-\log\mathrm{SCHIF}_{\mathrm{Pooled}}(z)\right)^2\right).\end{aligned}\qquad(10)$$

In order to obtain an algebraic function for the pooled SCHIF we use nonlinear regression to estimate the SCHIF parameters with $\log\mathrm{SCHIF}_{\mathrm{Pooled}}(z)$ defining the data for the regression. We also model the SE of the pooled SCHIF in a manner similar to that for each cohort separately. The variance of the pooled SCHIFs is a function of both the variance of each cohort-specific SCHIF prediction and the squared difference between the cohort-specific SCHIF predictions and the pooled SCHIF prediction. This latter term captures the uncertainty in both the shape and the magnitude of the HR predictions among the three cohorts. The SCHIF parameters for each CanCHEC cohort represent the most extreme allowable supralinear shape with (α, μ, τ) at the lower boundary of their respective search intervals.

Adjustment for NO_2 and O_3 We estimated ambient NO_2 concentrations at each postal code location based on a national land-use regression model that predicted ground-monitoring concentrations for the year 2006 using 10-km^2 gridded remote-sensing-derived NO_2 estimates and highly resolved land-use data (Hystad et al. 2011). This model has a spatial resolution of 100 m^2. Eight-hour average daily maximum concentrations of O_3 were estimated based on chemical transport modeling of surface observations in the warm season from 2002 to 2015 (Environment and Climate Change Canada). From 2002 to 2009 the spatial resolution of the O_3 model was 21 km^2 and was subsequently improved to 10 km^2. Hourly O_3 model output was fused with ground monitor data (Robichaud and Ménard 2014; Robichaud et al. 2016) as part of the routine Canadian air quality forecast modeling system. These hourly data were then processed into warm-season (May–September) 8-hour daily maximum concentrations and interpolated to Canadian six-digit postal codes by the Canadian Urban Environmental Health Research Consortium (see Additional Materials 2 of the Investigators' Report, containing Appendix C Pappin et al. 2019, available on the HEI website).

We applied spatiotemporal adjustments to estimate NO_2 for years prior to 2006 and for O_3 prior to 2002 by first developing an annual time series of both NO_2 and O_3 in 24 of Canada's largest cities, based on available ground monitoring data for the 1981–2016 period. We then estimated yearly adjustment factors equal to the ratio of the observed concentration in the desired year to the average concentration in the reference year(s) (i.e., 2006 for NO_2 and 2002–2015 for O_3) for each of the 24 cities separately. We scaled the NO_2 concentration estimates per postal code in 2006 over the 1981–2016 period using the annual adjustment factors based on the city most proximate to that postal code location. A similar time scaling was applied to the 2002–2015 reference O_3 surface.

Subanalyses

In order to inform the main analyses conducted on the multiple (1991, 1996, and 2001) CanCHEC and CCHS cohorts, we conducted several subanalyses on the 2001 CanCHEC to address specific issues. Table 2 provides a summary of the cohorts included in the main analysis, the year of enrollment, the temporal and spatial scales of $PM_{2.5}$ exposure, whether or not immigrants were included in the analyses, and the primary purpose of each analysis. Note that all of these subanalyses were conducted on a version of the 2001 CanCHEC cohort with only 10 years of follow-up (compared with 15 years in the main analyses) and where linkage to mortality records was conducted with probabilistic linkage, whereas the main analyses used deterministic linkage using the individual's social insurance number.

Exposure Assessment Sensitivity Analyses in the 2001 CanCHEC Cohort The temporal and spatial scales of exposure assessment may influence the magnitudes of associations between $PM_{2.5}$ and mortality at low mass concentrations, but few studies have specifically examined this question. In addition, $PM_{2.5}$–mortality relationships may be sensitive to copollutant exposures. The purpose of this subanalysis was to examine the sensitivity of $PM_{2.5}$–mortality associations to different spatial and temporal scales of exposure assessment and to different approaches for characterizing coexposure to gaseous pollutants. Results of this subanalysis informed the analysis approach described above for the CanCHEC and CCHS cohorts with respect to spatial and temporal exposure scales and copollutant adjustment. Specific causes of death were included in this subanalysis in order to also inform future analyses of $PM_{2.5}$ disease-specific mortality associations in the main 3-cohort CanCHEC and CCHS analyses.

Table 2. Description of Cohort Analyses

Analysis/ Primary Purpose	Cohort Used[a]	Enrollment Year	End of Follow Up[b]	Scale of $PM_{2.5}$ Exposure		Adjustment for NO_2, O_3, or O_x[c]	Immigrants Included[d]
				Temporal (yrs)	Spatial (km^2)		
Main Analysis							
Characterize the shape of the concentration–response curve for $PM_{2.5}$ and non-accidental mortality	Pooled CanCHEC	1991, 1996, 2001	2011	3	1	Yes	Yes
	Pooled mCCHS	2001, 2003, 2005, 2007, 2008, 2009, 2010, 2011, 2012	2016				
Subanalysis							
Exposure sensitivity analysis	2001 CanCHEC	2001	2011	1, 3, 8	1, 5, 10	Yes	No
Evaluate method of indirect adjustment for missing covariates	2001 CanCHEC	2001	2011	3	1	No	No
Immigrant effect analysis	2001 CanCHEC	2001	2011	3	1	No	Yes
Contributing causes of death	2001 CanCHEC	2001	2011	3	1	No	No

[a] CanCHEC = Canadian Census Health and Environment Cohort, CCHS = Canadian Community Health Survey.

[b] Follow-up ended on December 31 of the year shown.

[c] NO_2 = nitrogen dioxide, O_3 = ozone, O_x = combined oxidant capacity of NO_2 and O_3.

[d] All analyses excluded very recent immigrants (<10 years since immigration) except for the immigrant effect analyses, where such participants were also included.

We followed 2.4 million people in the 2001 CanCHEC for nonaccidental and cause-specific mortality between 2001 and 2011. $PM_{2.5}$ exposures were assigned to residential locations using satellite-based estimates. The base exposure model consisted of annual $PM_{2.5}$ estimates at a spatial resolution of 1 km^2 over a 3-year exposure window. We examined sensitivity of the $PM_{2.5}$–mortality associations to the exposure assignment temporal scale using a constant spatial scale of 1-km^2. We developed survival models for this sensitivity analysis using either a 1- or 8-year moving average and compared results to the base model. We then examined the sensitivity of $PM_{2.5}$–mortality associations to the exposure assignment spatial scale using a constant temporal moving average of 3 years. We calculated mean $PM_{2.5}$ values for buffers of 5 km^2 and 10 km^2 around annual residential postal codes and compared results to our base model.

We developed survival models that incorporated variable spatial buffers (i.e., 1 km^2 or 10 km^2) according to select individual characteristics, as an alternative evaluation of fixed spatial scale. We selected characteristics that may influence individual-level mobility patterns and activity space, such as age, employment status, and whether the postal code indicated an urban or rural residence. Since there is a greater potential for exposure misclassification using a 1-km^2 model among subjects with rural postal codes, we considered models in which the 1-km^2 buffer was used for urban residences and the 10-km^2 buffer for rural residences.

As further sensitivity analyses, we developed survival models that adjusted for coexposure to ambient O_3, NO_2, or O_x. Exposure estimates for O_3 and NO_2 were derived from existing data sets. We modeled O_3 data to represent eight-hour average daily maximum concentrations in the warm seasons between 2002 and 2009 at a resolution of 21 km^2. As described earlier, we derived NO_2 data from a national land-use regression model for the year 2006 developed from fixed-site monitoring data and incorporating land-use predictors and satellite-derived NO_2 estimates. Both data sets were year-adjusted using ground-based time-series measurements. For years 1981–2012, National Air Pollution Surveillance annual average measurements from 24 census divisions were available from across Canada. We fit a cubic spline to model the association between year and concentration for each census division. We then used the ratios to adjust the original NO_2 and O_3 data. We assigned oxidant gas concentrations using 3-year moving averages with a 1-year lag as with the main $PM_{2.5}$ model described previously. We calculated O_x as a weighted average at each residential location, with weights equivalent to the respective redox potentials of NO_2 and O_3 (i.e., $[(1.07 \times NO_2) + (2.075 \times O_3)]/3.14$). Following inspection of results from the main analyses, we repeated the analyses including adjustment for oxidant gases using an 8-year moving window for $PM_{2.5}$ (and the same 1-km^2 spatial buffer).

Cox proportional hazards models were used to estimate HRs and 95% CIs for associations between $PM_{2.5}$ exposure (per 10-$\mu g/m^3$) and mortality in the various models for seven causes of death: nonaccidental (ICD-10: A to R); cardiometabolic (i.e., circulatory plus diabetes; ICD-10: I10 to I69, E10 to E14); cardiovascular diseases (ICD-10: I10 to I69); ischemic heart disease (ICD-10: I20 to I25); cerebrovascular disease (ICD-10: I60 to I69); nonmalignant respiratory disease (ICD-10: J00 to J99); and lung cancer (ICD-10: C33 to C34). We stratified the survival models by 5-year age groups and by sex, and adjusted for the following individual-level variables: indigenous identity, visible minority status, marital status, highest level of education, employment status, and household income quintiles. We also controlled for airshed and time-varying contextual variables: community size, urbanization, and the CANMarg indicators.

Indirect Adjustment in the 2001 CanCHEC Cohort The purpose of this subanalysis was to describe and evaluate the indirect adjustment method for air pollution–mortality relationships within the 2001 CanCHEC (n = 2.4 million), using the 2001 CCHS as the representative matching data set (n = 130,000) with detailed behavioral risk factor information. We applied the method proposed by Shin and colleagues (2014) to evaluate the methodology using nonlinear Cox proportional hazard models. We compared the distribution of exposure to fine PM ($PM_{2.5}$) among subjects across multiple characteristics (age, sex, etc.) and examined the direction and magnitude of correlations among variables common to both data sets. We assessed the performance of indirect adjustment on Cox proportional hazard models by comparing estimates in the CanCHEC with and without indirect adjustment for known variables. As two novel additions, we incorporated a time-varying exposure measure in the representative data set and applied a weighting scheme to account for sampling differences between the two data sets. Lastly, we applied an indirect adjustment for missing risk factors (cigarettes/day, alcohol use, fruit and vegetable intake, leisure exercise) using the CanCHEC and CCHS and compared the adjustment direction and magnitude to models that were not missing those variables (the mCCHS cohort) using an equivalent longitudinal cohort.

Figure 4 depicts a visual summary of the evaluation process. The first step was to assess the representativeness of

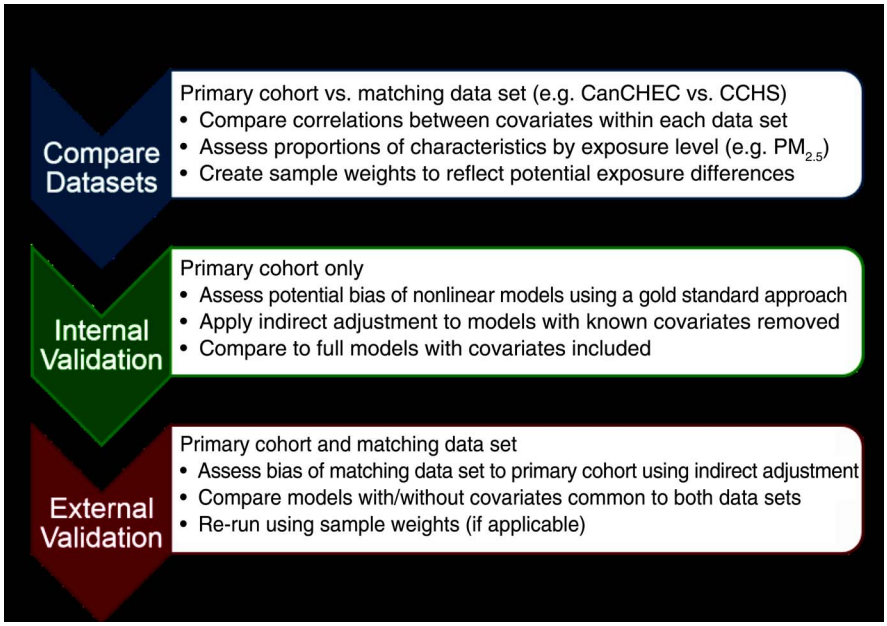

Figure 4. Schematic showing the steps involved in evaluating the data sets used for indirect adjustment. Reprinted from Erickson et al. 2019 with permission from Elsevier.

the ancillary matching data set (i.e., CCHS) to the primary data set (i.e., CanCHEC). We compared absolute and proportional differences in the $PM_{2.5}$ exposure distribution by demographic and socioeconomic characteristics at baseline year (2001). We then assessed temporal changes in the $PM_{2.5}$ distribution across the 10 follow-up years between the two data sets. Sample weights to account for differences in the sampling scheme between the two data sets were produced, using health regions as the sampling unit, and applied to the CCHS to emulate CanCHEC proportions. Health regions represent administrative areas defined by the Ministry of Health in each province (Statistics Canada 2019). We down-weighted rural areas with lower $PM_{2.5}$ levels that are typically over-sampled in the CCHS and up-weighted under-sampled urban areas.

In Step 2, we performed an internal validation to assess the degree of bias in adjusted HRs when applying indirect adjustment to nonlinear Cox proportional hazards models. We used a *gold-standard* methodology that involved comparison of the result following removal and indirect adjustment for variables available in CanCHEC (education and income) to a *true model* that included both variables and used coefficients and SEs derived internally from the true model. Three sets of models were estimated for each mortality outcome. First, the gold-standard HRs and 95% CIs for $PM_{2.5}$ exposure on mortality were obtained from an age–sex stratified true model adjusted for education, income, and the other individual-level covariates. We then ran the same models with education and income removed to obtain the *partial model* $PM_{2.5}$ coefficients and SEs. Instead of using literature values, we ran the true model but with $PM_{2.5}$ excluded in order to obtain the coefficient and variance terms for education and income, which were then used in the indirect adjustment formula to calculate the adjustment factor and applied to the internal and external (validation) models. We derived the X and U matrices (described later in this section) for the baseline year of 2001 only (no follow-up years included) from CanCHEC, and employed a static as well as a time-varying $PM_{2.5}$ exposure value. We then compared $PM_{2.5}$–mortality HRs from the true model (with direct measurement of income and education) with the internal model incorporating indirect adjustment for education and income (i.e., values obtained from the true model were used to indirectly adjust the partial model to calculate the internal model, which was then compared with the true model).

In Step 3, we performed an external validation to assess the bias of using the CCHS as the ancillary matching data set to indirectly adjust for the CanCHEC. We applied a similar approach to the internal validation by removing and indirectly adjusting for variables available in both data sets (education and income). Here the 2001 cycle of the CCHS,

instead of CanCHEC, was used to create the X and U matrices. As in the internal validation, we used both a static and a time-varying $PM_{2.5}$ value in the X-matrix, and applied the same mortality outcomes and related education and income coefficients in order to determine the true bias of using the CCHS in place of the CanCHEC for removed variables.

We constructed the X and U matrices to represent the covariance structure between the missing (U-matrix) and nonmissing (X-matrix) variables, including the exposure variable. We incorporated stratification of age and sex into the X-matrix by creating a series of 5-year age–sex dummy codes assigning a value of "1" to the reference category (males 25 to 29). We categorized the remaining variables into 0/1 dummy codes with the reference group assigned a value of "0" along with the continuous $PM_{2.5}$ values as separate columns in the X-matrix. As an example, a 3-category marital status variable would be represented by two columns in the matrix. An X-matrix was created for each year of follow-up, transposed, and summed to account for the time-varying nature of $PM_{2.5}$ in the models. We set up the U-matrix representing missing covariates in a similar manner as the X-matrix, except it is time invariant. As a new addition to this method, we incorporated a sampling weights matrix (W-matrix) to adjust for CanCHEC and CCHS urban-rural sampling differences. The W-matrix contained only one column of values, which is the ratio of the proportion of CanCHEC subjects to the proportion of CCHS subjects by health region for each individual in the CCHS. By including the W-matrix, we gave more weight to urban respondents and less weight to rural respondents, thus making the CCHS more like the CanCHEC.

Lastly, we applied the indirect adjustment above to a real missing data scenario to estimate adjusted $PM_{2.5}$–mortality HRs and compared the results to HRs estimated using the mCCHS in which smoking, alcohol consumption, fruit and vegetable intake, and physical activity were measured directly. Similar to the external validation in this step, we used the CCHS to create the X, U, and W matrices with time-varying $PM_{2.5}$ to indirectly adjust for missing behavioral risk factors not available in the CanCHEC. We used risk estimates from published meta-analyses for specific mortality risk factors, such as smoking intensity (Thun et al. 2013), alcohol consumption (Xi et al. 2017), BMI (Yu et al. 2017), fruit and vegetable intake (Leenders et al. 2014), and physical activity (Hupin et al. 2015).

Cox proportional hazard models were used to examine the association between ambient $PM_{2.5}$ exposure with four causes of death: nonaccidental (ICD-10 codes A to R), cardiovascular diseases (ICD-10: I10 to I69), ischemic heart disease (ICD-10: I20 to I25), and lung cancer (ICD-10: C33 to C34). We followed respondents until death or the end of follow-up. All models were stratified by 5-year age categories and sex. We adjusted models for the individual covariates of marital status, indigenous identity, visible minority identity, and employment status. As education and income were available in the CanCHEC and CCHS data sets, we removed and indirectly adjusted these two variables in the validation tests and directly adjusted for them in the final indirect adjustment. We further adjusted the models by contextual ecological covariates in the final indirect adjustment.

Immigrant Effect Analysis in the 2001 CanCHEC Cohort Immigrants make up approximately 20% of the Canadian population (Morency et al. 2017); yet recent immigrants (<20 years in Canada) have been excluded from most Canadian air pollution mortality cohort analyses given the lack of historical information on past $PM_{2.5}$ exposures and because immigrants tend to be healthier than the general Canadian population. The purpose of this subanalysis was to examine the mortality impacts of long-term $PM_{2.5}$ exposure on the immigrant population (after arriving in Canada) and compare these mortality impacts with those of the nonimmigrant population. We also aimed to determine the influence of several immigrant-specific variables on the $PM_{2.5}$–mortality association, including number of years in Canada, country of birth, age at immigration, and neighborhood ethnic concentration.

We used the 2001 CanCHEC, restricting the analytical cohort to persons between the ages of 25 and 89 years at baseline. Subjects not matched to air pollution estimates and any person-years with nongeocoded postal codes were excluded. A total of 684,400 respondents in the cohort were immigrants. We followed an analytical methodology similar to the one used throughout the MAPLE project as described earlier, but with the additional focus on immigrant-specific variables such as year-of-immigration, age-at-immigration, and country-of-birth. Respondents were followed from census baseline year (2001) to either the year of death or final year of follow-up (2016 in this subanalysis). All immigrants were considered in the models and grouped by time since becoming a permanent resident of Canada (>30 years, 21–30 years, 11–20 years, ≤10 years). Because of this designation, even the very recent immigrants (≤10 years) have likely spent an additional 1–5 years in Canada while applying for their permanent residency. The following causes of death were considered in order to assess whether patterns differed from those for nonaccidental mortality (ICD codes A to R): cardiovascular diseases (ICD-10: I10 to I69, with and without diabetes, E10 to E14), ischemic heart disease (ICD-10: I20 to I25), cerebrovascular disease (ICD-10: I60 to I69), nonmalignant respiratory disease

(ICD-10: J00 to J99), chronic obstructive pulmonary disease (ICD-10: J19 to J46), and lung cancer (ICD-10: C33 to C34).

We fit Cox proportional hazards models to examine the associations between ambient $PM_{2.5}$ exposure and nonaccidental and cause-specific mortality. All survival models were stratified by 5-year age groups and sex, and adjusted for individual and contextual variables. Results of this subanalysis informed the main analysis approach described above for the pooled CanCHEC and CCHS cohorts with respect to the inclusion of immigrants and analyses stratified by immigrant status.

Contributing Causes of Death in the 2001 CanCHEC Cohort Type 2 diabetes has also been associated with air pollution and included in recent Global Burden of Disease assessments (Global Burden of Disease 2018). However, while type 2 diabetes is infrequently coded as the primary cause of death, it may contribute to cardiovascular disease mortality in response to $PM_{2.5}$ exposure. As such, analyses of the relationship between air pollution exposures and diabetes mortality may underestimate the true overall impact. We leveraged the availability of contributing causes of death information within the 2001 CanCHEC to examine susceptibility of people with diabetes to cardiovascular disease mortality from long-term exposure to $PM_{2.5}$.

We linked a subset of the 2001 CanCHEC cohort with 10 years of follow-up to all causes of death listed on death certificates. We used survival models to examine the association between cardiovascular disease deaths (n = 123,500) and exposure to $PM_{2.5}$ among deaths that cooccurred with type 2 diabetes (n = 20,600) on the death certificate. We complemented the analysis with more detailed information on behavioral covariates and type 2 diabetes status at baseline available in the mCCHS (n = 12,400 cardiovascular disease deaths, with 2,800 diabetes deaths). Details are provided in the study by Pinault and colleagues (2018).

SUMMARY OF FINDINGS

EXPOSURE ASSESSMENT

Overview of $PM_{2.5}$ Concentrations

Figure 5 provides an overview of the satellite-derived $PM_{2.5}$ concentrations at 1 km × 1 km resolution and performance for Canada and the northern United States. Comparison versus ground-based monitors yields a coefficient of determination (R^2) of 0.82, slope of 1.00, and root mean square difference (RMSD) of 1.5 μg/m^3. Table 3 contains descriptive statistics for Canadian provinces.

Ground-Based Monitoring

Sample collection and analysis continues at all five sites. In addition to ongoing analyses of filter measurements for mass, black carbon, ions and elements, organic composition information from filters will also be evaluated. That is anticipated to yield valuable information for constraining the GEOS-Chem simulation used to relate AOD to $PM_{2.5}$.

Enhancing $PM_{2.5}$ Estimates and GEOS-Chem Simulations of the $PM_{2.5}$–AOD Relationship

A core goal of taking additional surface measurements is to further reduce the scatter in the relationship between satellite-derived estimates and surface measurements of $PM_{2.5}$. We estimated that the absolute error in exposure estimates of $PM_{2.5}$ in comparison with surface monitors decreased at lower concentrations and was not multiplicative. Figure 6 shows the relationship after all values (satellite-based estimates and surface monitors) with concentrations >10 μg/m^3 were removed. The resulting RMSD was 1.5 μg/m^3. Figure 7 shows the relationship after all values (satellite-based estimates and surface monitors) with concentrations >8 μg/m^3 were removed. The resulting RMSD further decreased slightly to 1.3 μg/m^3. Corresponding figures for North America are given in Additional Materials 1, Figures C3 and C4, available on the HEI website.

Using colocated measurements of aerosol scatter and mass from IMPROVE network sites between 2000 and 2015, we found a positive bias in mass scattering efficiency simulated by GEOS-Chem, given current assumptions of aerosol size distributions and particle hygroscopicity in the model. This bias was most significant when $PM_{2.5}$ mass was dominated by secondary inorganic or organic aerosols. Incorporating changes in aerosol size and hygroscopicity into the GEOS-Chem model resulted in an increase of 16% in simulated annual average aerosol mass scattering efficiency over North America, with larger increases of 25% to 45% in northern regions with high relative humidity and hygroscopic aerosol fractions, and with decreases in aerosol mass scattering efficiency up to 15% in the southwestern United States where relative humidity is low. Details are provided in the article included in Additional Materials 2, Appendix B (Latimer and Martin 2019), available on the HEI website.

Backcasting

Information about historical $PM_{2.5}$ concentrations is needed to understand long-term changes in exposure and associated health risks. We estimated historical $PM_{2.5}$

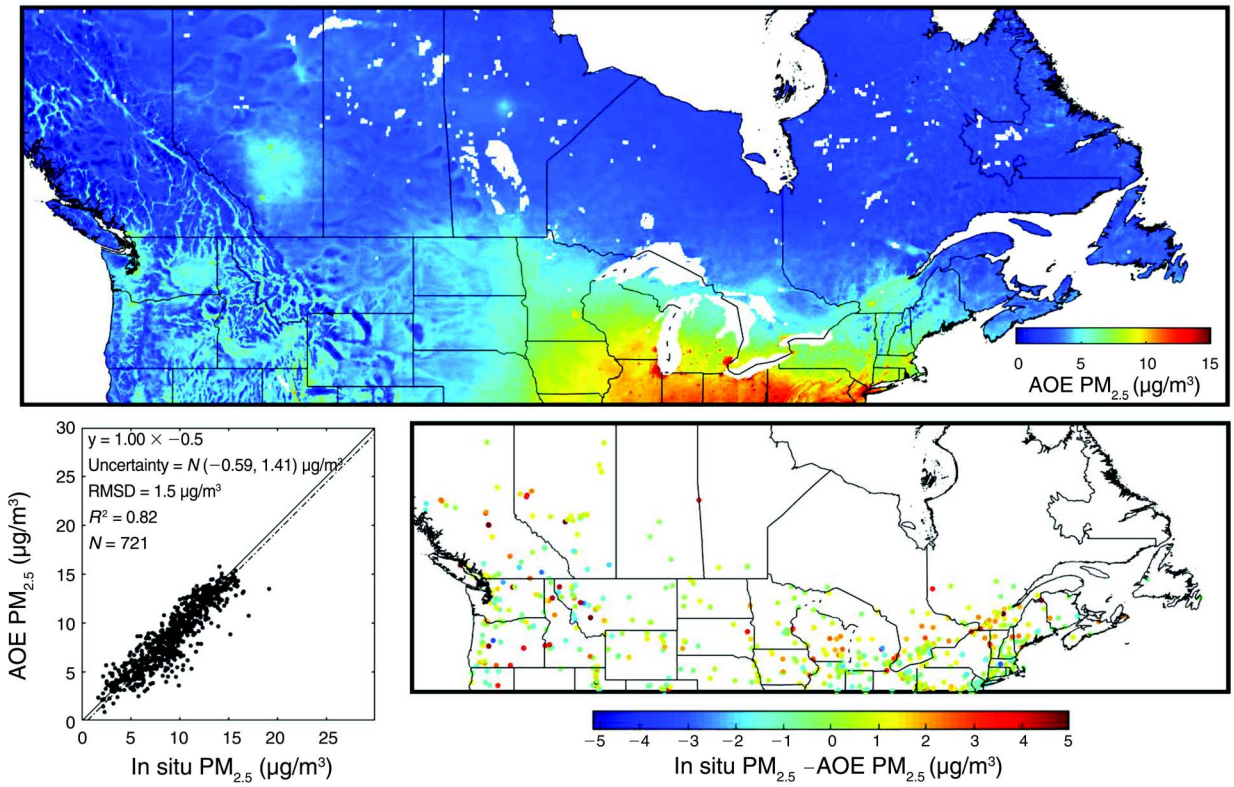

Figure 5. $PM_{2.5}$ for Canada and the northern United States. The top panel shows mean 1-km^2 satellite-derived $PM_{2.5}$ estimates for 2004–2008. The lower-right panel displays the observed difference between in situ $PM_{2.5}$ and satellite-derived $PM_{2.5}$ observations. White denotes water, missing data, or values above 10 µg/m^3. Values in the lower-left panel include the slope from reduced major axis linear regression (y), N (bias, variance), root mean square difference (RMSD), coefficient of determination (R^2), and the number of comparison sites (N). The 1:1 line is solid, and the best fit line is dashed. AOE = adjusted optimal estimates.

Table 3. Regional Mean $PM_{2.5}$ Concentrations for 2004–2008

Region	$PM_{2.5}$ Concentration (µg/m^3)
Canada	7.1
British Columbia	6.2
Alberta	5.7
Manitoba	4.9
Saskatchewan	4.3
Ontario	8.5
Quebec	7.4
New Brunswick	4.1
Newfoundland and Labrador	3.8
Nova Scotia	4.7
Prince Edward Island	3.4
Yukon Territory	2.6
Northwest Territories	3.5
Nunavut	3.9

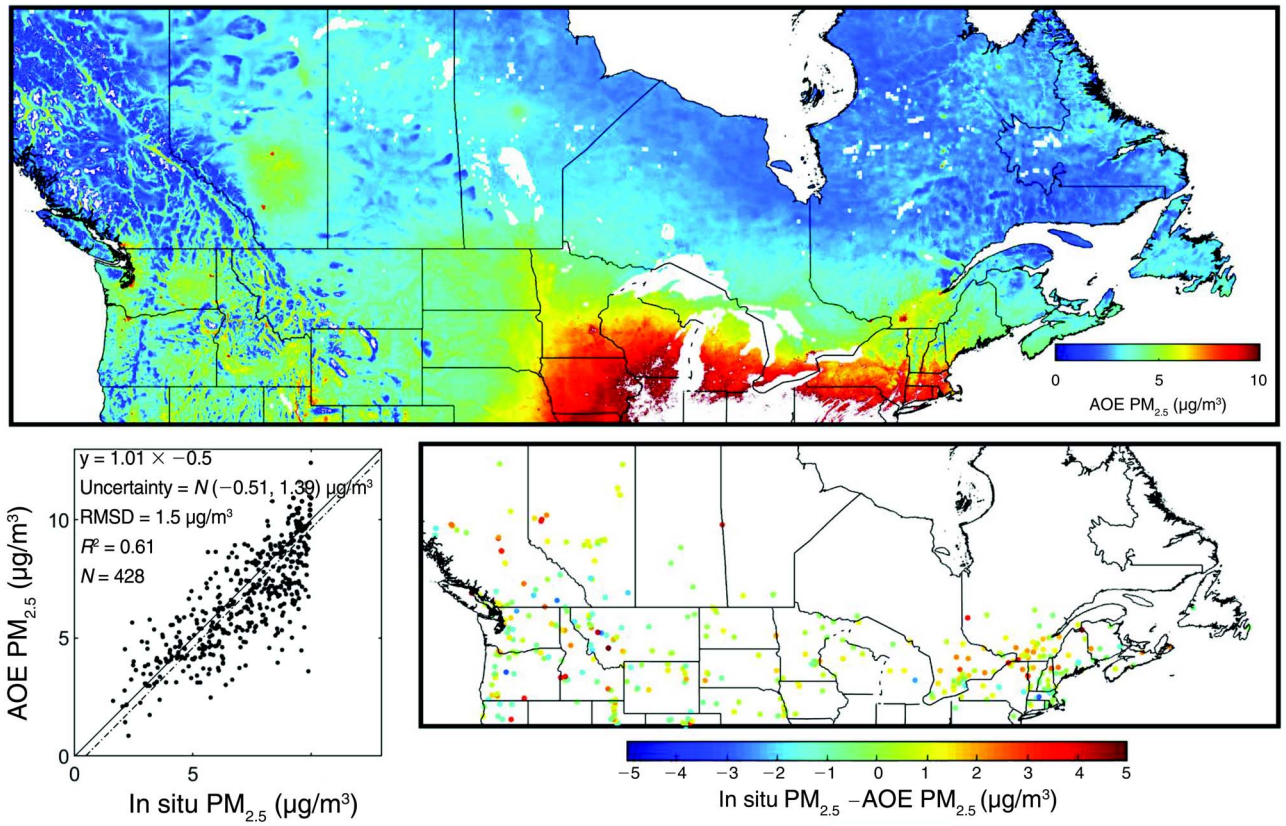

Figure 6. $PM_{2.5}$ at low concentrations (≤10 µg/m³) for Canada and the northern United States. The top panel shows mean 1-km² satellite-derived $PM_{2.5}$ estimates for 2004–2008. The lower right panel displays the observed difference between in situ $PM_{2.5}$ and satellite-derived $PM_{2.5}$ observations. White denotes water or missing data. Values in the lower left panel include the slope from reduced major axis linear regression (y), N (bias, variance), root mean square difference (RMSD), coefficient of determination (R^2), and the number of comparison sites (N). The 1:1 line is solid, and the best fit line is dashed. AOE = adjusted optimal estimates.

concentrations over North America for 1981–2016 inclusive by combining information from GEOS-Chem, satellite remote sensing, and ground-based measurements. We constrained and evaluated our estimates with direct ground-based $PM_{2.5}$ measurements when available and otherwise with historical estimates of $PM_{2.5}$ from PM_{10} measurements or TSP measurements. The distribution of monitoring sites in North America and $PM_{2.5}$ estimates for the different time periods are shown in Figure 8. The estimated $PM_{2.5}$ concentrations were generally consistent with direct ground-based $PM_{2.5}$ measurements over their duration from 1988 onward (R^2 = 0.6–0.85) and to a lesser extent with $PM_{2.5}$ inferred from PM_{10} measurements (R^2 = 0.5–0.6) (Meng et al. 2019).

We first evaluated the approach for years when only $PM_{2.5}$ stations were used for GWR adjustment and found that the GWR model using all available sites significantly reduced the mean bias and RMSD over both Canada and the United States (Figure 9). The R^2 of all sites increased from 0.52 to 0.77, and the RMSD decreased from 3.1 to 1.9 µg/m³. Cross validation using 50% of randomly selected sites to train the GWR model still exhibited significantly improved performance (R^2 = 0.69, RMSD = 2.3 µg/m³). Limiting the GWR-based adjustment to sites that were also available on or before 1999 (<70 sites in total consisting mostly of remote and rural U.S.-based sites) provided no improvement in agreement compared with the initial geophysical estimates without GWR.

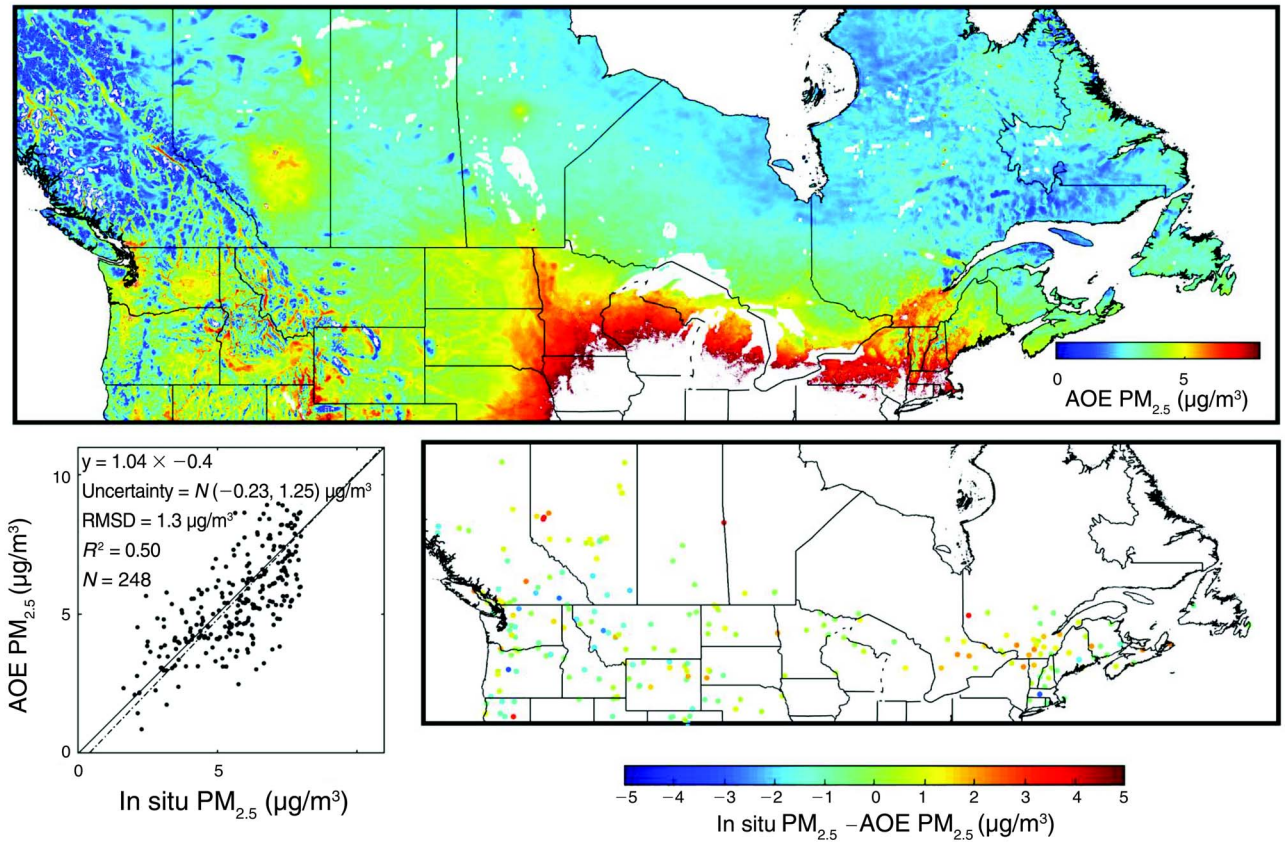

Figure 7. $PM_{2.5}$ at low concentrations (≤8 µg/m³) for Canada and the northern United States. The top panel shows mean 1-km² satellite-derived $PM_{2.5}$ estimates for 2004–2008. The lower right panel displays the observed difference between in situ $PM_{2.5}$ and satellite-derived $PM_{2.5}$ observations. White denotes water or missing data. Values in the lower left panel include the slope from reduced major axis linear regression (y), N (bias, variance), root mean square difference (RMSD), coefficient of determination (R^2), and the number of comparison sites (N). The 1:1 line is solid, and the best fit line is dashed. AOE = adjusted optimal estimates.

Figure 10 shows R^2 and RMSD for each year (1981–2016) of the estimates versus ground-based measurements. Only $PM_{2.5}$ data were used over 1999–2016 since more $PM_{2.5}$ measurements were available after 1999. Since the number of PM_{10} sites is reduced significantly before 1989, the backcasting from 1981–1985 was based primarily on trend information from TSP-based estimates and is expected to be more uncertain. R^2 increased with the increase in the number of PM_{10} sites for years 1985–1990. The decrease in R^2 after 2008 reflects weaker spatial $PM_{2.5}$ gradients in recent years as $PM_{2.5}$ levels decline. Higher RMSD errors are expected before 1999 due to more uncertainties in emission inventories as well as larger uncertainties in the monitoring data for GWR adjustments. Overall, the GWR-adjusted $PM_{2.5}$ estimates yielded an estimated error of less than 20% since 2000 when $PM_{2.5}$ measurements became more widespread, and of less than 30% for 1981–1999.

Across time, enhancements in both GWR-adjusted estimates and ground-based measurements are apparent across the eastern United States and California (Figure 9). The estimated $PM_{2.5}$ was generally consistent with ground-based measurements, especially with direct $PM_{2.5}$

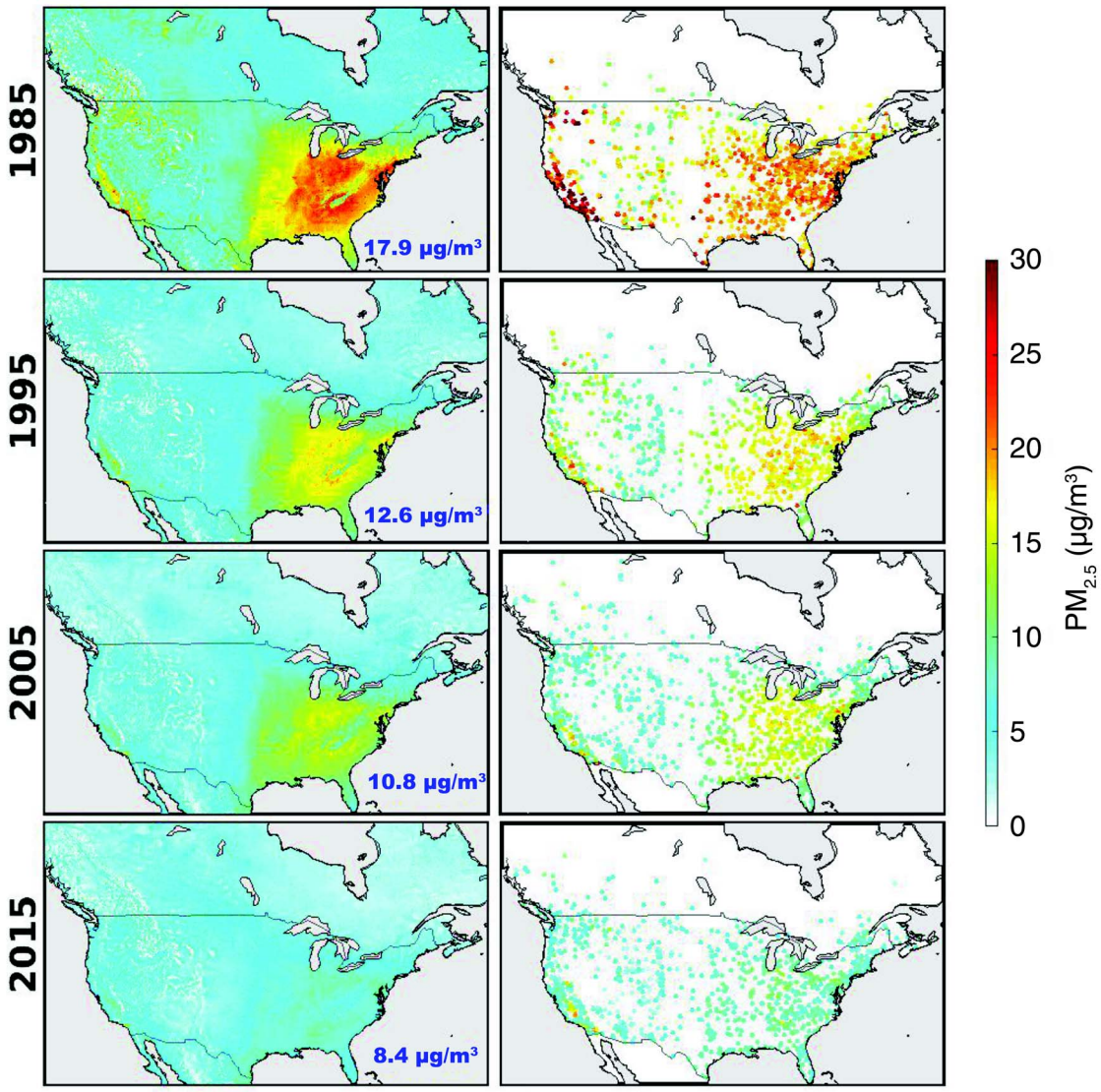

Figure 8. Estimated $PM_{2.5}$ annual means in 1985, 1995, 2005, and 2015 over North America. Left panels are estimated $PM_{2.5}$. Inset values in left panels are the population-weighted average $PM_{2.5}$ mass. Right panels indicate $PM_{2.5}$ derived from ground-based measurements of $PM_{2.5}$, PM_{10}, and TSP. Reprinted from Meng et al. 2019 (doi:10.1021/acs.est.8b06875) with permission from American Chemical Society (ACS). Further permission related to this article should be directed to ACS.

measurements. Figure 11 shows a time series of population-weighted annual average $PM_{2.5}$ concentrations across North America. The colocated comparisons of the trends of population-weighted annual average $PM_{2.5}$ from our estimates and ground-based measurements were highly consistent (RMSD = 0.66 µg/m³). The population-weighted annual average $PM_{2.5}$ over North America decreased from 22 µg/m³ in 1981 to 12 µg/m³ in 1998 and to 8.0 µg/m³ in 2016. Population-weighted annual average $PM_{2.5}$ calculated from direct $PM_{2.5}$ sites was 20% lower than that calculated from all in situ PM (including TSP and PM_{10}) sites, illustrating the effects of changes in monitor placement over time when assessing long-term changes in ambient $PM_{2.5}$, and the value of spatiotemporally continuous $PM_{2.5}$ estimates from this work.

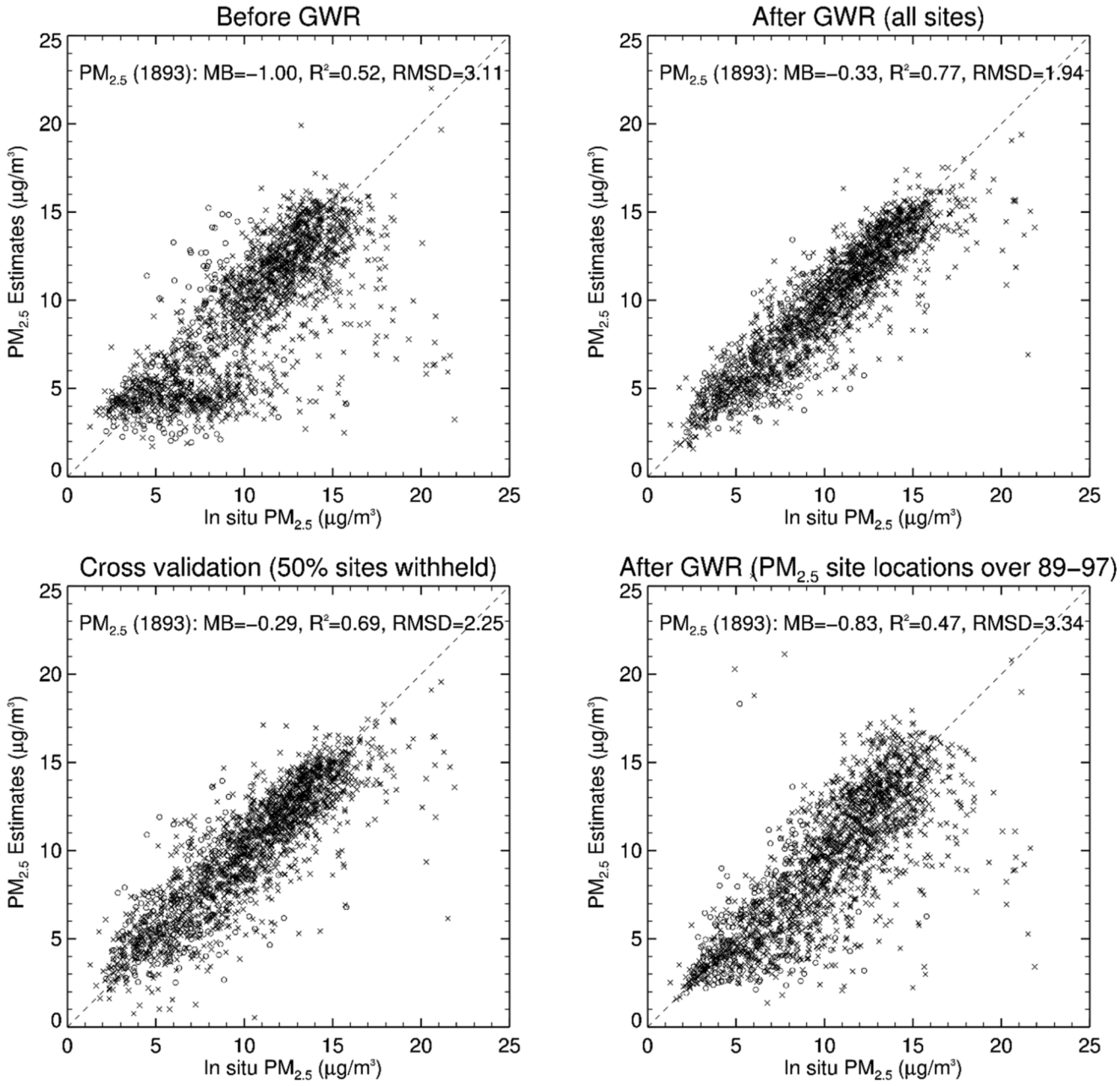

Figure 9. Comparison of 2004–2009 mean $PM_{2.5}$ estimates with in situ measurements for $PM_{2.5}$ before (top left) and after GWR adjustment using all sites (top right), cross validation sites using 50% random holdout (bottom left), and $PM_{2.5}$ sites present over 1989–1997 (bottom right). Open circles are Canadian sites and crosses are U.S. sites. Number of sites is shown in parentheses. Statistics shown are mean bias (MB, in µg/m³), coefficient of determination (R^2) and root mean square difference (RMSD, in µg/m³). Reprinted from Meng et al. 2019 (doi:10.1021/acs.est.8b06875) with permission from American Chemical Society (ACS). Further permission related to this article should be directed to ACS.

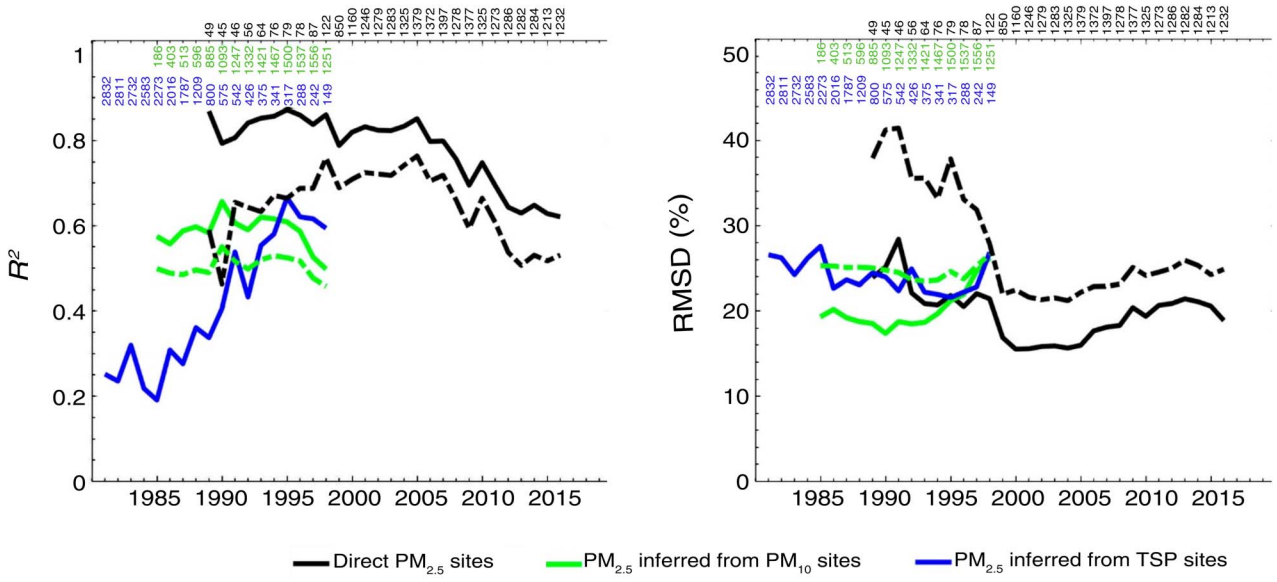

Figure 10. R^2 and RMSD of estimated $PM_{2.5}$ compared with ground-based measurements from 1981 to 2016. Solid lines indicate the performance of base estimates. Dashed lines indicate the performance of sensitivity estimates that exclude satellite remote sensing information. Numbers at the top of each panel indicate the number of monitors of direct $PM_{2.5}$ (black), $PM_{2.5}$ inferred from PM_{10} (green), and $PM_{2.5}$ inferred from TSP (blue). Reprinted from Meng et al. 2019 (doi:10.1021/acs.est.8b06875) with permission from American Chemical Society (ACS). Further permission related to this article should be directed to ACS.

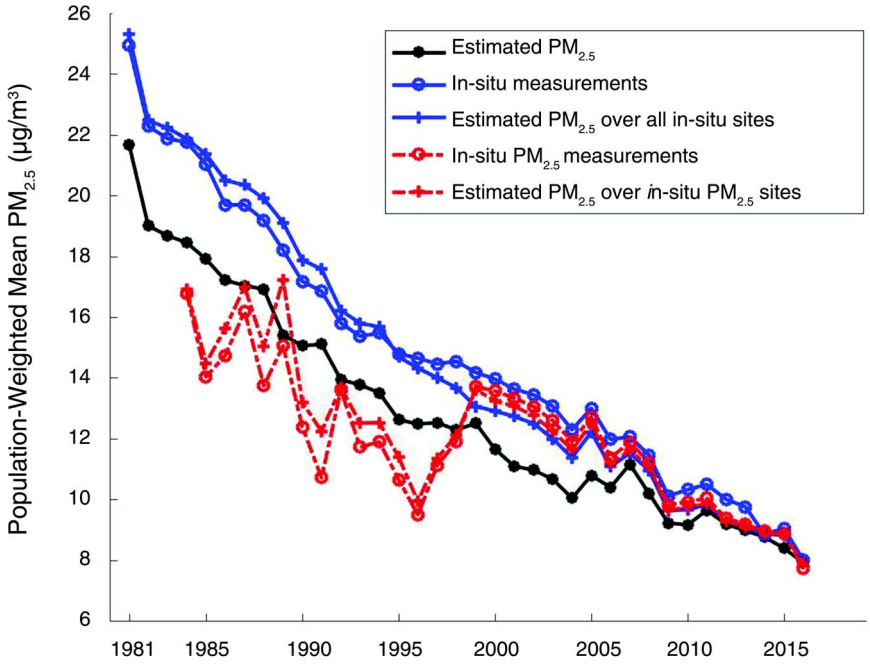

Figure 11. Time series of population-weighted annual average $PM_{2.5}$ concentrations across North America (1981–2016). Reprinted from Meng et al. 2019 (doi:10.1021/acs.est.8b06875) with permission from American Chemical Society (ACS). Further permission related to this article should be directed to ACS.

EPIDEMIOLOGICAL ANALYSIS

The results of our analyses to date are summarized below. Table 4 provides a summary of the cohorts included in the main analyses and the primary purpose of each analysis.

Main Analysis: Nonaccidental Mortality (CanCHEC Cohorts: 1991, 1996, 2001)

$PM_{2.5}$ by Cohort and Covariate Categories Table 5 presents percentiles of the $PM_{2.5}$ distribution based on person-years for each of the three cohorts separately (Pappin et al. 2019). Concentrations were highest for the 1991

Table 4. Summary of Cohorts Included in Each Analysis and Primary Purpose of the Analysis

Analysis	Cohort	Enrollment Year	Primary Purpose
Main Analysis			
	All CanCHEC	1991, 1996, 2001	Characterize the shape of the concentration–response curve for $PM_{2.5}$ and nonaccidental mortality
	mCCHS	2001–2012	
Subanalysis			
	2001 CanCHEC	2001	Exposure sensitivity analysis Indirect adjustment Immigrant analysis Contributing causes of death

Table 5. $PM_{2.5}$ Distribution by Cohort with Restricted Cubic Spline Lowest (2nd percentile) and Highest (98th percentile) Knot Values

	2001	1996	1991
100% Maximum	18.50	20.00	20.00
99%	12.30	15.00	17.26
98% (highest knot)	11.70	13.97	17.03
95%	10.70	12.20	14.63
90%	9.80	10.70	12.60
75% Q3	8.23	8.84	9.83
50% Median	6.40	6.75	7.40
25% Q1	4.87	5.04	5.38
10%	3.97	4.10	4.26
5%	3.57	3.67	3.80
2% (lowest knot)	3.00	3.29	3.43
1%	3.00	3.05	3.13
0% Minimum	0.37	0.37	0.37
Mean	6.68	7.18	7.95
Standard deviation	2.24	2.70	3.28

Q = quintile.

(From Pappin et al. 2019.)

cohort, moderate for the 1996 cohort, and lowest for the 2001 cohort. Concentrations differences were well within 1 μg/m^3 among cohorts for median and lower percentiles, with greater differences for the higher percentiles, suggesting that greater declines in exposure are observed in locations with higher levels. Table 6 reports both the number of person-years and percentage among the categories of mortality predictors for each cohort separately, in addition to the mean and standard deviation (SD) of $PM_{2.5}$ assigned to each category. Males tended to be assigned higher concentrations than females in all three cohorts, although the difference was very small (<1 μg/m^3). There was a U-shaped pattern with age at cohort commencement for all three cohorts, with concentration declining with age to the 55- to 64-year-olds and then increasing. Immigrants were consistently assigned higher concentrations than nonimmigrants; however, concentrations were similar over the length of time that an immigrant subject had lived in Canada. Subjects who defined themselves as visible minorities had higher assigned concentrations than those subjects who did not in the 1991 and 1996 cohorts. Subjects who defined themselves as indigenous had lower concentrations. Married and common-law subjects had lower assigned exposures compared with other marital categories in all cohorts. Exposure monotonically increased with educational attainment in all cohorts. However, exposure monotonically declined with income. Subjects employed at the time of the interview had higher exposures than those who were unemployed. Exposure tended to decline over the occupational class categories moving from management and professional to semi-skilled and unskilled workers. Note that the *not in the labor force* and *not-applicable occupational class* categories had the highest exposures, possibly to due to older subjects who tended to have higher than average exposures. There was a tendency for exposure to increase over the quintiles of three of the CAN-Marg dimensions: residential instability, material deprivation, and ethnic concentration, with no clear trend for the fourth dimension, dependence. Exposure generally increased with community size, and for the inner-city categories of urban form. Of the six airsheds, the East Central contained 58% of person-years and had the highest exposures. Based on the associations between several geographic and subject-based covariates, there exists some potential that adjustment for these variables could influence the magnitude of our estimates of the $PM_{2.5}$–mortality association.

HR Estimates Table 7 reports the HR and 95% CIs, per 10-μg/m^3 for a linear model for each cohort separately and pooled among the three cohorts. The baseline hazard function is stratified by categories of immigrant status, age, and sex for both the DAG and full models. There was a tendency for the HR to be larger under the full model compared with the DAG for the 1991 and 1996 cohorts, but smaller for the 2001 cohort. Consequently, there was less variation among the HRs between cohorts under the full compared with the DAG models. The Akaike information criterion (AIC) and Schwarz Bayesian Criterion (SBC) statistics (Table 8) under the full model are considerably lower than those under the DAG model, suggesting the addition of the subject level covariates greatly improves mortality predication. We therefore focus our interpretation on the results using the full model.

Table 6. Descriptive Statistics of the 1991, 1996, and 2001 CanCHEC Study Cohorts

	1991 CanCHEC				1996 CanCHEC				2001 CanCHEC			
	Person-Years		$PM_{2.5}$ Concentration ($\mu g/m^3$)		Person-Years		$PM_{2.5}$ Concentration ($\mu g/m^3$)		Person-Years		$PM_{2.5}$ Concentration ($\mu g/m^3$)	
Covariate	*n*	%	Mean	SD	*n*	%	Mean	SD	*n*	%	Mean	SD
Total	54,042,100	—	8.10	3.44	54,082,700	—	7.18	2.70	42,871,700	—	6.68	2.24
Sex												
Male	27,769,300	51.4	8.14	3.43	28,240,300	52.2	7.23	2.69	22,308,500	52.0	6.72	2.24
Female	26,272,800	48.6	8.06	3.45	25,842,400	47.8	7.13	2.70	20,563,200	48.0	6.64	2.24
Age group												
24–34 years	3,540,300	6.6	10.56	3.96	3,170,900	5.9	8.37	3.18	2,659,100	6.2	7.18	2.52
35–44 years	10,088,100	18.7	8.75	3.58	10,368,100	19.2	7.37	2.82	8,518,300	19.9	6.64	2.29
45–54 years	14,381,600	26.6	7.72	3.25	14,364,600	26.6	6.99	2.61	11,112,700	25.9	6.58	2.21
55–64 years	11,986,800	22.2	7.55	3.19	11,839,400	21.9	6.93	2.56	9,401,200	21.9	6.57	2.17
65–74 years	8,227,800	15.2	7.84	3.32	8,259,400	15.3	7.12	2.64	6,335,700	14.8	6.69	2.21
75–89 years	5,817,700	10.8	7.88	3.13	6,080,300	11.2	7.26	2.55	4,844,600	11.3	6.90	2.20
Immigrant status												
Nonimmigrant	45,568,900	84.3	7.82	3.34	45,280,200	83.7	6.94	2.62	35,465,100	82.7	6.46	2.20
Immigrant, 11–20 yrs	2,711,900	5.0	9.48	3.48	2,114,600	3.9	8.40	2.60	1,871,300	4.4	7.82	2.00
Immigrant, 21–30 yrs	2,585,500	4.8	9.57	3.57	3,148,000	5.8	8.45	2.69	2,055,200	4.8	7.69	2.06
Immigrant, >30 yrs	3,175,800	5.9	9.63	3.74	3,539,800	6.6	8.47	2.84	3,480,100	8.1	7.69	2.23
Visible minority status												
No	51,309,700	94.9	8.02	3.42	51,075,900	94.4	7.10	2.69	37,791,200	88.2	6.69	2.22
Yes	2,732,400	5.1	9.61	3.40	3,006,700	5.6	8.56	2.49	5,080,500	11.9	6.60	2.41
Indigenous status												
No	51,920,400	96.1	8.17	3.43	51,916,000	96.0	7.28	2.68	40,921,000	95.5	6.78	2.22
Yes	2,121,800	3.9	6.28	3.06	2,166,700	4.0	4.90	1.99	1,950,700	4.6	4.61	1.69
Marital status												
Never married/ not common-law	6,776,600	12.5	8.52	3.49	6,597,000	12.2	7.57	2.74	5,233,700	12.2	7.05	2.29
Common-law	4,035,500	7.5	7.73	3.24	5,066,100	9.4	6.81	2.50	4,693,200	11.0	6.50	2.15
Married	37,316,200	69.1	7.95	3.40	36,029,200	66.6	7.07	2.68	27,590,800	64.4	6.57	2.22
Separated	1,275,500	2.4	8.46	3.53	1,323,000	2.5	7.49	2.78	1,032,800	2.4	6.89	2.29
Divorced	2,524,900	4.7	8.62	3.46	2,861,000	5.3	7.65	2.68	2,404,100	5.6	7.09	2.21
Widowed	2,113,400	3.9	9.11	3.76	2,206,300	4.1	7.83	2.91	1,917,000	4.5	7.09	2.37

Table continues next page

Table 6 (*Continued*). Descriptive Statistics of the 1991, 1996, and 2001 CanCHEC Study Cohorts

	1991 CanCHEC				1996 CanCHEC				2001 CanCHEC			
	Person-Years		$PM_{2.5}$ Concentration ($\mu g/m^3$)		Person-Years		$PM_{2.5}$ Concentration ($\mu g/m^3$)		Person-Years		$PM_{2.5}$ Concentration ($\mu g/m^3$)	
Covariate	*n*	%	Mean	SD	*n*	%	Mean	SD	*n*	%	Mean	SD
Educational attainment												
< High school graduation	17,025,100	31.5	8.00	3.55	16,190,200	29.9	7.01	2.80	11,564,900	27.0	6.50	2.34
High school – with or without trades certificate	20,516,400	38.0	8.00	3.39	19,575,600	36.2	7.11	2.65	15,491,200	36.1	6.60	2.22
Postsecondary non-university	8,940,200	16.5	8.11	3.35	10,185,400	18.8	7.23	2.63	8,542,100	19.9	6.71	2.17
University degree	7,560,400	14.0	8.55	3.38	8,131,400	15.0	7.64	2.62	7,273,600	17.0	7.08	2.16
Income inadequacy												
Q1 (lowest income)	8,373,700	15.5	8.25	3.61	8,693,400	16.1	7.21	2.81	7,216,300	16.8	6.76	2.36
Q2	9,989,100	18.5	8.22	3.50	9,949,900	18.4	7.28	2.75	8,078,000	18.8	6.74	2.28
Q3	11,417,600	21.1	8.09	3.42	11,248,900	20.8	7.21	2.69	8,772,600	20.5	6.70	2.23
Q4	12,023,900	22.3	8.03	3.37	11,875,400	22.0	7.15	2.65	9,194,600	21.5	6.64	2.19
Q5 (highest income)	12,237,800	22.6	7.97	3.34	12,315,200	22.8	7.08	2.62	9,610,200	22.4	6.58	2.17
Employment status												
Employed	38,679,600	71.6	8.00	3.36	36,133,000	66.8	7.13	2.64	28,781,900	67.1	6.65	2.20
Unemployed	3,380,300	6.3	7.65	3.42	3,018,000	5.6	6.72	2.71	1,739,800	4.1	6.06	2.29
Not in labor force	11,982,200	22.2	8.53	3.63	14,931,700	27.6	7.41	2.82	12,350,000	28.8	6.82	2.32
Occupational class												
Management	4,811,500	8.9	8.17	3.36	4,107,400	7.6	7.25	2.62	3,806,700	8.9	6.75	2.18
Professional	6,718,300	12.4	8.25	3.35	6,598,700	12.2	7.39	2.62	5,593,100	13.1	6.87	2.17
Skilled, technical, and supervisory	14,058,800	26.0	7.77	3.33	12,379,800	22.9	6.89	2.61	10,290,500	24.0	6.45	2.18
Semi-skilled	14,023,100	26.0	7.99	3.40	13,401,200	24.8	7.11	2.67	9,410,200	22.0	6.62	2.22
Unskilled	4,339,400	8.0	7.92	3.46	4,091,000	7.6	6.95	2.72	2,996,100	7.0	6.46	2.29
Not applicable	10,090,900	18.7	8.64	3.66	13,504,600	25.0	7.47	2.82	10,775,000	25.1	6.88	2.33
Residential instability (CanMARG)												
Q1 (lowest marginalization)	12,129,000	22.4	7.28	3.19	12,537,400	23.2	6.50	2.53	10,200,700	23.8	6.06	2.09
Q2	13,959,900	25.8	7.46	3.29	14,328,200	26.5	6.63	2.61	11,519,100	26.9	6.20	2.16
Q3	11,234,900	20.8	8.18	3.56	11,059,600	20.5	7.23	2.79	8,645,800	20.2	6.69	2.29
Q4	9,674,400	17.9	8.86	3.41	9,488,700	17.5	7.92	2.62	7,407,900	17.3	7.37	2.14
Q5 (highest marginalization)	7,044,000	13.0	9.58	3.25	6,668,800	12.3	8.53	2.37	5,098,300	11.9	7.97	1.95

Table continues next page

Table 6 (*Continued*). Descriptive Statistics of the 1991, 1996, and 2001 CanCHEC Study Cohorts

	1991 CanCHEC				1996 CanCHEC				2001 CanCHEC			
	Person-Years		$PM_{2.5}$ Concentration ($\mu g/m^3$)		Person-Years		$PM_{2.5}$ Concentration ($\mu g/m^3$)		Person-Years		$PM_{2.5}$ Concentration ($\mu g/m^3$)	
Covariate	*n*	%	Mean	SD	*n*	%	Mean	SD	*n*	%	Mean	SD
Dependence (CanMARG)												
Q1 (lowest marginalization)	8,881,200	16.4	8.30	3.48	8,958,200	16.6	7.14	2.68	7,416,500	17.3	6.44	2.12
Q2	9,310,000	17.2	8.44	3.43	8,908,400	16.5	7.38	2.65	6,938,000	16.2	6.73	2.11
Q3	9,079,900	16.8	8.67	3.55	8,702,200	16.1	7.65	2.75	6,663,500	15.5	7.06	2.25
Q4	11,665,500	21.6	8.22	3.43	11,497,400	21.3	7.36	2.71	8,882,800	20.7	6.93	2.31
Q5 (highest marginalization)	15,105,600	28.0	7.32	3.22	16,016,500	29.6	6.72	2.62	12,970,900	30.3	6.41	2.27
Material deprivation (CanMARG)												
Q1 (lowest marginalization)	11,497,200	21.3	7.59	3.07	10,947,700	20.2	7.00	2.52	8,651,800	20.2	6.61	2.04
Q2	12,268,900	22.7	8.18	3.24	11,270,800	20.8	7.29	2.49	8,383,500	19.6	6.86	2.06
Q3	10,965,300	20.3	8.46	3.43	10,652,500	19.7	7.44	2.63	8,375,900	19.5	6.85	2.16
Q4	8,826,900	16.3	8.59	3.49	9,190,500	17.0	7.61	2.73	7,335,900	17.1	7.08	2.29
Q5 (highest marginalization)	10,483,800	19.4	7.76	3.88	12,021,200	22.2	6.70	2.98	10,124,600	23.6	6.15	2.47
Ethnic concentration (CanMARG)												
Q1 (lowest marginalization)	15,066,600	27.9	6.81	3.20	17,014,800	31.5	6.08	2.38	14,272,200	33.3	5.71	1.96
Q2	12,404,500	23.0	7.79	3.22	13,274,500	24.5	7.02	2.54	10,882,100	25.4	6.57	2.16
Q3	9,435,300	17.5	8.37	3.33	9,457,600	17.5	7.48	2.63	7,569,000	17.7	6.93	2.22
Q4	8,678,400	16.1	9.18	3.34	7,620,700	14.1	8.26	2.66	5,616,300	13.1	7.71	2.16
Q5 (highest marginalization)	8,457,300	15.7	9.43	3.48	6,715,100	12.4	8.65	2.64	4,532,100	10.6	8.28	1.80
CMA/CA size (population)												
> 1,500,000	15,000,000	27.8	10.07	3.32	14,932,200	27.6	8.85	2.36	12,159,300	28.4	8.13	1.83
500,000–1,499,999	8,747,700	16.2	8.16	2.82	8,679,700	16.1	7.40	2.18	6,991,200	16.3	6.95	1.81
100,000–499,999	9,759,400	18.1	8.68	3.56	9,751,700	18.0	7.83	2.92	7,826,800	18.3	7.16	2.42
30,000–99,999	5,510,600	10.2	7.66	3.27	5,267,500	9.7	6.68	2.42	4,081,700	9.5	6.14	1.98
10,000–29,000	2,111700	3.9	6.44	2.51	2,107,400	3.9	5.73	1.88	1,699,900	4.0	5.27	1.42
Non-CMA/CA	12,912,700	23.9	5.78	2.33	13,344,100	24.7	5.13	1.72	10,112,800	23.6	4.83	1.39

Table continues next page

Table 6 (*Continued*). Descriptive Statistics of the 1991, 1996, and 2001 CanCHEC Study Cohorts

	1991 CanCHEC				1996 CanCHEC				2001 CanCHEC			
	Person-Years		$PM_{2.5}$ Concentration ($\mu g/m^3$)		Person-Years		$PM_{2.5}$ Concentration ($\mu g/m^3$)		Person-Years		$PM_{2.5}$ Concentration ($\mu g/m^3$)	
Covariate	*n*	%	Mean	SD	*n*	%	Mean	SD	*n*	%	Mean	SD
Urban form												
Active urban core	4,152,200	7.7	10.02	3.26	4,006,700	7.4	8.95	2.40	3,220,700	7.5	8.32	1.92
Transit-reliant suburb	3,490,900	6.5	10.50	3.26	3,405,600	6.3	9.31	2.30	2,689,000	6.3	8.58	1.69
Car-reliant suburb	21,595,500	40.0	9.16	3.30	21,787,500	40.3	8.18	2.50	17,930,300	41.8	7.53	2.00
Exurban	2,951,100	5.5	6.57	2.59	3,000,100	5.6	5.98	2.06	2,471,500	5.8	5.68	1.72
Non-CMA/CA	21,852,400	40.4	6.50	2.87	21,882,700	40.5	5.70	2.16	16,560,200	38.6	5.27	1.74
Airshed												
Western	6,532,200	12.1	7.92	3.44	6,404,500	11.8	6.58	2.08	5,137,600	12.0	5.95	1.55
Prairie	6,942,700	12.9	6.45	2.07	7,016,900	13.0	5.92	1.73	5,675,500	13.2	5.61	1.54
West Central	3,205,600	5.9	5.86	1.73	3,322,900	6.1	5.30	1.41	2,589,400	6.0	5.01	1.25
Southern Atlantic	5,312,600	9.8	5.41	1.87	5,324,000	9.8	4.80	1.30	4,044,400	9.4	4.54	1.05
East Central	31,626,600	58.5	9.23	3.48	31,439,700	58.1	8.25	2.71	24,932,700	58.2	7.65	2.17
Northern	422,300	0.8	4.19	1.37	574,600	1.1	3.80	1.11	492,100	1.2	3.67	1.05

(From Pappin et al. 2019.)

Q = quintile.

Table 7. HR Estimates and 95% CIs for the Association Between $PM_{2.5}$ and Nonaccidental Mortality per 10-μg/m^3 Increase in $PM_{2.5}$ by CanCHEC Cohort (1991, 1996, 2001) and Subject Characteristics. (Pooled HRs Among Cohorts Also Reported)

Subject Characteristic	Model Form[b]	1991 Cohort		1996 Cohort		2001 Cohort		Pooled Results[a]	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All subjects									
	DAG	0.982	(0.959–1.006)	1.033	(1.016–1.051)	1.120	(1.096–1.146)	1.044**	(1.031–1.056)
	Full	1.041	(1.016–1.066)	1.041	(1.024–1.059)	1.084	(1.060–1.108)	1.053**	(1.041–1.065)
Immigrant[c]									
No	DAG	0.975	(0.951–1.000)	1.024	(1.005–1.043)	1.105	(1.078–1.133)	1.032**	(1.019–1.045)
	Full	1.049	(1.022–1.076)	1.058	(1.039–1.078)	1.089	(1.062–1.116)	1.064	(1.050–1.078)
Yes	DAG	1.016	(0.945–1.092)	1.082	(1.040–1.125)	1.190	(1.131–1.253)	1.104**	(1.073–1.136)
	Full	1.006	(0.935–1.081)	1.027	(0.987–1.068)	1.109	(1.053–1.167)	1.049*	(1.019–1.079)
Sex[c]									
Female	DAG	0.956	(0.921–0.993)	1.001	(0.976–1.026)	1.121	(1.084–1.160)	1.022**	(1.004–1.040)
	Full	1.009	(0.972–1.048)	1.008	(0.983–1.034)	1.093	(1.056–1.130)	1.031**	(1.013–1.050)
Male	DAG	0.993	(0.963–1.024)	1.055	(1.032–1.078)	1.116	(1.083–1.150)	1.055**	(1.039–1.071)
	Full	1.053	(1.021–1.086)	1.062	(1.039–1.086)	1.071	(1.040–1.104)	1.062	(1.046–1.079)
Age during follow-up[c]									
<65 Years	DAG	1.022	(0.971–1.075)	1.057	(1.019–1.097)	1.176	(1.119–1.236)	1.078**	(1.051–1.106)
	Full	1.079	(1.026–1.136)	1.095	(1.056–1.136)	1.165	(1.108–1.225)	1.109	(1.081–1.137)
65–74 Years	DAG	0.984	(0.939–1.031)	1.079	(1.044–1.116)	1.176	(1.122–1.232)	1.077**	(1.052–1.103)
	Full	1.069	(1.020–1.120)	1.092	(1.057–1.130)	1.130	(1.078–1.184)	1.096	(1.070–1.122)
>75 Years	DAG	0.929	(0.899–0.961)	0.986	(0.964–1.009)	1.062	(1.031–1.094)	0.994**	(0.978–1.010)
	Full	0.972	(0.940–1.005)	0.985	(0.963–1.008)	1.031	(1.001–1.062)	0.995*	(0.979–1.011)

Table continues next page

[a] Tests for heterogeneity of HR among cohorts: $*P < 0.05$, $**P < 0.01$.

[b] The directed acyclic graph (DAG) model is stratified by 5-year age groups by age at baseline, sex, and immigrant status and includes the geographic-based covariates: four Can-Marg index dimensions, urban form, community size, and airshed. The full model is stratified by 5-year age groups by age at baseline, sex, and immigrant status and includes the geographic-based covariates: four Can-Marg index dimensions, urban form, community size, and airshed; and the subject-based covariates: marital status, education, income quintile, indigenous status, visible minority status, employment status, and occupational class.

[c] Note that the models by immigrant status are not stratified by immigrant status. The models by sex are not stratified by sex.

[d] $PM_{2.5}$ always uses 10 units; copollutants use: O_3 10.20 ppb, NO_2 6.63 ppb, O_x 8.05 ppb.

Table 7 (*continued*). HR Estimates and 95% CIs for the Association Between $PM_{2.5}$ and Nonaccidental Mortality per 10-μg/m^3 Increase in $PM_{2.5}$ by CanCHEC Cohort (1991, 1996, 2001) and Subject Characteristics.(Pooled HRs Among Cohorts Also Reported)

Subject Characteristic	Model Form[b]	1991 Cohort		1996 Cohort		2001 Cohort		Pooled Results[a]	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Single Pollutant									
NO_2	DAG	1.009	(1.004–1.015)	0.997	(0.993–1.001)	1.003	(0.998–1.008)	1.002**	(0.999–1.004)
	Full	1.015	(1.009–1.020)	1.001	(0.997–1.005)	1.003	(0.998–1.009)	1.005**	(1.002–1.008)
O_3	DAG	1.016	(1.006–1.027)	1.035	(1.029–1.041)	1.041	(1.034–1.049)	1.034**	(1.030–1.038)
	Full	1.044	(1.033–1.055)	1.076	(1.069–1.082)	1.081	(1.073–1.088)	1.073**	(1.068–1.077)
O_x	DAG	1.030	(1.018–1.043)	1.037	(1.029–1.044)	1.049	(1.040–1.058)	1.040*	(1.035–1.045)
	Full	1.068	(1.056–1.081)	1.086	(1.078–1.093)	1.094	(1.085–1.103)	1.086**	(1.080–1.091)
Two-Pollutant[d]									
Adjusted for NO_2									
$PM_{2.5}$	DAG	0.966	(0.942–0.991)	1.038	(1.02–1.057)	1.115	(1.089–1.142)	1.040**	(1.028–1.053)
NO_2		1.010	(1.004–1.015)	0.997	(0.993–1.001)	1.003	(0.998–1.009)	1.002**	(0.999–1.005)
$PM_{2.5}$	Full	1.014	(0.989–1.041)	1.039	(1.021–1.058)	1.078	(1.052–1.104)	1.043**	(1.030–1.056)
NO_2		1.015	(1.010–1.021)	1.001	(0.997–1.006)	1.004	(0.998–1.009)	1.006**	(1.003–1.009)
Adjusted for O_3									
$PM_{2.5}$	DAG	0.969	(0.944–0.994)	0.996	(0.978–1.014)	1.073	(1.048–1.098)	1.011**	(0.998–1.024)
O_3		1.016	(1.006–1.026)	1.034	(1.028–1.04)	1.040	(1.033–1.047)	1.033**	(1.029–1.037)
$PM_{2.5}$	Full	1.003	(0.978–1.029)	0.963	(0.946–0.981)	0.996	(0.973–1.020)	0.982*	(0.970–0.994)
O_3		1.043	(1.033–1.054)	1.074	(1.068–1.08)	1.079	(1.072–1.086)	1.071**	(1.067–1.075)
Adjusted for O_x									
$PM_{2.5}$	DAG	0.950	(0.925–0.977)	0.988	(0.97–1.007)	1.056	(1.031–1.083)	0.998**	(0.985–1.011)
O_x		1.028	(1.017–1.039)	1.034	(1.027–1.04)	1.045	(1.037–1.053)	1.037*	(1.032–1.041)
$PM_{2.5}$	Full	0.967	(0.941–0.994)	0.941	(0.923–0.959)	0.970	(0.946–0.994)	0.955	(0.943–0.968)
O_x		1.062	(1.051–1.074)	1.078	(1.071–1.085)	1.086	(1.077–1.094)	1.078**	(1.073–1.083)

[a] Tests for heterogeneity of HR among cohorts: $*P < 0.05$, $**P < 0.01$.

[b] The directed acyclic graph (DAG) model is stratified by 5-year age groups by age at baseline, sex, and immigrant status and includes the geographic-based covariates: four Can-Marg index dimensions, urban form, community size, and airshed. The full model is stratified by 5-year age groups by age at baseline, sex, and immigrant status and includes the geographic-based covariates: four Can-Marg index dimensions, urban form, community size, and airshed; and the subject-based covariates: marital status, education, income quintile, indigenous status, visible minority status, employment status, and occupational class.

[c] Note that the models by immigrant status are not stratified by immigrant status. The models by sex are not stratified by sex.

[d] $PM_{2.5}$ always uses 10 units; copollutants use: O_3 10.20 ppb, NO_2 6.63 ppb, O_x 8.05 ppb.

(From Pappin et al. 2019.)

Table 8. Akaike Information Criterion (AIC) and Schwarz Bayesian Criterion (SBC) Values with Covariates for $PM_{2.5}$ Mortality Models with the 1991, 1996, and 2001 CanCHEC Cohorts

Subject Characteristic	Model Form[a]	1991 Cohort		1996 Cohort		2001 Cohort	
		AIC	SBC	AIC	SBC	AIC	SBC
All respondents							
	DAG	4,607,944	4,608,266	11,594,177	11,594,525	8,585,618	8,585,956
	Full	4,589,687	4,590,227	11,542,271	11,542,854	8,544,931	8,545,498
Immigrant status[b]							
No	DAG	4,176,837	4,177,155	9,618,970	9,619,311	7,037,006	7,037,337
	Full	4,159,461	4,159,994	9,571,618	9,572,190	7,000,482	7,001,037
Yes	DAG	430,941.7	431,196	1,974,414	1,974,710	1,548,046	1,548,334
	Full	429,796.7	430,223.2	1,969,037	1,969,533	1,543,415	1,543,899
Sex[b]							
Female	DAG	1,928,558	1,928,853	5,261,734	5,262,057	3,840,820	3,841,133
	Full	1,921,461	1,921,955	5,241,019	5,241,561	3,824,369	3,824,895
Male	DAG	2,678,893	2,679,198	6,330,959	6,331,288	4,743,882	4,744,202
	Full	2,667,590	2,668,102	6,299,445	6,299,996	4,719,449	4,719,986
Age during follow-up[b]							
<65 Years	DAG	1,055,226	1,055,499	2,494,220	2,494,518	1,857,729	1,858,018
	Full	1,046,185	1,046,644	2,467,224	2,467,724	1,834,585	1,835,069
65–74 Years	DAG	1,157,518	1,157,797	2,790,514	2,790,817	1,974,175	1,974,467
	Full	1,151,192	1,151,660	2,773,119	2,773,627	1,961,714	1,962,204
>75 Years	DAG	2,338,415	2,338,718	6,184,696	6,185,026	4,664,254	4,664,575
	Full	2,334,431	2,334,939	6,174,201	6,174,754	4,656,525	4,657,064
Single Pollutant							
NO_2	DAG	4,607,933	4,608,266	11,594,177	11,594,536	8,585,618	8,585,968
	Full	4,589,659	4,590,209	11,542,272	11,542,866	8,544,931	8,545,509
O_3	DAG	4,607,936	4,608,268	11,594,051	11,594,410	8,585,488	8,585,837
	Full	4,589,621	4,590,171	11,541,701	11,542,295	8,544,452	8,545,030
O_x	DAG	4,607,922	4,608,254	11,594,080	11,594,439	8,585,493	8,585,843
	Full	4,589,573	4,590,124	11,541,762	11,542,357	8,544,487	8,545,066
Two Pollutant[c]							
NO_2 adjustment	DAG	4,607,933	4,608,266	11,594,177	11,594,536	8,585,618	8,585,968
	Full	4,589,659	4,590,209	11,542,272	11,542,866	8,544,931	8,545,509
O_3 adjustment	DAG	4,607,936	4,608,268	11,594,051	11,594,410	8,585,488	8,585,837
	Full	4,589,621	4,590,171	11,541,701	11,542,295	8,544,452	8,545,030
O_x adjustment	DAG	4,607,922	4,608,254	11,594,080	11,594,439	8,585,493	8,585,843
	Full	4,589,573	4,590,124	11,541,762	11,542,357	8,544,487	8,545,066

[a] The directed acyclic graph (DAG) model is stratified by 5-year age groups by age at baseline, sex, and immigrant status and includes the geographic-based covariates: four Can-Marg index dimensions, urban form, community size, and airshed. The full model is stratified by 5-year age groups by age at baseline, sex, and immigrant status and includes the geographic-based covariates: four Can-Marg index dimensions, urban form, community size, and airshed; and the subject-based covariates: marital status, education, income quintile, indigenous status, visible minority status, employment status, and occupational class.

[b] Note that the models by immigrant status are not stratified by immigrant status. The models by sex are not stratified by sex.

[c] $PM_{2.5}$ always uses 10 units; copollutants use: O_3 10.20 ppb, NO_2 6.63 ppb, O_x 8.05 ppb.

(From Pappin et al. 2019, Supplemental Material.)

When all subjects were considered together, HR estimates were similar for the 1991 and 1996 cohorts (HR = 1.041) with a larger estimate observed for the 2001 cohort (HR = 1.084) (Table 7). The pooled cohort HR estimate was 1.053 (95% CI: 1.041–1.065). HR estimates for nonimmigrants were higher than for immigrants in the 1991 and 1996 cohorts, but lower in the 2001 cohort. HR estimates for males were higher than for females in the 1991 and 1996 cohorts but lower in the 2001 cohort. The pooled cohort HR estimates were higher for males (HR = 1.06) than for females (HR = 1.03). HR estimates declined with age in all three cohorts, however.

Shape of Association Between $PM_{2.5}$ and Mortality

The shape of the association between $PM_{2.5}$ and mortality is displayed in Figure 12 for the three cohorts separately, based on the RCS model with 15 knots (solid red line). Note that these shapes represent the HRs for each level of exposure, relative to a HR of 1 at a counterfactual concentration of 0.4 μg/m^3, the lowest concentration observed in the data. These nonlinear HRs therefore cannot be directly compared with those assuming a linear relationship with concentration (e.g., a 10-μg/m^3 change as in Table 7). The marginal change in risk for a nonlinear model will vary by concentration, while the marginal

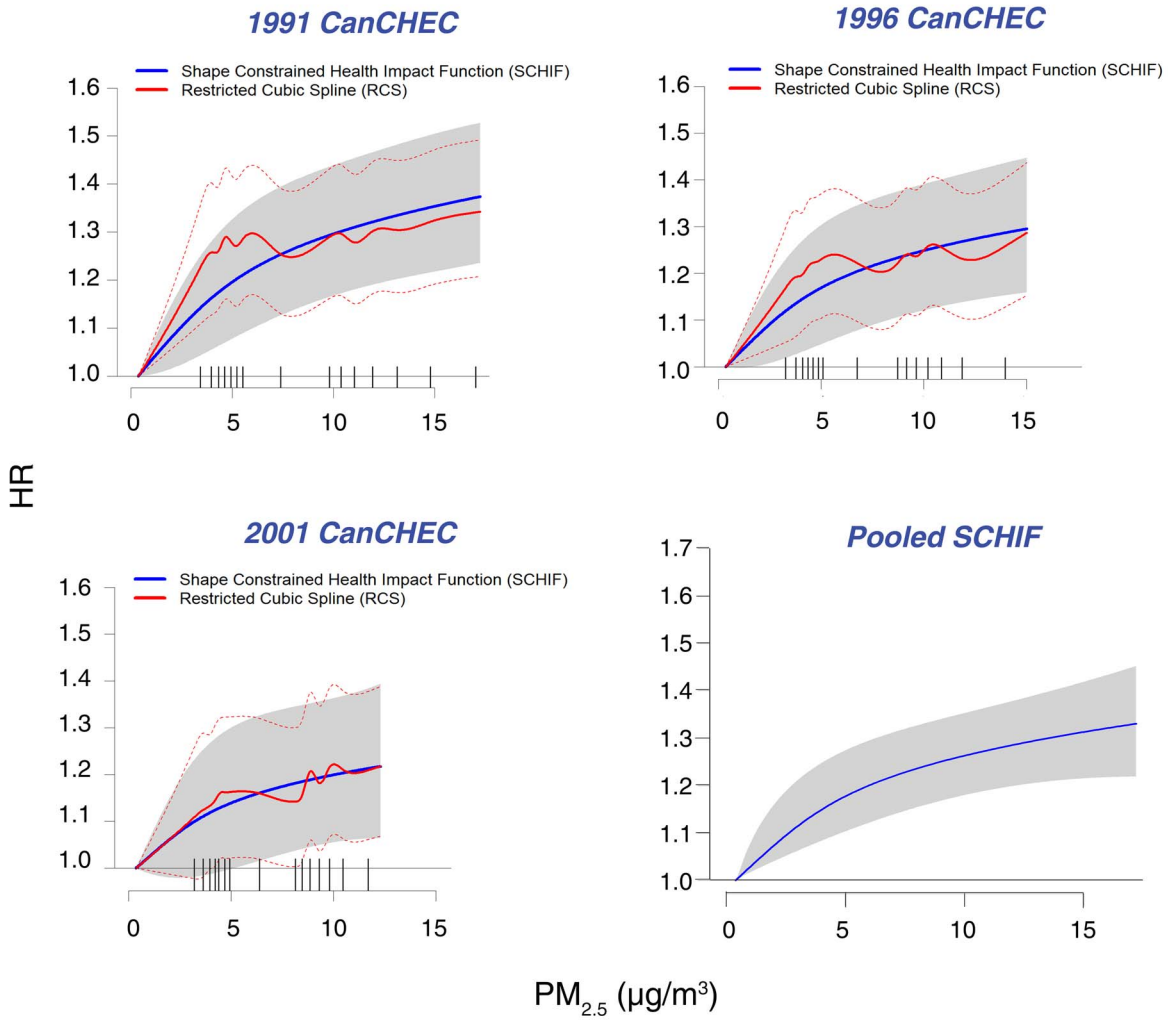

Figure 12. CanCHEC Cohort (1991, 1996, 2001) and pooled cohort HR predictions. These were based on RCS with 15 knots (solid red line) with 95% confidence intervals applied to the RCS predictions (dashed red line) and SCHIF (solid blue line) with uncertainty bounds (gray-shaded area). Tick marks on the $PM_{2.5}$ axis indicate the 1st, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 99th percentiles of person-year based $PM_{2.5}$ distribution.

change for the linear model is constant for all concentrations. The marginal change for a supralinear model, such as those observed in this study, will be greater than that of a linear model for lower concentrations, and less than the linear model for higher concentrations. For each cohort, the RCS increased rapidly over lower concentrations, slightly declined between the 25th and 75th percentiles, and then increased beyond the 75th percentile. The steepness of the increase in the RCS over lower concentrations appeared to diminish as the cohort start date increased. The SCHIFs (solid blue line) displayed a similar supralinear association in each of the three cohorts but with less curvature due to constraints on the amount of allowable curvature. Thus, the SCHIF for the 2001 cohort was a better predictor of this increase than the SCHIF for the 1996 cohort, and still better than the SCHIF for 1991 cohort. These shapes are for single-pollutant ($PM_{2.5}$) models only. Our model for the RCS SEs as a function of concentration (the gray-shaded areas of Figure 12) generally approximates the observed RCS SEs (dashed red lines of Figure 12).

Main Analysis: Nonaccidental Mortality (Pooled CCHS)

We pooled several cycles of the CCHS for simultaneous analysis of the shape of the concentration–response association between $PM_{2.5}$ and nonaccidental mortality in a 15-year follow-up period. Exposure to $PM_{2.5}$ was higher in women, more recent immigrants, and nonindigenous people. Being single, university educated, and in the poorest income quintile were also associated with higher exposures (Christidis et al. 2019). Higher exposure to $PM_{2.5}$ was observed in people living in the largest CMAs and in the East Central airshed (which includes the cities of Toronto and Montreal). Lower mortality rates were observed in immigrants and nonindigenous people. Being employed, holding a university degree, and being married were associated with a lower risk of mortality. We observed clear trends showing mortality rates decreased as income increased and as immigrants lived longer in Canada. Descriptive statistics and mortality HRs for covariates are provided in Table 9.

To more directly compare with our model building strategy employed for the CanCHEC cohorts, we examined three model specifications comprising different sets of covariates in addition to models in which covariates were included if they led to a change in the HR by more than 10%. The first model was the DAG model (Figure 3B) consisting of urban form, airshed, community size, and the four CAN-Marg components. The second model included the DAG covariates plus covariates that were available in CanCHEC, such as income, education, marital status, indigenous status, visible minority, and employment status (DAG+SES). (Note that the occupational class variable was included in CanCHEC but is not available in the CCHS.) The third and final model (DAG+SES+BEHAV) also included the variables only available in the CCHS: smoking behavior, alcohol consumption, BMI, exercise, and fruit and vegetable consumption. The HR estimates declined with increasing model complexity, ranging from the DAG (HR = 1.16, 95% CI: 1.09–1.24), DAG+SES (HR = 1.11; 95% CI: 1.04–1.18), to the smallest HR under the most complex DAG+SES+BEHAV model (HR = 1.08, 95% CI: 1.02–1.16) (Table 10). Using the DAG+SES+BEHAV model, we observed a supralinear concentration–response shape with a steep increase in the spline predictions below 5 $\mu g/m^3$, with a more modest change above 5 $\mu g/m^3$ (Figure 13). The SCHIF displayed a similar pattern with much less curvature. We note caution in interpreting specifics about this shape since the uncertainty bounds are considerable (Figure 13), in part due to the potential overfitting by using 15 knots

Table 9. Descriptive Statistics of the CCHS Cohort and $PM_{2.5}$, O_3, and NO_2 Exposure, with Cox Proportional HRs for Nonaccidental Mortality[a]

Covariate	Person-Years[b]	HR	95% CI	$PM_{2.5}$	SD	O_3	SD	NO_2	SD
All	4,452,700	—	—	5.9	2.0	36.0	7.5	8.6	5.9
Sex									
Male	1,995,100	—	—	5.9	2.0	35.9	7.6	8.5	5.9
Female	2,457,600	—	—	6.0	2.0	36.0	7.5	8.6	5.9
Age group (years)									
25–29	381,100	—	—	5.9	2.0	35.7	7.6	8.8	5.9
30–39	869,300	—	—	5.9	2.0	35.9	7.7	8.7	5.9
40–49	887,000	—	—	5.9	2.0	35.8	7.6	8.7	6.0
50–59	918,100	—	—	5.8	2.0	35.8	7.4	8.2	5.7
60–69	753,800	—	—	5.9	2.0	36.2	7.3	8.3	5.8
70–79	497,100	—	—	6.1	2.1	36.4	7.4	8.9	6.1
80–89	146,200	—	—	6.2	2.1	36.3	7.6	9.6	6.3
Immigrant status									
Nonimmigrant	3,945,800	1.00	—	5.8	2.0	35.7	7.4	8.1	5.6
In Canada for 30+ years	317,900	0.86	(0.83–0.88)	6.8	2.1	38.5	8.0	11.2	6.5
In Canada for 20–29 years	92,300	0.74	(0.68–0.80)	7.0	2.0	37.4	8.0	13.2	7.0
In Canada for 10–19 years	96,800	0.62	(0.56–0.69)	7.2	1.9	37.6	7.7	14.5	7.0
Visible minority identity									
Not a visible minority	4,119,200	1.00	—	5.9	2.0	36.1	7.4	8.4	5.7
Visible minority	244,900	0.89	(0.84–0.93)	6.6	2.1	34.9	8.9	12.8	7.2
Missing (dummy variable)	88,600	1.48	(1.37–1.59)	4.9	1.6	31.7	8.3	6.5	4.3
Indigenous identity									
Nonindigenous or not stated	4,295,500	1.00	—	6.0	2.0	36.2	7.4	8.6	5.9
Indigenous	146,000	1.58	(1.50–1.67)	4.9	1.7	30.3	8.8	6.9	4.7
Missing (dummy variable)	11,300	1.16	(0.99–1.35)	5.6	1.8	35.0	7.5	8.2	5.6
Marital status									
Married or common-law	2,823,000	1.00	—	5.8	2.0	36.1	7.6	8.1	5.5
Separated, widowed, or divorced	945,100	1.42	(1.39–1.45)	6.1	2.1	36.1	7.5	9.1	6.2
Single	681,400	1.57	(1.52–1.62)	6.2	2.1	35.4	7.5	9.8	6.8
Missing (dummy variable)	3,200	1.58	(1.20–2.07)	5.9	1.9	34.5	8.0	9.4	6.1

Table continues next page

[a] SD = standard deviation

[b] Numbers were rounded to the nearest 100 for confidentiality.

Table 9 (*Continued*). Descriptive Statistics of the CCHS Cohort and $PM_{2.5}$, O_3, and NO_2 Exposure, with Cox Proportional HRs for Nonaccidental Mortality[a]

Covariate	Person-Years[b]	HR	95% CI	$PM_{2.5}$	SD	O_3	SD	NO_2	SD
Educational attainment									
No high school diploma	980,900	1.00	—	5.7	2.1	35.2	7.5	7.8	5.8
High School	757,200	0.82	(0.80–0.84)	6.0	2.0	36.6	7.7	8.6	5.8
Any post-secondary	1,926,400	0.77	(0.75–0.78)	5.9	2.0	36.0	7.5	8.4	5.7
University	752,100	0.55	(0.54–0.57)	6.2	2.0	36.4	7.4	10.1	6.5
Missing (dummy variable)	36,000	0.98	(0.91–1.06)	5.9	2.0	35.6	7.7	8.8	5.8
Employment status									
Employed	2,701,800	1.00	—	5.9	2.0	36.0	7.6	8.7	5.8
Unemployed	115,100	1.67	(1.54–1.82)	5.8	2.1	34.9	7.7	8.4	6.3
Not in work force	1,630,100	2.02	(1.96–2.08)	6.0	2.1	36.0	7.4	8.5	6.0
Missing (dummy variable)	5,800	1.62	(1.24–2.12)	5.5	1.8	34.0	7.2	8.8	5.4
Income quintile									
Q1 (lowest income)	788,200	1.00	—	6.1	2.1	35.6	7.4	9.2	6.5
Q2	788,700	0.76	(0.74–0.78)	6.0	2.0	36.1	7.4	8.7	6.1
Q3	808,500	0.64	(0.62–0.66)	6.0	2.0	36.3	7.4	8.5	5.8
Q4	828,500	0.53	(0.52–0.55)	5.9	2.0	36.2	7.5	8.4	5.7
Q5 (highest income)	909,000	0.44	(0.43–0.46)	5.7	1.9	35.9	7.7	8.2	5.5
Missing (dummy variable)	329,800	0.74	(0.72–0.77)	5.8	2.0	35.5	8.0	8.6	5.8
Alcohol consumption									
Never drinker	392,400	1.00	—	5.8	2.0	35.8	7.3	8.0	5.9
Occasional drinker	840,300	0.84	(0.81–0.86)	5.8	2.0	35.7	7.6	8.3	5.8
Regular drinker, binging unknown	1,332,300	0.64	(0.62–0.66)	6.1	2.0	36.7	7.3	9.1	6.0
Regular, nonbinge drinker	1,169,600	0.69	(0.67–0.72)	5.8	2.0	35.8	7.5	8.4	5.7
Regular, binge drinker	260,400	1.08	(1.03–1.14)	5.9	2.0	35.8	7.8	8.1	5.8
Former drinker	447,500	1.10	(1.07–1.14)	5.9	2.1	35.3	8.0	8.8	6.2
Missing (dummy variable)	10,200	0.93	(0.81–1.07)	5.6	1.9	34.8	7.5	8.5	5.5
Smoking behaviors									
Never smoker	1,293,700	1.00	—	6.0	2.0	36.4	7.5	9.0	6.1
Occasional smoker	177,200	2.11	(2.00–2.23)	6.0	2.0	35.6	7.7	9.0	6.3
Smoke under 10 cigarettes/day	263,000	2.45	(2.35–2.55)	5.9	2.1	35.3	7.9	8.7	6.2
Smoke 11–20 cigarettes /day	398,900	2.76	(2.66–2.86)	5.9	2.0	35.6	7.7	8.3	5.8
Smoke 20+ cigarettes /day	255,300	3.69	(3.55–3.82)	5.9	2.1	36.0	7.6	8.2	5.9
Former smoker	2,058,700	1.32	(1.29–1.35)	5.9	2.0	35.9	7.4	8.4	5.8
Missing (dummy variable)	6,100	1.51	(1.26–1.80)	5.7	1.8	35.6	7.4	8.3	5.7

Table continues next page

[a] SD = standard deviation

[b] Numbers were rounded to the nearest 100 for confidentiality.

Table 9 (*Continued*). Descriptive Statistics of the CCHS Cohort and $PM_{2.5}$, O_3, and NO_2 Exposure, with Cox Proportional HRs for Nonaccidental Mortality[a]

Covariate	Person-Years[b]	HR	95% CI	$PM_{2.5}$	SD	O_3	SD	NO_2	SD
Fruit and vegetable consumption									
Under 5 servings/day	2,411,900	1.00	—	5.9	2.0	36.0	7.7	8.6	5.9
5–10 servings/day	1,450,300	0.82	(0.80–0.83)	6.0	2.0	36.6	7.5	8.8	5.9
10+ servings/day	132,700	0.82	(0.77–0.87)	6.1	2.0	36.6	7.5	8.9	6.0
Missing (dummy variable)	457,900	1.19	(1.16–1.23)	5.6	1.9	33.6	5.8	7.9	6.1
Leisure exercise frequency									
Active	1,005,700	1.00	—	5.9	2.0	36.1	7.6	8.6	5.7
Moderate	1,123,600	1.10	(1.07–1.14)	5.9	2.0	36.1	7.5	8.6	5.8
Inactive	2,224,700	1.70	(1.65–1.74)	5.9	2.0	35.9	7.5	8.5	6.0
Missing (dummy variable)	98,700	2.49	(2.39–2.60)	5.9	2.1	35.2	7.8	9.0	6.2
Body mass index (BMI)									
Normal weight (18.5–24.9)	1,425,400	1.00	—	6.1	2.0	36.1	7.4	9.1	6.2
Overweight (25.0–29.9)	1,671,700	0.81	(0.80–0.83)	5.9	2.0	36.0	7.5	8.5	5.8
Obese 1 (30.0–34.9)	800,500	0.93	(0.90–0.95)	5.8	2.0	35.9	7.6	8.1	5.6
Obese 2 (≥35)	355,300	1.33	(1.28–1.37)	5.7	2.0	35.7	7.7	7.9	5.5
Underweight (<18.5)	57,700	2.13	(2.00–2.26)	6.2	2.1	36.0	7.4	9.7	6.5
Missing	142,200	1.61	(1.53–1.68)	5.8	2.0	35.8	7.8	8.2	5.5
Residential Instability									
Q1 (lowest marginalization)	993,500	1.00	—	5.3	1.8	36.9	7.8	7.1	4.8
Q2	1,231,300	0.98	(0.95–1.00)	5.6	1.9	36.7	7.9	7.1	4.8
Q3	957,500	0.98	(0.95–1.01)	5.9	2.0	34.6	7.7	8.6	5.5
Q4	780,100	0.96	(0.93–0.99)	6.5	2.0	35.7	6.8	10.0	6.2
Q5 (highest marginalization)	490,300	1.04	(1.01–1.07)	7.2	1.9	35.5	6.1	13.0	7.6
Dependency									
Q1 (lowest marginalization)	701,400	1.00	—	5.7	1.9	33.4	8.7	10.0	6.2
Q2	601,900	0.96	(0.92–0.99)	6.1	1.9	35.8	7.3	9.9	6.0
Q3	602,400	0.92	(0.89–0.95)	6.3	2.1	37.4	7.5	9.7	6.1
Q4	945,800	0.90	(0.87–0.93)	6.2	2.1	37.6	7.5	8.6	5.8
Q5 (highest marginalization)	1,601,300	0.88	(0.86–0.91)	5.7	2.0	35.7	6.7	7.0	5.3

Table continues next page

[a] SD = standard deviation

[b] Numbers were rounded to the nearest 100 for confidentiality.

Table 9 (*Continued*). Descriptive Statistics of the CCHS Cohort and $PM_{2.5}$, O_3, and NO_2 Exposure, with Cox Proportional HRs for Nonaccidental Mortality[a]

Covariate	Person-Years[a]	HR	95% CI	$PM_{2.5}$	SD	O_3	SD	NO_2	SD
Material deprivation									
Q1 (lowest marginalization)	713,600	1.00	—	6.0	1.8	37.7	7.4	9.8	5.2
Q2	777,700	1.03	1.00–1.06)	6.2	1.9	38.0	8.0	9.4	5.4
Q3	897,400	1.04	1.01–1.07)	6.2	1.9	37.5	7.3	8.8	5.5
Q4	783,800	1.08	1.04–1.11)	6.2	2.1	35.7	7.5	9.2	6.3
Q5 (highest marginalization)	1,280,200	1.15	1.12–1.19)	5.3	2.0	32.9	6.4	6.8	6.2
Ethnic concentration									
Q1 (lowest marginalization)	1,839100	1.00	—	5.2	1.7	35.7	6.9	5.9	3.8
Q2	1,211,600	1.02	(1.00–1.04)	6.0	2.0	36.7	8.0	8.0	4.8
Q3	749,900	1.01	(0.99–1.04)	6.3	2.0	35.5	7.8	10.1	5.7
Q4	409,500	1.04	(1.00–1.07)	7.0	2.1	35.7	8.2	14.2	6.9
Q5 (highest marginalization)	242,600	0.98	(0.94–1.02)	7.7	1.7	36.4	7.5	17.7	6.2
Census Metropolitan Area/Census Agglomeration size									
Not applicable (non-CMA/CA)	1,485,900	1.00	—	4.7	1.3	33.9	7.1	4.9	2.7
10,000–29,999	355,900	1.03	(0.99–1.06)	5.0	1.3	31.6	7.9	6.0	3.1
30,000–99,999	570,900	1.03	(1.00–1.06)	5.8	1.8	36.6	6.9	7.1	3.3
100,000–499,999	872,600	1.00	(0.98–1.03)	6.8	2.2	39.5	8.0	8.9	4.6
500,000–1,499,999	506,400	0.94	(0.91–0.97)	6.7	1.7	36.5	6.2	13.2	6.2
>1,500,000	661,000	0.91	(0.89–0.94)	7.5	1.7	37.4	6.5	15.5	6.9
Urban form									
Active urban core	304,800	1.00	—	7.6	1.9	36.7	7.1	14.5	7.1
Transit-reliant suburb	179,500	0.98	(0.93–1.04)	7.8	1.7	36.7	7.1	16.1	7.4
Car-reliant suburb	1,242,700	0.81	(0.78–0.84)	7.0	1.9	38.3	7.0	12.1	6.0
Exurban	216,400	0.83	(0.78–0.87)	5.5	1.6	38.7	7.0	6.8	3.6
Non-CMA/CA	2,509,400	0.93	(0.90–0.96)	5.1	1.6	34.4	7.5	5.7	3.2
Airshed									
East Central	2,041,500	1.00	—	7.0	2.1	41.3	6.0	9.9	6.6
Northern	117,800	1.18	(1.11–1.27)	3.9	1.2	26.0	7.0	4.7	2.6
Southern Atlantic	711,700	1.11	(1.08–1.13)	4.4	1.0	30.7	3.1	3.9	2.6
Prairie	666,900	1.00	(0.97–1.02)	5.2	1.4	34.1	5.7	9.5	4.9
West Central	397,100	1.07	(1.03–1.10)	4.9	1.1	31.3	5.0	8.0	4.9
Western	517,600	1.04	(1.01–1.07)	5.7	1.5	30.6	5.9	9.8	5.0

[a] SD = standard deviation

[b] Numbers were rounded to the nearest 100 for confidentiality.

Table 10. Cox Proportional HRs for Nonaccidental Mortality per 10-μg/m^3 Increase in $PM_{2.5}$, for the mCCHS Cohort (50,700 Nonaccidental Deaths)[a]

Model	95% CI			
	HR	Lower	Upper	−2 LL[b]
Unadjusted (Stratified by Age, Sex, and Immigrant Status)	1.02	0.97	1.07	727,818.2
Geography Covariates (Unadjusted Model +)				
Airshed	1.15	1.08	1.21	727,730.2
Census metropolitan area / census agglomeration Size	1.08	1.02	1.14	727,774.8
Urban form	1.07	1.02	1.13	727,609.4
Can-Marg: residential instability	1.01	0.96	1.06	727,817.1
Can-Marg: dependency	1.01	0.97	1.06	727,712.3
Can-Marg: material deprivation	1.05	1.00	1.10	727,730.0
Can-Marg: ethnic concentration	0.98	0.93	1.03	727,798.0
Adjusted by all geography covariates (DAG)	1.16	1.09	1.24	727,264.4
Socioeconomic Covariates (Adjusted by Geography Covariates +)				
Visible minority identity	1.16	1.09	1.24	727,194.5
Indigenous identity	1.17	1.10	1.25	727,100.8
Educational attainment	1.15	1.07	1.22	725,933.7
Marital status	1.14	1.07	1.22	725,853.8
Income quintile	1.12	1.05	1.19	724,395.7
Employment status	1.16	1.09	1.24	725,155.3
Adjusted by all geography + socioeconomic covariates (Full model - mostly comparable to CanCHEC) "DAG+SES"	1.11	1.04	1.18	721,830.7
Behavioral Covariates (Adjusted by Geography + Socioeconomic Covariates +)				
Fruit and vegetable consumption	1.12	1.05	1.19	721,424.6
Leisure exercise frequency	1.10	1.03	1.17	718,877.7
Alcohol consumption	1.10	1.03	1.17	720,673.8
Smoking behavior	1.11	1.04	1.18	717,041.2
Adjusted by all geography + socioeconomic + behavioral covariates "DAG+SES+BEHAV"	1.08	1.02	1.16	713,549.1

[a] Covariates are included one at a time in unadjusted model.

[b] LL = log-linear; Q = quintile.

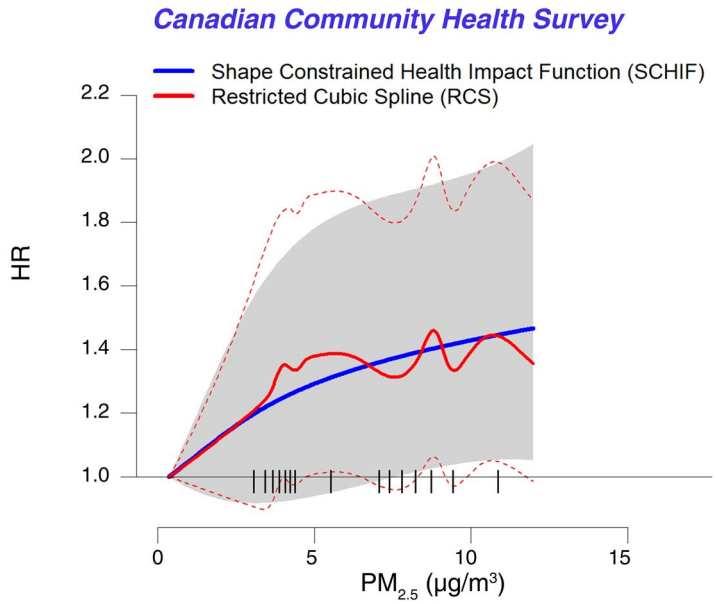

Figure 13. CCHS cohort HR predictions. These were based on RCS with 15 knots (solid red line) with 95% confidence intervals applied to the RCS predictions (dashed red line) and SCHIF (solid blue line). RCS 95% confidence intervals (dashed red line) and SCHIF uncertainty bounds (gray area) are shown. Tick marks on the $PM_{2.5}$ axis represent the 15 knot locations. The plot is truncated at the 99th percentile of the $PM_{2.5}$ distribution, as the RCS is linear beyond the last (98th percentile) knot, which can distort the SCHIF shape.

We conducted additional analyses to evaluate model sensitivity based upon an unadjusted model stratified only by age, sex, and cycle with stepwise addition of covariate, as described in Christidis and colleagues (2019). The modeling results using the 10% rule were similar to those of the three models that were defined a priori. We observed similar HR estimates based on these two different approaches to model building. All covariates except for BMI, employment status, and urban form met the 10% sensitivity criteria and were included in the final model. When we added the behavioral covariates to a model that included only socioeconomic covariates, the HR increased from 1.05 (95% CI: 1.00–1.09) to 1.09 (95% CI: 1.05–1.15) per 10 µg/m^3 increase in exposure (Table 11). Conversely, when we added the behavioral covariates to a (final) model that included both the socioeconomic and ecological covariates, they lowered the $PM_{2.5}$ HR 2.3% from 1.13 (95% CI: 1.06–1.21) to 1.11 (95% CI: 1.04–1.18). This suggests that behavioral covariates associated with mortality, and typically not found in census-based cohorts, do not dramatically confound the $PM_{2.5}$–mortality relationship. Mortality risks associated with exposure to $PM_{2.5}$ were increased for males (male HR = 1.13 and female HR = 1.09), those under age 65 (<65 years HR = 1.14, >65–74 years HR = 1.13, and ≥ 75 years HR = 1.04), and nonimmigrants (nonimmigrant HR = 1.14 and immigrant HR = 0.98) (Table 12). HRs for $PM_{2.5}$ and mortality were attenuated when gaseous pollutants were included in the models (Table 13).

Subanalysis: Exposure Measurement Sensitivity

Even though the magnitudes of association between $PM_{2.5}$ and mortality at low mass concentrations may be influenced by the temporal and spatial scales of exposure assessment, few studies have specifically examined this question. In this subanalysis, 2.4 million people in the 2001 CanCHEC were followed between 2001 and 2011 for nonaccidental and cause-specific mortality. We assigned $PM_{2.5}$ exposures employing satellite-based estimates to residential locations using exposure assignment for three different temporal moving averages (1 year, 3 years, and 8 years), and three spatial scales (1 km^2, 5 km^2, and 10 km^2) were compared. We also examined different spatial scales based on age, employment status, and urban/rural location, as well as adjustment for O_3, NO_2, or O_x. Correlations

Table 11. Cox Proportional HRs for Nonaccidental Mortality per 10-μg/m^3 Increase in $PM_{2.5}$, for the CCHS Cohort, All Respondents

Model	HR	95% CI		−2 LL[a]
		Lower	Upper	
Unadjusted (Stratified by Age, Sex, and Cycle)	0.96	0.92	1.00	769,047.5
Socioeconomic Covariates (Unadjusted Model +)				
Visible minority identity	0.98	0.93	1.02	768,923.2
Indigenous identity	0.98	0.94	1.03	768,812.8
Immigrant status	1.02	0.98	1.07	768,784.2
Educational attainment	1.05	1.01	1.10	767,553.7
Marital status	0.92	0.88	0.96	767,479.4
Income quintile	0.94	0.90	0.98	766,080.2
Adjusted by socioeconomic covariates	1.05	1.00	1.09	764,396.4
Behavioral Level Covariates (Unadjusted Model +)				
Fruit and vegetable consumption	1.00	0.96	1.05	768,304.6
Leisure exercise frequency	1.00	0.96	1.05	768,304.6
Alcohol consumption	1.04	1.00	1.09	766,726.1
Smoking behaviors	0.97	0.93	1.02	762,432.6
Adjusted by all socioeconomic + behavioral covariates	1.09	1.05	1.15	756,074.0
Contextual Covariates (Adjusted by Socioeconomic Covariates +) (DAG Model)				
Ethnic concentration	1.00	0.95	1.05	764,411.6
Material deprivation	1.04	0.99	1.09	764,411.2
Residential instability	1.06	1.01	1.11	764,408.0
Census Metropolitan Area/Census Agglomeration size	1.04	0.98	1.09	764,401.7
Airshed	1.11	1.05	1.17	764,378.8
Dependency	1.03	0.98	1.08	764,314.1
Adjusted by all socioeconomic + ecological covariates	1.13	1.06	1.21	764,157.5
Contextual Covariates (Adjusted by Socioeconomic + Behavioral Covariates +)				
Ethnic concentration	1.05	1.00	1.10	756,050.7
Material deprivation	1.12	1.07	1.17	756,049.0
Census metropolitan area/census agglomeration size	1.05	0.99	1.10	756,039.5
Dependency	1.08	1.03	1.13	755,985.4
Airshed	1.11	1.05	1.17	755,969.1
Residential instability	1.08	1.03	1.13	755,962.9
Final Model (Adjusted by all Socioeconomic + Behavioral + Contextual Covariates)				
	1.11	1.04	1.18	755,760.2

[a] LL = log-linear.

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Table 12. Cox Proportional HRs for Nonaccidental Mortality per 10-μg/m^3 Increase in $PM_{2.5}$, for the CCHS Full Cohort and for the CCHS Final Model Separated by Sex, Age at Survey Date, and Immigrant Status

	HR	Lower	Upper
Full Cohort[a]	1.11	1.04	1.18
Sex[b]			
Male	1.13	1.03	1.23
Female	1.09	0.99	1.19
Pooled HR	1.11	1.04	1.18
Age[b]			
Under 65	1.14	1.01	1.29
65–74	1.13	1.01	1.27
75 or over	1.04	0.94	1.16
Pooled HR	1.10	1.03	1.17
Immigrant status[b]			
Nonimmigrant	1.14	1.07	1.23
Immigrant	0.98	0.83	1.16
Pooled HR	1.12	1.05	1.19

[a] Excludes immigrants who have been living in Canada for fewer than ten years.

[b] The Cochrane Q was calculated for the final model HRs to test for significant differences between groups (males vs. females, under 65 vs. 65–74, under 65 vs. 75 or over, nonimmigrants vs. immigrants), and no *P* values were below 0.05.

Table 13. Cox Proportional HRs for Nonaccidental Mortality and $PM_{2.5}$, NO_2, O_3, and O_x, and Multiple-Pollutant Models for the CCHS Cohort[a]

Pollutant[b]	HR	Lower (95% CI)	Upper (95% CI)	−2 LL	SBC	AIC
Single-Pollutant Models						
$PM_{2.5}$	1.03	1.01	1.05	755,760.2	756,453.5	755,888.2
O_3	1.05	1.03	1.07	755,742.1	756,435.4	755,870.1
NO_2	1.03	1.02	1.05	755,756.9	756,450.3	755,884.9
O_x	1.06	1.04	1.09	755,734.0	756,427.3	755,862.0
Multiple-Pollutant Models						
$PM_{2.5}$,	1.01	1.00	1.03			
O_3	1.05	1.03	1.07	755,740.0	756,444.2	755,870.0
$PM_{2.5}$,	1.02	1.00	1.04			
NO_2	1.03	1.01	1.05	755,753.4	756,457.6	755,883.4
$PM_{2.5}$,	1.01	0.99	1.03			
O_x	1.06	1.04	1.09	755,733.7	756,437.9	755,863.7
$PM_{2.5}$,	1.00	0.98	1.02			
O_3,	1.05	1.03	1.07			
NO_2	1.03	1.01	1.05	755,732.5	756,447.5	755,864.5

[a] HRs are per increase in interquartile range: $PM_{2.5}$ 2.80 μg/m^3, O_3 10.20 ppb, NO_2 6.63 ppb, O_x 8.05 ppb.

[b] The combined oxidant capacity of NO_2 and O_3.

LL = log-linear.

Table 14. Correlations Between Exposure Variables in Exposure Sensitivity Analyses for the 2001 CanCHEC Cohort[a]

	$PM_{2.5}$ (1 yr)	$PM_{2.5}$ (8 yr)	$PM_{2.5}$ (10 km^2)	O_x	O_3	NO_2
$PM_{2.5}$ (3 yr)	0.893	0.858	0.759	0.676	0.503	0.582
$PM_{2.5}$ (1 yr)	1	0.771	0.713	0.616	0.445	0.553
$PM_{2.5}$ (8 yr)		1	0.650	0.758	0.580	0.624
$PM_{2.5}$ (10 km^2)			1	0.602	0.462	0.492
O_x				1	0.894	0.592
O_3					1	0.168

[a] $PM_{2.5}$ 10 km^2 is measured as a 3-year moving average; $PM_{2.5}$ 1 yr, $PM_{2.5}$ 3 yr, and $PM_{2.5}$ 8 yr are measured at 1-km^2 spatial resolution.

between the exposure variables used in this analysis are presented in Table 14.

Longer moving averages and smaller spatial scales resulted in improved model fit and stronger associations between $PM_{2.5}$ and mortality (Figure 14). In this analysis, the 8-year moving average consistently resulted in the strongest associations (and lowest AIC values) among the different temporal scales, with the exception of lung cancer mortality, for which a 3-year moving average resulted in the best fitting models. We found in general that the 1-km^2 buffer size resulted in the strongest associations and lowest AIC values. Compared with cardiovascular outcomes, respiratory and lung cancer mortality were more sensitive to the spatial scale of exposure assessment (Figures 14 and 15). For all outcomes, varying the buffer size according to age, employment status, or urban/rural status attenuated HRs slightly and did not improve model fit.

Adjustment for oxidant gases attenuated associations between $PM_{2.5}$ and cardiovascular disease mortality, strengthened associations between $PM_{2.5}$ and lung cancer mortality, and was included in all of the best fitting models. We observed an association between $PM_{2.5}$ with increased mortality in nearly all of the models examined, with the exception of cerebrovascular disease mortality at a 1-km^2 spatial resolution. These findings further support the relationship between long-term exposure to $PM_{2.5}$ at low mass concentrations and mortality and suggest the importance of longer exposure windows, more spatially resolved exposure metrics, and copollutant adjustment in characterizing this relationship.

Important advantages of this analysis include a large population-based cohort with detailed exposure data for multiple pollutants. However, it is important that several limitations be noted. Data availability limited our choices of spatial- and temporal-scales. Longer exposure windows will be able to be considered in the future as follow-up time increases. O_3 data were available on a relatively broad spatial scale (21 km^2), and while consistent with most prior analyses and with the generally regional scale of this pollutant, this spatial resolution would not address near-road O_3 scavenging by NO, for example. Our results may have been impacted by exposure measurement error for this pollutant. This could contribute to residual confounding in models adjusted for O_3 and O_x and lead to underestimation of the true impact of O_3/O_x on HRs for $PM_{2.5}$.

Subanalysis: Indirect Adjustment

At baseline (2001) both the CanCHEC and CCHS cohorts had very similar $PM_{2.5}$ distributions across population characteristics, although levels for CCHS participants were consistently 1.8–2.0 $\mu g/m^3$ lower (Table 15). Applying sample weighting largely corrected for this discrepancy.

Results of the validation tests are presented in Figure 16 for four different causes of mortality: nonaccidental, cardiovascular diseases, ischemic heart disease, and lung cancer. The true model is the gold-standard model showing HRs adjusted for education and income, whereas the partial model shows HRs with education and income removed. The internal validation tests showed minimal downward bias in $PM_{2.5}$ mortality HRs of 0.4% to 0.6% using a static exposure and 1.7% to 3% using a time-varying exposure measure. The external validation of the CCHS as the ancillary data set showed slight upward bias of −0.7% to −1.2% and downward bias of 1.3% to 2.3% using the static and time-varying approaches respectively.

The CCHS was found to be fairly well representative of CanCHEC, and its use in Canada for indirect adjustment is

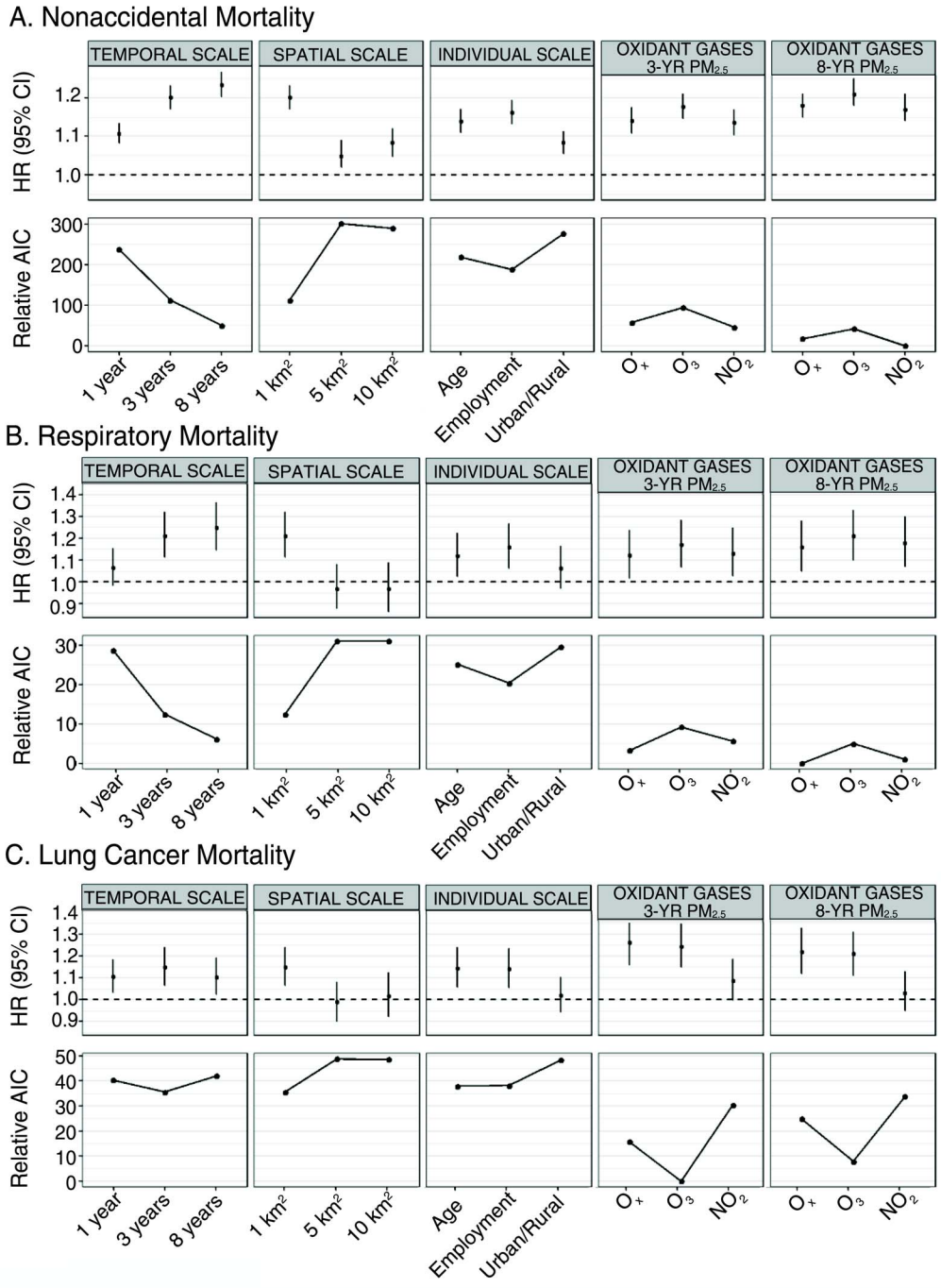


Figure 14. HRs (95% CIs) for $PM_{2.5}$ and (A) nonaccidental, (B) respiratory, and (C) lung cancer mortality in the 2001 CanCHEC cohort–exposure sensitivity analysis. The individual scale facet reflects different buffer sizes (1 km^2 vs. 10 km^2) by age, employment status, and urban or rural status. Oxidant gas facets reflect $PM_{2.5}$ models adjusted for oxidant gases. Relative AIC values closest to zero indicate the best-fitting models. HRs reflect a 3-year moving average and 1-km^2 spatial scale if not otherwise indicated.

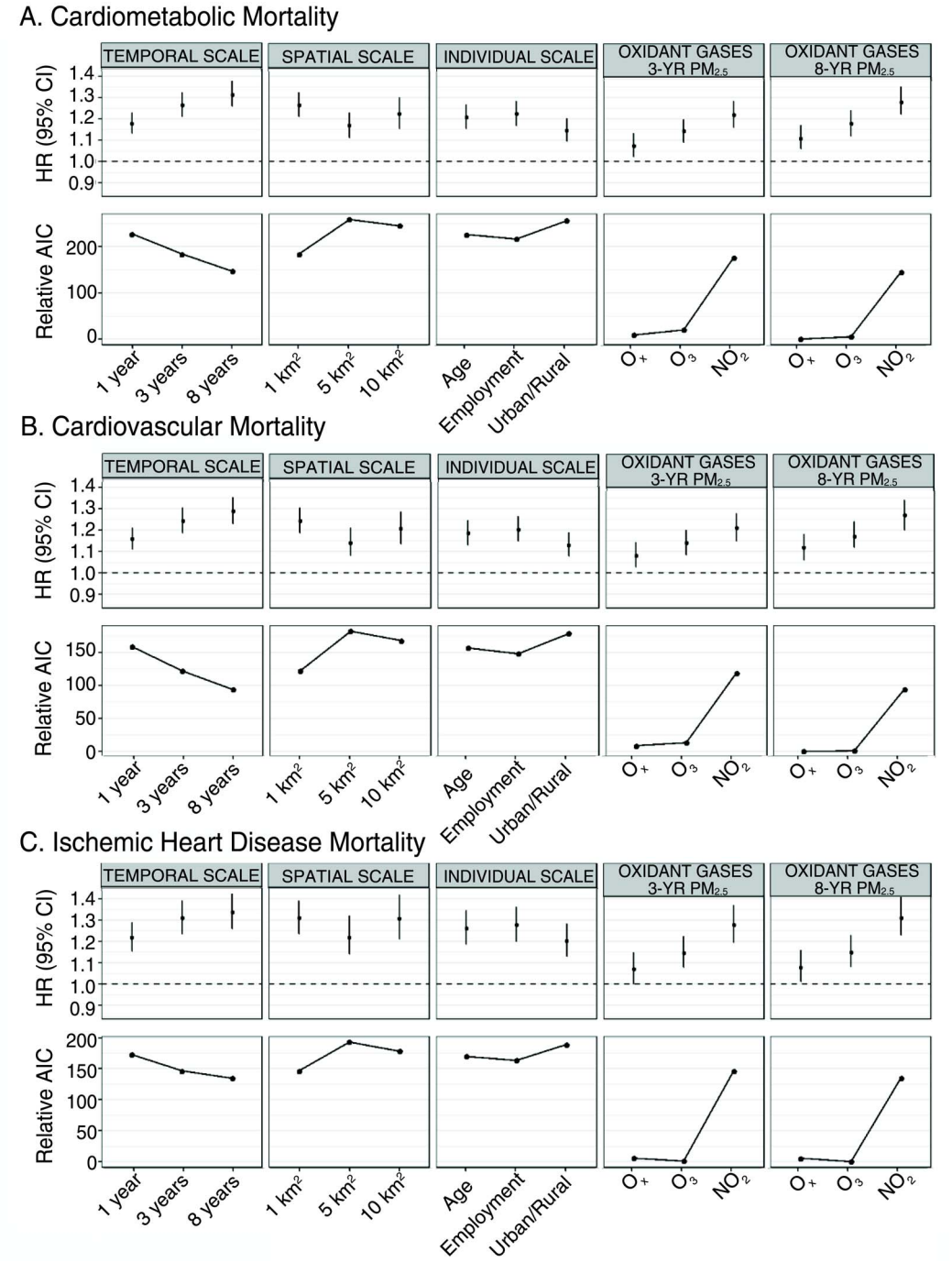


Figure 15. HRs (95% CIs) for $PM_{2.5}$ and (A) cardiometabolic, (B) cardiovascular, and (C) ischemic heart disease in the 2001 CanCHEC cohort–exposure sensitivity analysis. The individual scale facet reflects different buffer sizes (1 km^2 vs 10 km^2) by age, employment status, and urban or rural status. Oxidant gas facets reflect $PM_{2.5}$ models adjusted for oxidant gases. Relative AIC values closest to zero indicate the best fitting models. HRs reflect a 3-year moving average and 1-km^2 spatial scale if not otherwise indicated.

Table 15. Adjustment Bias (%) of Indirect Adjustment of Missing Risk Factors on $PM_{2.5}$ HRs for Different Causes of Death in the 2001 CanCHEC Cohort with Comparison to Equivalent Models Using the mCCHS Cohort

	CanCHEC Model[a]	mCCHS Model[b]
Unadjusted	1.201 (1.171–1.231)	1.163 (1.002–1.348)
Adjusted	1.161 (1.126–1.197)	1.136 (0.979–1.318)
Weighted adjustment	1.178 (1.142–1.214)	—
Adjustment bias (%)[c]	−3.5	−2.4
Weighted adjustment bias (%)[d]	−2.0	—

[a] CanCHEC model stratified by 5-year age-sex groups, adjusted by marital status, visible minority, indigenous identity, employment, income quintile, education, CAN-Marg index, community size, airshed, and indirectly adjusted for smoking, alcohol use, exercise, diet. Excludes all immigrants.

[b] mCCHS: equivalent model using CCHS-mortality linked cohort with no indirect adjustment.

[c] Adjustment bias% calculated using: $([HR_{adjust} - HR_{unadjust}] / HR_{adjust}) \times 100$.

[d] Weighted: indirect adjustment used sample weight (W-matrix).

warranted. This analysis suggested a possible downward bias adjustment in CanCHEC (2001 cohort) of 2%–3.5% where the adjustment bias percentage is calculated as $([HR_{full} - HR_{adj}] / HR_{full}) \times 100$.

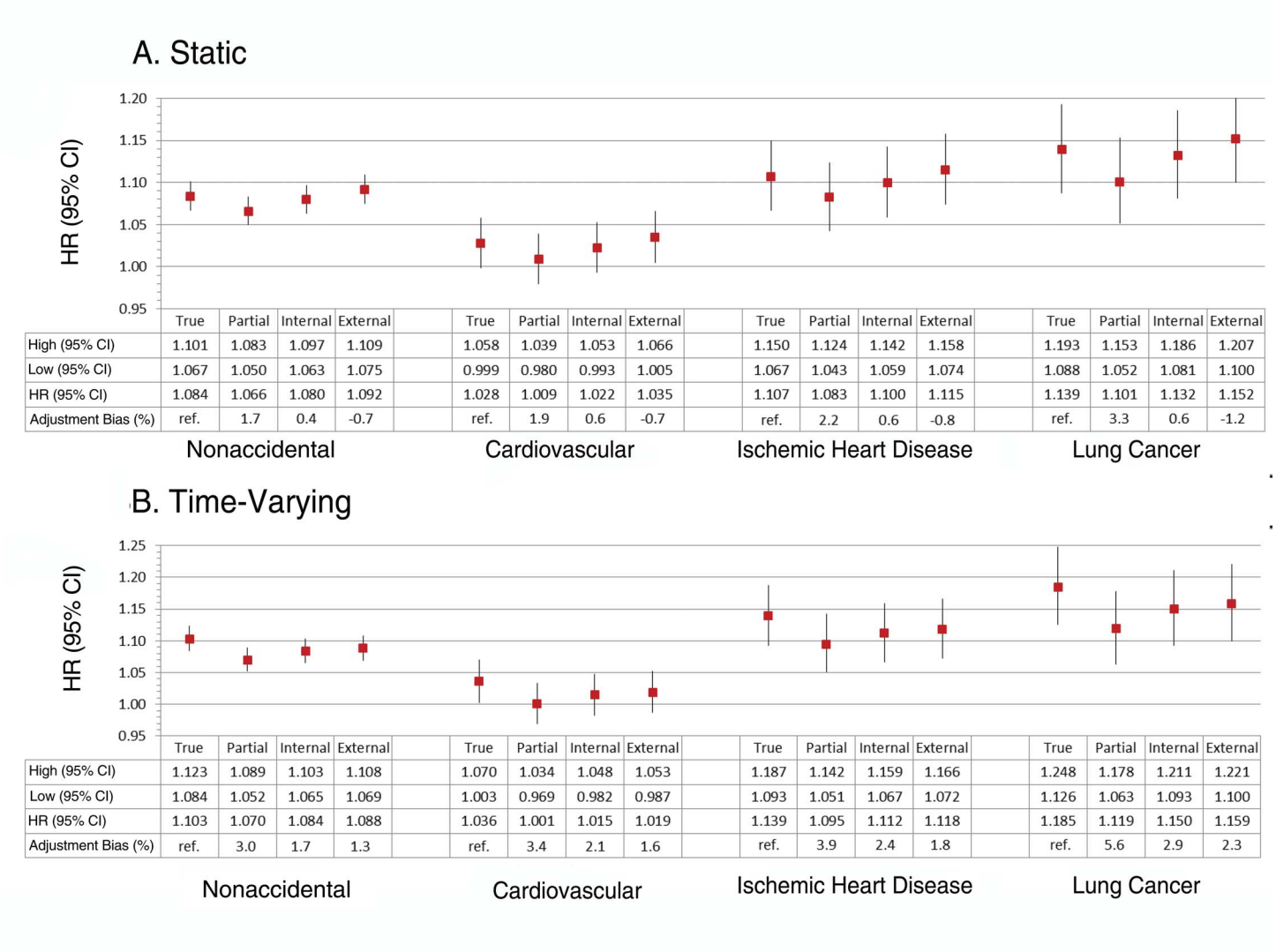
Figure 17 shows the adjustment correction of indirectly adjusted models missing four common confounding risk factors (smoking, diet, exercise, and alcohol use). These models are compared with equivalent models using the mCCHS cohort, which is directly adjusted by the same risk factors. With the exception of lung cancer, indirect adjustment for the missing risk factors in the individual covariate models increases the HRs consistent with the mCCHS. The individual + ecological covariate models include CAN-Marg, CMA-size, and airshed. These show the opposite adjustment direction, lowering the HRs after (indirect) adjustment for the missing risk factors. This adjustment direction and magnitude is comparable with observed values from the mCCHS. With the exception of ischemic heart disease, the weighted indirect adjustment performed slightly better for all mortality outcomes compared with the unweighted version using the mCCHS adjustment correction as the guidepost. Indirect adjustment for lung cancer was found to be inconsistent.

Analyses including indirect adjustment and sensitivity to indirect adjustment will be included in the final report. In this report we also assess the impact of behavioral risk factors through the comparison of HRs between models with the same covariates in the CCHS and CanCHEC cohorts and sequential inclusion of behavioral risk factors in the CCHS cohort.

Subanalysis: Immigrant Effect Analysis

We examined the mortality impacts of exposure to $PM_{2.5}$ on the immigrant population in the 2001 CanCHEC cohort (Erickson et al. In press.). Immigrants on average had 20% higher exposure to ambient $PM_{2.5}$ compared with nonimmigrants (9.3 $\mu g/m^3$ vs. 7.5 $\mu g/m^3$). Mean $PM_{2.5}$ exposure increased slightly with shorter duration in Canada. Clear differences in cohort characteristics were observed between nonimmigrants, established immigrants (pre-1971) and more recent immigrants (1971–2000), and even further distinction was observed among recent immigrants (post-1980). Recent immigrants were generally younger, and included a greater proportion of women, visible minorities, married individuals and those with higher education, but were also more likely to have lower incomes and to be unemployed. As most immigrants live in the largest metropolitan areas, all immigrant groups were more likely to live in the Western (i.e., Vancouver) or East Central (i.e., Toronto, Montreal) airsheds. Recent immigrants were also more likely to live in neighborhoods with higher ethnic population density and with a younger, working class demographic (i.e., low neighborhood dependence).

Figure 18 shows the relationship (HRs and 95% CIs) between $PM_{2.5}$ and nonaccidental and cause-specific mortality among the immigrant and nonimmigrant populations. These results show that the risk for nonaccidental, cardiovascular, cardiometabolic, ischemic heart disease, and



	Nonaccidental				Cardiovascular				Ischemic Heart Disease				Lung Cancer			
	True	Partial	Internal	External	True	Partial	Internal	External	True	Partial	Internal	External	True	Partial	Internal	External
High (95% CI)	1.101	1.083	1.097	1.109	1.058	1.039	1.053	1.066	1.150	1.124	1.142	1.158	1.193	1.153	1.186	1.207
Low (95% CI)	1.067	1.050	1.063	1.075	0.999	0.980	0.993	1.005	1.067	1.043	1.059	1.074	1.088	1.052	1.081	1.100
HR (95% CI)	1.084	1.066	1.080	1.092	1.028	1.009	1.022	1.035	1.107	1.083	1.100	1.115	1.139	1.101	1.132	1.152
Adjustment Bias (%)	ref.	1.7	0.4	-0.7	ref.	1.9	0.6	-0.7	ref.	2.2	0.6	-0.8	ref.	3.3	0.6	-1.2

	Nonaccidental				Cardiovascular				Ischemic Heart Disease				Lung Cancer			
	True	Partial	Internal	External	True	Partial	Internal	External	True	Partial	Internal	External	True	Partial	Internal	External
High (95% CI)	1.123	1.089	1.103	1.108	1.070	1.034	1.048	1.053	1.187	1.142	1.159	1.166	1.248	1.178	1.211	1.221
Low (95% CI)	1.084	1.052	1.065	1.069	1.003	0.969	0.982	0.987	1.093	1.051	1.067	1.072	1.126	1.063	1.093	1.100
HR (95% CI)	1.103	1.070	1.084	1.088	1.036	1.001	1.015	1.019	1.139	1.095	1.112	1.118	1.185	1.119	1.150	1.159
Adjustment Bias (%)	ref.	3.0	1.7	1.3	ref.	3.4	2.1	1.6	ref.	3.9	2.4	1.8	ref.	5.6	2.9	2.3

Figure 16. Internal and external validation model results of $PM_{2.5}$-mortality HRs in the 2001 CanCHEC cohort: (**A**) Static and (**B**) Time-varying. The time-varying internal validation HRs (95% CI) used the static $PM_{2.5}$ X-matrix with time-varying coefficients. True model: adjusted by marital status, visible minority, indigenous identity, employment, education, and income. Partial model: adjusted by marital status, visible minority, indigenous identity, and employment. The internal and external validation models are the same as the partial model but indirectly adjusted for education and income using the CanCHEC and CCHS, respectively. Adjustment bias % = ($[HR_{true} - HR_{adj}] / HR_{true}$) × 100. All models are stratified by 5-year age–sex groups; HRs are per 10-μg/m^3 increase in $PM_{2.5}$. (Reprinted from Erickson et al. 2019 with permission from Elsevier.)

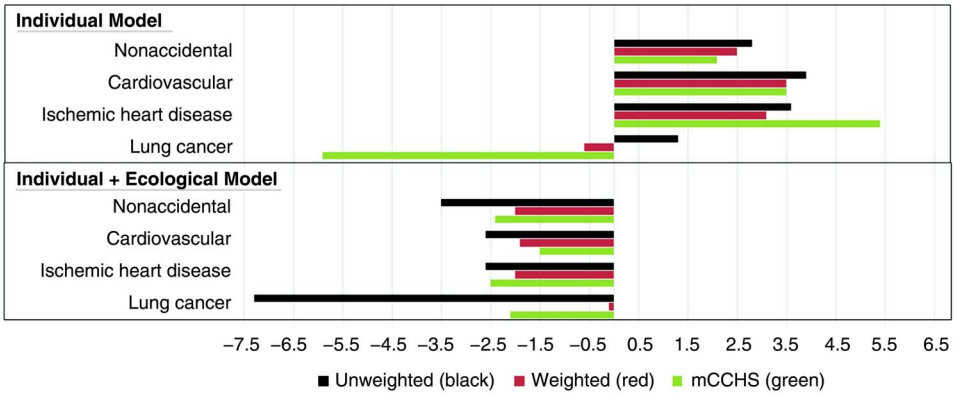
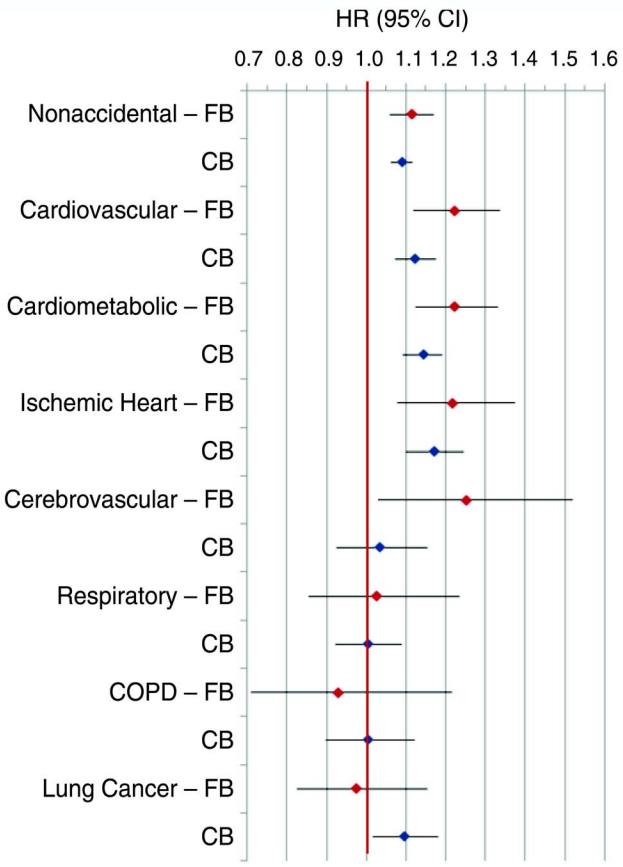


Figure 17. Adjustment correction (%) of indirect adjustment for missing behavioral risk factors on $PM_{2.5}$-mortality HRs in the 2001 CanCHEC. Individual model: stratified by 5-year age–sex groups, adjusted by marital status, visible minority, indigenous identity, employment, income quintile, and education — *indirectly* adjusted by smoking, alcohol use, exercise, and diet. Individual + ecological model: includes CAN-Marg index, community size, airshed. mCCHS: equivalent models using the CCHS-mortality linked cohort — *directly* adjusted by smoking, alcohol use, exercise, diet. Weighted vs. unweighted models used sample weights (W-matrix) in the indirect adjustment formula. Adjustment correction % = $([HR_{adjust} - HR_{unadjust}] / HR_{adjust}) \times 100$. (Reprinted from Erickson et al. 2019 with permission from Elsevier.)



	HR	Low (95% CI)	High (95% CI)
Nonaccidental – FB	1.11	1.06	1.17
CB	1.09	1.06	1.12
Cardiovascular – FB	1.22	1.12	1.34
CB	1.12	1.07	1.18
Cardiometabolic – FB	1.22	1.13	1.33
CB	1.14	1.09	1.19
Ischemic Heart – FB	1.22	1.08	1.38
CB	1.17	1.10	1.25
Cerebrovascular – FB	1.25	1.03	1.52
CB	1.03	0.93	1.15
Respiratory – FB	1.03	0.86	1.23
CB	1.00	0.92	1.09
COPD – FB	0.93	0.71	1.22
CB	1.00	0.90	1.12
Lung Cancer – FB	0.98	0.83	1.15
CB	1.10	1.02	1.18

Figure 18. Adjusted HR (95% CI) of $PM_{2.5}$ for cause-specific mortality, per 10-µg/m^3 $PM_{2.5}$ increase, among all foreign-born (FB) immigrants and Canadian-born (CB) nonimmigrants in the 2001 CanCHEC. HRs are stratified by sex and by 5-year age groups and adjusted for: visible minority, indigenous identity (CB models only), marital status, education, income quintile, employment status, occupational class, community size, urban form, airshed, and for neighborhood instability, deprivation, dependency, and ethnic concentration. COPD = chronic obstructive pulmonary disease. (From Erickson et al. in press, with permission of *Health Reports*.)

cerebrovascular causes of mortality with increased $PM_{2.5}$ exposure tended to be higher for immigrants compared with nonimmigrants, but tests for differences between the two groups were not significant using the Cochran Q test. The models stratified by number of years since immigration are shown in Figure 19. Recent immigrants tended to exhibit similar or greater sensitivity to $PM_{2.5}$ exposure compared with established immigrants and nonimmigrants in fully adjusted models, although the ability to interpret observed trends is challenged by wide CIs. The impact of place of

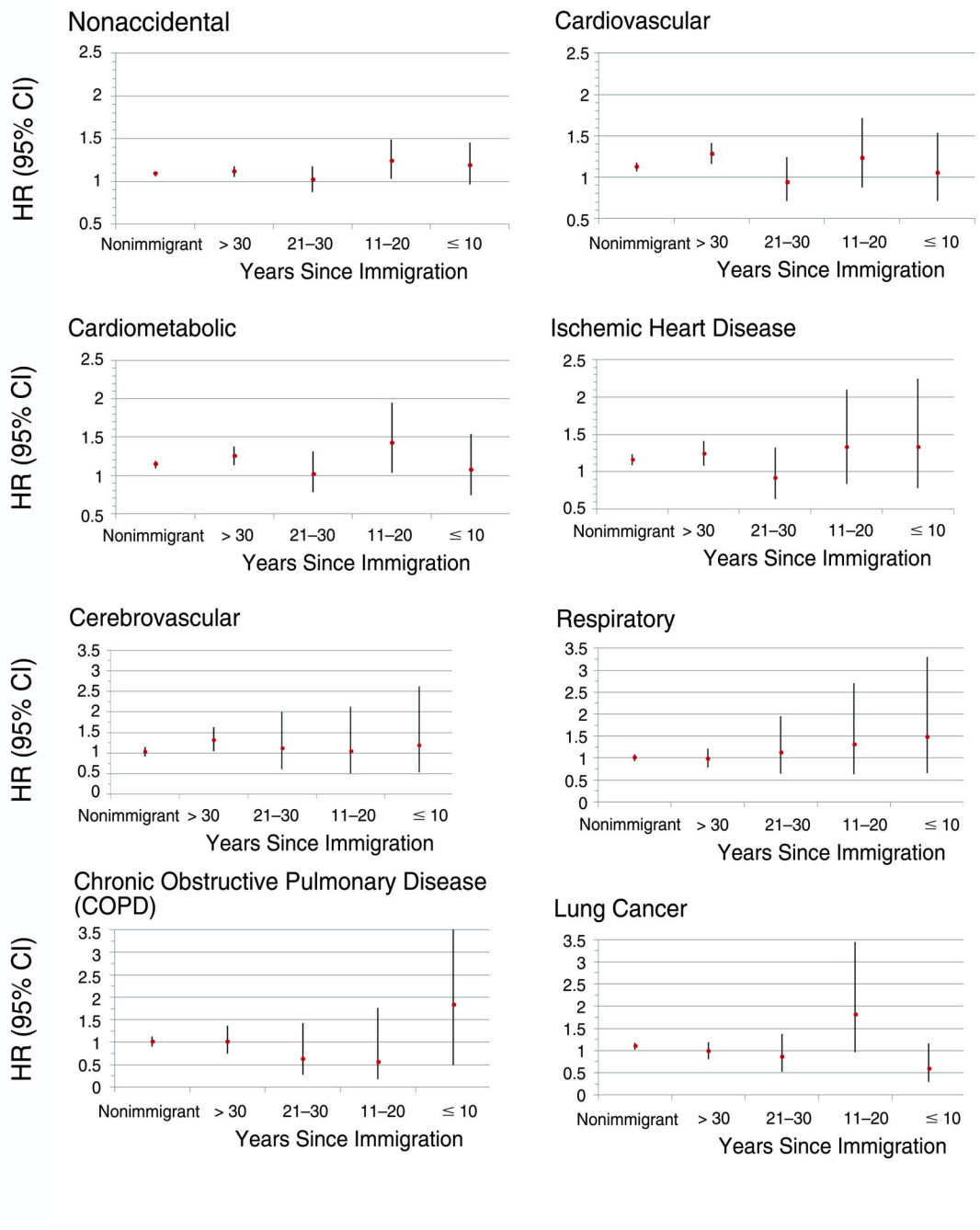


Figure 19. HR (95% CI) of $PM_{2.5}$ for cause-specific mortality, per 10-μg/m^3 $PM_{2.5}$ increase, by immigrant status in the 2001 CanCHEC. HRs are adjusted for visible minority, indigenous identity (CB models only), marital status, education, income quintile, employment status, occupational class, community size, urban form, airshed, and for neighborhood instability, deprivation, dependency, and ethnic concentration. (From Erickson et al. in press, with permission of *Health Reports*.)

birth, age at immigration, and neighborhood ethnic concentration, while themselves important mortality risk factors, on $PM_{2.5}$-related mortality was negligible (results not shown).

Subanalysis: Contributing Causes of Death

Co-mention of type 2 diabetes on death certificates of 2001 CanCHEC participants increased the risk for cardiovascular disease mortality with exposure to $PM_{2.5}$ (HR = 1.51, 95% CI: 1.39–1.65 per 10 μg/m^3) as compared with all cardiovascular disease deaths (HR = 1.25, 1.21–1.29) or cardiovascular disease deaths without co-mention of type 2 diabetes (HR = 1.20, 1.16–1.25). CCHS subjects with type 2 diabetes who used insulin or medication (included as proxies for diabetes severity) had a higher risk for cardiovascular disease deaths from exposure to $PM_{2.5}$ (HR = 1.51, 1.08–2.12) compared with the risk for cardiovascular disease death for all respondents (HR = 1.31, 1.16–1.47). Details are provided in the study by Pinault and colleagues (2018).

DISCUSSION

The pooled CanCHEC analysis represents the largest population-based air pollution cohort analysis conducted to date, with 8.5 million adults and 150 million person-years of follow-up and nearly 1.5 million deaths included. An HR of 1.053 (95% CI: 1.041–1.065) per 10 μg/m^3 change in $PM_{2.5}$ was observed after pooling the three cohort-specific HRs. The HRs varied among cohorts, with similar HRs observed for the 1991 and 1996 cohorts (HR = 1.041) and a larger observed HR for the 2001 cohort (HR = 1.084). It should be noted that the relationship between $PM_{2.5}$ exposure and mortality is not fully characterized by HR estimates based on a log-linear model. To characterize this relationship, we relied on two methods. The first was to fit an RCS with a very large number of knots (15), enabling us to visually inspect detailed patterns in the HR estimates over the range of exposures. We then summarized the RCS predictions in a manner that we suggest is useful for impact and benefits assessment; we fit the SCHIF to the RCS predictions for each cohort separately. The RCS and SCHIFs revealed a supralinear association in each cohort. The RCS predictions appeared to display less curvature with the more recent start dates of the cohorts.

Variation among the cohorts in the sensitivity of covariate model specification was observed. For both the 1991 and 1996 cohorts, larger HR estimates were yielded by the full model compared with the DAG model. The opposite pattern was observed in the 2001 cohort. As the change in exposure among the covariate categories was similar in all three cohorts, it is not clear why such patterns occurred (Table 5), although generally declining concentrations over time may explain the decreasing differences in exposure among the categories with more recent cohort start dates. There is, however, one major difference between the 2001 cohort and the 1991 and 1996 cohorts. As we examined a three-year moving average, the $PM_{2.5}$ exposure window lagged by one year in all analyses; for the 2001 cohort, the initial exposure window assigned to the 2001 follow-up year was a 1998–2000 average; thus, there were no backcasted exposures in the 2001 CanCHEC analysis. Also, the 1991 cohort used more backcasted exposures compared with the 1996 cohort.

We have chosen to fit the RCS with a very large number of knots in order to characterize a variety of shapes associating $PM_{2.5}$ exposure with mortality. We have not chosen to build RCS models based on both the number and location of knots, since this could potentially take numerous computer runs, and thus would not be any more efficient than the Nasari and colleagues (2016) SCHIF fitting procedure. We will, however, consider in the final report a more judicious selection of knots by selecting several knots for low concentrations, say below the 25th percentile, possibly a single knot at the 50th percentile, and then several more knots above the 75th percentile. In this manner we will focus effort on modeling the shape of the curve at both the low and high concentration ends, with fewer knots located in the concentration range connecting the shapes between these exposure extremes. We suggest that the uncertainty in the RCS predictions could decrease with a smaller number of well-placed knots yielding similar predictive power.

This current work supports the observations of a supralinear concentration–response similar to that reported in Crouse and colleagues (2012 and 2015) for the 1991 cohort, and Pinault and colleagues (2017) for the 2001 cohort. The observation that the $PM_{2.5}$ HR can be partially explained by NO_2 and fully explained by O_3 also supports previously reported results (Crouse et al 2015). We have previously postulated that $PM_{2.5}$ mass toxicity is enhanced in the presence of the redox potential (O_x) of these two gases (Weichenthal et al. 2017). In the final report, we plan to examine the shape of the association with $PM_{2.5}$ and mortality in locations with varying levels of O_x to further explore this relationship.

The mCCHS (Pinault et al. 2016b) was updated with a new linkage of survey respondents to death records, inclusion of additional survey cycles, extension of the annual residential history and mortality follow-up period, a finer scale of air pollution exposure, time-varying ecological

covariates, and the inclusion of immigrants. We found that exposure to $PM_{2.5}$ was associated with an 11% increase in nonaccidental mortality per 10-μg/m^3 after extensive adjustment for socioeconomic, behavioral, and ecological covariates. The inclusion of behavioral covariates in a model adjusting for socioeconomic covariates led to a 4% increase in the HR, whereas their addition to a model including socioeconomic and ecological covariates lowered the $PM_{2.5}$ HR by 2%. These adjustment corrections of $PM_{2.5}$ HRs from the inclusion of behavioral covariates are similar in magnitude and direction to those estimated using the indirect adjustment methodology on a subset of the mCCHS-based longitudinal mortality cohort (Erickson et al. 2019). This study, through its inclusion of multiple covariates and an explicit a priori analysis approach for model building, therefore provides the most extensive evidence to date that, in the Canadian context, missing data on behavioral risk factors for mortality have a minimal confounding bias on the $PM_{2.5}$–mortality association.

The HR for the full CCHS cohort (1.11, 95% CI: 1.04–1.18) was similar to that of a cohort in the United States (1.13, 1.05–1.22) that included adjustment for individual-level socioeconomic and behavioral covariates (Hart et al. 2015). Similarly, Burnett and colleagues (2018) reported a pooled HR of 1.09 (1.05–1.12) for a 10-μg/m^3 change in long-term exposure to $PM_{2.5}$ and nonaccidental mortality in 36 cohorts drawn from around the globe that included behavioral risk factors. In contrast, the pooled CanCHEC analysis produced $PM_{2.5}$–mortality HRs that were 6% lower (1.05, 1.04–1.07). However, the 2001 HR of 1.08 (1.06–1.11) was more similar to the global results and to the CCHS. This may be due to both the 2001 CanCHEC and CCHS using the same exposure model (1998–2015) and follow-up time (2001–2016); it is supported by the differences in effect estimates for the 2001 versus 1991 and 1996 CanCHEC cohorts. The CCHS sampling design was also different than that for CanCHEC. In particular, CCHS subjects were oversampled by health region compared with the region's population, in order to obtain interpretable information at the health region level, whereas CanCHEC was sampled by population. Accordingly, a higher proportion of CanCHEC subjects were sampled in large cities compared with that for CCHS, where air pollution is typically higher, and residents are healthier.

The CCHS cohort and the analysis were limited by the data available. Postal code history was derived from tax and administrative data. Historical postal codes reflect the mailing addresses as reported on tax returns, which are not necessarily the same as residences; in 92.9% of cases the postal code reflects the person's residence at time of survey (Bérard-Chagnon 2017). Actual exposure may not be reflected by outdoor $PM_{2.5}$ ambient levels at a person's residence. In our sensitivity analysis performed with the 2001 CanCHEC, we found that finer-scale resolution (1-km^2) estimates of $PM_{2.5}$ resulted in higher HRs and lower AIC values in the $PM_{2.5}$–mortality model for nonaccidental death compared with those using a 10-km^2 or 5-km^2 grid. This indicates that exposure estimates more specific to a person's residence are appropriate (Crouse et al. 2019). While the NO_2 exposure estimates were at a high spatial resolution (100 m^2), those for O_3 were at a relatively more coarse resolution and may have resulted in exposure misclassification. Gaps in postal code history were imputed under the assumption that the participant did not leave the country or community during the study period. In assigning ecological covariates by postal code, misclassification may occur from taking the mode or mean when estimating a single value to represent multiple points of latitude and longitude for a single postal code. Similar limitations were also present in the CanCHEC cohorts. In contrast to the CanCHEC cohorts, the CCHS cohort does not completely represent the full Canadian population. Also, subjects were removed in creating this cohort if they did not consent to data linkage or if they could not be linked to the Social Data Linkage Environment. Although behavioral covariates were included in this cohort, these were self-reported, and there were missing responses in some cases. We used dummy variables to code missing information instead of excluding nonrespondents outright to avoid introducing bias into the analysis. Lastly, the cohort is limited by follow-up, with some persons having as few as four years of follow-up (with a maximum follow-up of 15 years), whereas follow-up in CanCHEC was at least 15 years and as long as 25 years.

In the CCHS analyses, the risk of nonaccidental mortality from exposure to $PM_{2.5}$ was 4% higher in males compared with females; a similar difference was observed in CanCHEC (HR = 1.06 for males and HR = 1.03 for females). In both the CCHS and CanCHEC cohorts HRs were larger for younger ages.

Of direct relevance to Canada, where immigrants comprise approximately 20% of the population, we incorporated stratified analyses by immigrants (>10 years since immigration), compared with those participants born in Canada. Immigrants have greater overall survival, and their sensitivity to the impact of $PM_{2.5}$ on survival was somewhat lower than those participants who were born in Canada in both the 1991 and 1996 CanCHEC analyses and much lower in the CCHS (nonimmigrant HR = 1.14 and immigrant HR = 0.98). However, in the 2001 CanCHEC, the nonimmigrant HR = 1.09 was similar to that of immigrants

(HR = 1.11). This may be due to the further adjustment for behavioral risk factors in the CCHS and the oversampling of rural areas with fewer immigrants. The larger effects for nonimmigrants in the CCHS and in the 1991 and 1996 CanCHEC cohorts may result from the healthy immigrant effect (Beiser 2005, Ng 2011, Omariba et al. 2014) and may also be influenced by the preferential settlement of immigrants into the largest cities, which have higher $PM_{2.5}$ exposure. Reasons for the different patterns in the 2001 CanCHEC are unclear, but they may result from changes in immigration patterns or their patterns of settlement within Canada.

Findings from the exposure assessment sensitivity subanalyses suggest that there are stronger associations between $PM_{2.5}$ and mortality with longer-term moving averages and smaller spatial scales (1 km^2 vs. 10 km^2). To our knowledge, there were no previous studies specifically examining the sensitivity of $PM_{2.5}$–mortality associations to the spatial scale of exposure assessment. In their evaluation of $PM_{2.5}$ and birthweight, Ebisu and colleagues (2014) examined different spatial buffers (5–30 km^2) and noted that the magnitude of the $PM_{2.5}$ and birthweight association was not sensitive to the spatial scale of exposure assessment, but that there were variations in relationships for $PM_{2.5}$ constituents across different spatial scales. In at least one other study, the authors evaluated the impact of different temporal scales of exposure assessment on $PM_{2.5}$–mortality associations. Specifically, Puett and colleagues (2018) observed stronger relationships between $PM_{2.5}$ and all-cause mortality with moving averages up to 48 months in the Nurses' Health Study, consistent with our findings of larger effect estimates for longer duration exposure estimates.

No other studies to our knowledge have explored the use of different buffer sizes based on factors influencing individual-level activity spaces. Our results suggest that this approach may not be warranted without further refinement in approaches to predict individual-level mobility patterns. Model fit in our analyses did not improve using different buffer sizes according to age, employment status, or rural/urban residence, suggesting that at these spatial scales, exposure measurement error introduced through varying individual level mobility patterns was not reduced with this approach. In order to accurately predict the individual-level activity space dimensions, more refined information at the individual level may be needed for the purposes of assigning spatial buffers. There are likely substantial between-subject variations in mobility within categories of age, employment status, and urban/rural status. These adjustments for mobility may be more relevant for pollutants with high spatial variability (e.g., NO_2, ultrafine particles) compared with that of $PM_{2.5}$ mass concentrations. Our analysis does suggest that smaller buffer sizes and the fine-scale resolution of the 1-km^2 $PM_{2.5}$ exposure estimates result in larger HRs and improved model fit. While we were not able to directly assess the uncertainty of these residence-based exposure estimates, this analysis does suggest that exposure measurement error is likely to have reduced the magnitude of the reported mortality HRs. As indicated above, the larger estimates of effect from the 2001 CanCHEC, compared with the 1991 and 1996 cohorts, may suggest higher degrees of exposure measurement error in the two earlier cohorts where backcasted exposure estimates were included.

In both the CCHS and CanCHEC analyses, multiple pollutant linear models indicated that the relationship between nonaccidental mortality and $PM_{2.5}$ exposure was attenuated when we included O_3 or O_x in the models. In the CCHS analysis, $PM_{2.5}$ estimates were also attenuated by the inclusion of NO_2 in models, whereas in CanCHEC NO_2 did not affect $PM_{2.5}$ HRs. These results are generally consistent with other Canadian studies, which found that $PM_{2.5}$ HRs were reduced after the addition of NO_2 and O_3 (from 1.04 to 1.01) (Crouse et al. 2015) and O_x (from 1.07 to 1.04) (Weichenthal et al. 2017). In a subanalysis restricted to the 2001 CanCHEC, we found that adjustment for oxidant gases attenuated associations between $PM_{2.5}$ and nonaccidental, respiratory, and cardiovascular disease mortality, and that this attenuation was particularly strong for cardiometabolic and ischemic heart disease mortality. This may be explained by a direct relationship between spatial variation in oxidant gases and mortality (Crouse et al. 2015, Weichenthal et al. 2017), but evidence to date is limited (Atkinson et al. 2016). Alternatively, spatial variations in oxidant gases may act as surrogate measures of air pollution sources and particle components that are more or less relevant to health. Although our main goal was to assess the sensitivity of the $PM_{2.5}$–mortality relationship to inclusion of gaseous copollutants (vs. directly analyzing the effects of gaseous copollutants on mortality), the exposure models for O_3, and O_x have more coarse resolution (10- or 21-km^2) compared with the $PM_{2.5}$ exposure estimates. This may have biased the estimates of O_3 and O_x toward the null and consequently reduced their impact on the $PM_{2.5}$–mortality relationship even more so than what we observed. Alternatively, it is possible that the more coarse spatial resolution of the O_3 and O_x exposure estimates failed to capture the complexity of the gaseous pollutant interactions with $PM_{2.5}$. However, our results do suggest that excluding oxidant gases from the analyses may overestimate the magnitude of associations between

long-term exposures to outdoor $PM_{2.5}$ and cardiovascular disease mortality in Canada, and it may underestimate the strength of associations between $PM_{2.5}$ and lung cancer mortality.

We demonstrated the application and evaluation of the indirect adjustment method using secondary ancillary data to adjust for missing covariates in a primary data set. Applying the method developed by Shin and colleagues (2014) we showed that the adjustment bias for nonlinear survival models (internal validation) was under 1% with static $PM_{2.5}$ exposure models and less than 3% for time-varying models. External validation assessing the CCHS as the ancillary matching data set performed well, indicating small downward (over) adjustment bias for time-varying $PM_{2.5}$ models. Our findings are comparable to those using a similar longitudinal cohort (1991 CanCHEC) from Shin and colleagues (2014), where indirect adjustment for smoking and BMI led to a 3% increase in the association between $PM_{2.5}$ and ischemic heart disease (Shin et al. 2014), compared with no adjustment.

The adjustment correction from indirectly adjusted models using the CCHS as ancillary data in an analysis of missing behavioral risk factors from the CanCHEC (smoking, alcohol use, fruit and vegetable intake, and exercise) was comparable to equivalent models directly adjusting for the same risk factors using the mCCHS. Overall, the models with sample weights applied to correct for population sampling differences performed slightly better than unweighted models. The amount of subsequent adjustment required by the indirect adjustment of individual risk factors was reduced by including ecological socioeconomic covariates into the base models. This indicates that the adjustment was improved by indirect adjustment through reducing bias from models missing important confounding. However, in order to assess the amount and direction of adjustment, internal and external validation tests should be run prior to running the actual indirect adjustment. The inclusion of sampling weights could help improve adjustments if the proportion of respondents differ geographically between urban and rural areas in the primary cohort compared with the proportions in the ancillary survey data.

The indirect adjustment method could be universally generalizable to other cohorts; however, the availability of suitably representative ancillary data determines the effectiveness of this approach. Following the evaluation methodology described here, researchers can assess if available ancillary matching data are appropriate to use for indirect adjustment. We suggest running external validation tests in addition to descriptive and visual comparisons to quantify the representativeness of the ancillary data. This could be done by determining the magnitude and direction of adjustment bias when removing and indirectly adjusting for important variables available in both primary and ancillary data sets. Characteristics of an ideal ancillary matching data set include being drawn from the same target population as the main cohort, having similar geographic coverage, common matching variables such as age, sex, income, and education, and similar proportions of exposure-to-characteristics. Differing population sampling schemes in the primary cohort and ancillary data, may be corrected by applying custom sample weights. For instance, we categorized education in this analysis into a dichotomous variable since the proportional comparability among the higher education groups were less favorable between the CanCHEC and CCHS. How and in what regards the primary and ancillary data are different before the results produced by indirect adjustment are no longer acceptable can be examined using simulation tests and would be a valuable contribution to the literature.

In all of the CanCHEC cohorts and in the CCHS cohort a supralinear association was found, with a steep relationship at the low to median $PM_{2.5}$ range that leveled off slightly after approximately 10 $\mu g/m^3$. The SCHIF HR predictions indicated a positive and significant association between $PM_{2.5}$ and nonaccidental mortality for all concentrations. In the CCHS there was, however, substantial uncertainty in the shape of the concentration–response relationship precluding any clear conclusions regarding shape in this cohort. In most previous major cohort studies on $PM_{2.5}$, the shape of the concentration–mortality association were not examined at the low levels observed in our cohorts. For example, in the pooled CanCHEC analysis the 25th percentile was 5.1 $\mu g/m^3$, and the median was 6.9 $\mu g/m^3$. In contrast, the exposure distribution in the Medicare cohort was at a minimum of 6.2 $\mu g/m^3$ (Di et al. 2017), the National Health Interview Survey Cohort (NHIS) had a minimum of 7.6 $\mu g/m^3$ (Pope et al. 2018), and the American Cancer Society Cancer Prevention II Cohort (ACS) had a minimum of 6.7 $\mu g/m^3$ (1st percentile; Turner et al. 2016). In this study, little change in risk below 5 $\mu g/m^3$ was observed. To allow for more direct comparisons with these cohorts, the HR for a 5- to 15-$\mu g/m^3$ change in concentration from the SCHIF was estimated as 1.063 (95% CI: 1.052–1.073). This estimate was similar to the Medicare (Di et al. 2017) (HR = 1.073, 95% CI: 1.071–1.075), NHIS (HR = 1.056, 95% CI: 1.005–1.110) (Pope et al. 2018), and the ACS (HR = 1.07; 95% CI: 1.06–1.09) (Turner et al. 2016) cohorts.

Based on the CanCHEC cohorts, but also supported by the CCHS analysis, we report evidence of associations between $PM_{2.5}$ concentrations and nonaccidental

mortality, with no evidence of a threshold or sublinear association over very low concentrations. This suggests potential health benefits of further reductions in concentrations of air pollutants in locations where higher concentrations currently exist. Future analyses will address the question of low-level exposures more directly by sequentially excluding from the analysis those participants who were ever exposed to pollutant concentrations above specified levels (e.g., 6, 8, 10 $\mu g/m^3$). We will also conduct a detailed analysis of effect modification in the CanCHEC cohorts to evaluate the shape of $PM_{2.5}$–mortality associations across strata of oxidant gases (i.e., O_3, NO_2, and O_x).

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MATERIALS AVAILABLE ON THE HEI WEBSITE

Additional Materials 1 and 2 contain supplemental material not included in the printed report. They are available on the HEI website, *www.healtheffects.org/publications.*

Additional Materials 1. Supplemental Figures

Additional Materials 2. Publications Resulting from This Research

Appendix A: Meng et al. 2019. Estimated long-term (1981–2016) concentrations of ambient fine particulate matter across North America from chemical transport modeling, satellite remote sensing, and ground-based measurements. Environ Sci Technol 53:5071–5079; doi:10.1021/acs.est.8b06875.

Appendix B: Latimer and Martin. 2019. Interpretation of measured aerosol mass scattering efficiency over North America using a chemical transport model. Atmos Chem Phys 19:2635–2653. Available: *https://doi.org/10.5194/acp-19-2635-2019.*

Appendix C: Pappin AJ, et al. 2019. Examining the shape of the association between low levels of fine particulate matter and mortality across three cycles of the Canadian Census Health and Environment Cohort. Environ Health Perspect 127; doi/10.1289/EHP5204.

Appendix D: Christidis T, et al. 2019. Low concentrations of fine particle air pollution and mortality in the Canadian Community Health Survey cohort. Environ Health; doi: 10.1186/s12940-019-0518-y.

Appendix E: Erickson AC, et al. 2019. Evaluation of a method to indirectly adjust for unmeasured covariates in the association between fine particulate matter and mortality. Environ Res 175:108–116; doi:10.1016/j.envres.2019.05.010.

Appendix F: Pinault L, et al. 2017. Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. Environ Res 159:406–415; doi:10.1016/j.envres.2017.08.037.

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Dr. Richard T. Burnett is a senior research scientist at Health Canada in Ottawa.

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Erickson AC, Pappin A, Christidis T, Brook JR, Crouse DL, Hystad P, et al. In press. Disease assimilation: The mortality impacts of fine particulate matter on immigrants to Canada. Health Reports.

Christidis T, Erickson AC, Pappin AJ, Crouse DL, Pinault LL, Weichenthal SA, et al. 2019. Low concentrations of fine particle air pollution and mortality in the Canadian Community Health Survey cohort. Environ Health; doi: 10.1186/s12940-019-0518-y.

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COMMENTARY

HEI's Low-Exposure Epidemiology Studies Review Panel

Research Report 203, *Mortality–Air Pollution Associations in Low-Exposure Environments (MAPLE): Phase 1,* M. Brauer et al.

INTRODUCTION

This Commentary was prepared by the HEI Low-Exposure Epidemiology Studies Review Panel, convened to review HEI-funded studies on the health effects of exposure to low levels of ambient air pollution. Dr. Michael Brauer's study "Mortality-air pollution associations in low exposure environments (MAPLE)" was one of three studies funded under RFA 14-3, "Assessing Health Effects of Long-term Exposure to Low Levels of Ambient Air Pollution." More information about the RFA and the other two studies is included in the Preface to this report.

This Commentary includes the scientific and regulatory background for the research, a summary of the approach and key results, the Panel's evaluation of the Phase 1 report from the investigator team led by Dr. Michael Brauer, and the Panel's conclusions and suggestions for further analyses in the final phase 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 scientific and regulatory perspective.

SCIENTIFIC AND REGULATORY BACKGROUND

The setting of ambient air quality standards — at levels considered adequate to protect public health — is a central component of programs designed to reduce air pollution and improve public health under the U.S. Clean Air Act (U.S. CAA*) and similar measures in Canada, Europe, and around the world. Although the process for setting such standards varies, they all contain several common components:

- Identifying, reviewing, and synthesizing the scientific evidence on sources, exposures, and health effects of air pollution;
- Conducting risk and policy assessments to estimate what public health effects are likely to be seen at different levels of the standard;
- Identifying and setting standards based on scenarios considered in the risk analysis;
- Air quality monitoring to identify geographical areas that do not meet the standards; and
- Implementing air quality control interventions to reduce ambient concentrations to meet the standards.

SETTING NATIONAL AMBIENT AIR QUALITY STANDARDS UNDER THE U.S. CAA

The U.S. CAA requires that in setting the National Ambient Air Quality Standards (NAAQS), the U.S. Environmental Protection Agency (U.S. EPA) Administrator review all available science and set the NAAQS for all major ("criteria") pollutants (including ozone [O_3], particulate matter [PM], and nitrogen dioxide [NO_2]) at a level "requisite to protect the public health with an adequate margin of safety." In practice, since 2008 that review has had two principal steps:

1. Synthesis and evaluation of all new scientific evidence since the previous review in what is now called an *Integrated Science Assessment.* This document reviews the broad range of exposure, dosimetry, toxicology, mechanism, clinical research, and epidemiology. It then — according to a predetermined set of criteria (U.S. EPA 2015) — draws on all lines of evidence to make a determination of whether the exposure is causal, likely to be causal, or suggestive for a series of health outcomes.
2. Assessment of the risks based on that science is then conducted in a *Risk and Policy Assessment.* This further analysis draws on the Integrated Science Assessment to identify the strongest evidence — most often from human clinical and epidemiological studies — of the lowest concentration levels at which health effects are observed, the likely implications of such

Dr. Michael Brauer's four-year study, "Identifying the shape of the association between long-term exposure to low levels of ambient air pollution and the risk of mortality: An extension of the Canadian Census Health and Environment Cohort using innovative data linkage and exposure methodology," began in January 2016. The draft Phase 1 Investigators' Report from Brauer and colleagues was received for review in June 2019. A revised Phase 1 report, received in August 2019, was accepted for publication in July 2019. During the review process, HEI's Low-Exposure Epidemiology Studies Review Panel and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Panel's Commentary.

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

levels for health across the population, and the degree to which the newest evidence suggests that there are effects observed below the then-current NAAQS for a particular pollutant.

The Risk and Policy Assessment also examines the uncertainties around estimates of health impact and the shape of the concentration–response curve, especially at levels near and below the then-current NAAQS. Although a range of possible shapes of the concentration–response curves has been considered, including whether there is a threshold level below which effects are not likely, the U.S. EPA's conclusions in these reviews thus far have not found evidence of a threshold (although studies to date have not always had the power to detect one) (U.S. EPA 2004, 2013). Also, although the standard is set, according to statute, to protect public health with an adequate margin of safety, it has been generally understood that there are likely additional health effects below the NAAQS, although the presence and magnitude of these are more uncertain.

Both of these documents are subjected to extensive public comments and reviewed by the Clean Air Scientific Advisory Committee (CASAC), which was established under the U.S. CAA. CASAC is charged with peer-reviewing the documents, which includes providing guidance to the Administrator on the strength and uncertainties in the science and advising on alternative scenarios for retaining or changing the NAAQS.

EVOLUTION OF THE NAAQS

The reviews of the criteria pollutants have been ongoing for nearly 50 years, since the passage of the Clean Air Act Amendments of 1970. As the science has evolved, each subsequent review has examined the strength of the evidence for retaining or tightening the NAAQS. Although the process has frequently resulted in a decision to retain the then-current NAAQS, the NAAQS of both O_3 and fine PM (particulate matter ≤2.5 μm in aerodynamic diameter, or $PM_{2.5}$) have seen substantial revisions, especially over the last 20 years:

O_3 Starting in 1997, the NAAQS was converted from a 1-hour maximum standard to a standard averaged over 8 hours. In 1997, the NAAQS was set at 80 ppb; subsequently in 2008 it was lowered to 75 ppb, and then in 2015 to 70 ppb. Although there was epidemiological evidence of effects at or near these levels, the changes relied heavily on a series of carefully conducted human controlled-exposure studies.

$PM_{2.5}$ In 1997, based on dosimetric and biological information suggesting that fine particles ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$) were a more appropriate indicator than particles ≤10 μm in aerodynamic diameter (PM_{10}), the U.S. EPA for the first time proposed and established a NAAQS for $PM_{2.5}$. They set the annual standard at 15 μg/m^3 in part as a result of new long-term cohort evidence of associations of $PM_{2.5}$ with adverse health effects (Dockery et al. 1993; Pope et al. 1995). That was subsequently further reviewed in 2006 (no change) and again in 2012, when the NAAQS, based on additional epidemiological evidence, was reduced to 12 μg/m^3 (U.S. EPA, Table of Historical PM NAAQS).

IMPACT OF THE NAAQS

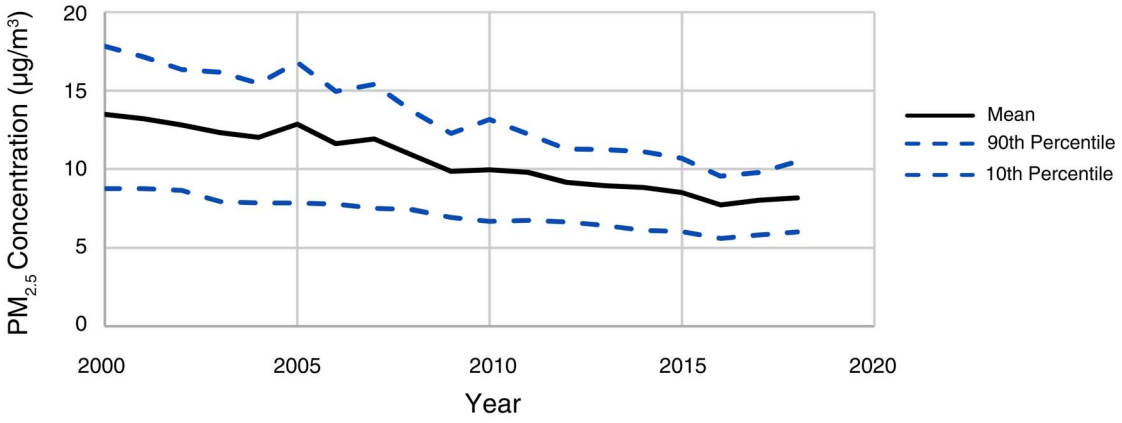
With the establishment of these standards, a host of national and regional regulatory actions began to reduce emissions from electric power plants, factories, motor vehicles, and other sources. As a result, there has been a steady and marked decline of ambient concentrations, so that much of the United States now attains the NAAQS (see, for example, the $PM_{2.5}$ data in Commentary Figure 1).

ADVENT OF RECENT STUDIES OBSERVING ASSOCIATIONS BELOW THE NAAQS

As the data on levels of $PM_{2.5}$ improved over the course of the first decade of this century, new studies began to emerge, starting in 2012 (e.g., in Canada and New Zealand), suggesting that associations of $PM_{2.5}$ and mortality could be observed down to levels well below the NAAQS of 12 μg/m^3 (Crouse et al. 2012; Hales et al. 2012). These studies found robust associations, with some evidence of even steeper slopes of effect at the lowest levels, findings which, if replicated in other populations and by other investigators, could change the basis for future determinations of the levels at which to set the NAAQS and other air quality standards.

At the same time, they posed several questions, for example:

- Would the results be robust to the application of a range of alternative analytic models and their uncertainty?
- Could other important determinants of population health, such as age, socioeconomic position, health status, and access to medical care, as well as differences in air pollution sources and time–activity patterns, modify or confound the associations seen?
- Would the results change if risk estimates corrected for the effects of important potential confounding



Commentary Figure 1. Trends in $PM_{2.5}$ concentrations from 2000 to 2018 (seasonally weighted annual average) as monitored by the U.S. EPA (data from U.S. EPA; *www.epa.gov/air-trends/particulate-matter-pm25-trends*).

variables, such as smoking, in the absence of such data at the individual level?

- What might be the effects of co-occurring pollutants on health effect associations at low ambient concentrations?

As described in the Preface in this volume, the advent of these studies and the desire to address these important questions formed the basis for the HEI Request for Applications (RFA 14-3), which sought and ultimately supported this study by Dr. Brauer and colleagues and two other studies that make up HEI's Program to Assess Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution.

STUDY SUMMARY

STUDY OBJECTIVES

The overall objective of the Mortality–Air Pollution Associations in Low-Exposure Environments (MAPLE) study is to assess the relationship, including a careful characterization of the shape of the concentration–response functions, between long-term exposure to low concentrations of $PM_{2.5}$ and nonaccidental mortality in four large population-based cohorts (total of ~9 million adults) in Canada. The study used detailed exposure estimation methods to apply novel satellite-based $PM_{2.5}$ annual exposure estimates at a fine spatial scale (1 km × 1 km) across North America from 1981 to 2016, derived by fusing remote sensing-based aerosol optical depth (AOD), the GEOS-Chem chemical transport model (GEOS-Chem), land-use information, and ground-monitoring data. Here we describe the overall approach and methods used in this study, which is reported in the accompanying Phase 1 Investigators' Report. It should be noted that further work is ongoing and will be reported in the Final Phase 2 report, which will be submitted in 2020.

To characterize the exposure estimates, MAPLE investigators proposed to do the following:

1. Develop and apply annual average satellite-based estimates of $PM_{2.5}$ across North America at a 1 km × 1 km spatial resolution.
2. Develop and evaluate $PM_{2.5}$ estimates using insight gained from comparisons of colocated measurements of $PM_{2.5}$ and AOD-based estimates with GEOS-Chem simulations.
3. Employ a combination of geophysical and statistical methods, together with land-use information, to further refine the $PM_{2.5}$ estimates.
4. Use available $PM_{2.5}$, PM_{10}, and total suspended particulate matter (TSP) monitoring data in Canada from 1981 to 1999 to scale the 1 km × 1 km 2004–2008 surface back in time annually through the 1981–1999 period, maintaining the 1 km × 1 km grid detail over the full study period.

5. Create annual estimates of $PM_{2.5}$ for 1981–2016, based on these methods.
6. Make the annual $PM_{2.5}$ estimates available to other HEI-funded studies covering Canada and the United States for incorporation into their analyses.

To examine the concentration–response relationship between $PM_{2.5}$ exposure and nonaccidental mortality, investigators planned to do the following:

1. Use four Canadian cohorts (~9 million adults) linked to mortality, vital statistics, and tax records up to December 31, 2016.
2. Examine the shape of the association between long-term exposure to ambient concentrations of $PM_{2.5}$ and nonaccidental mortality using restricted cubic splines (RCS) and shape-constrained health impact functions (SCHIF) in all four cohorts.
3. Conduct subanalyses in the 2001 Canadian Census Health and Environment Cohort (CanCHEC) to:
   - Evaluate the indirect adjustment for behavioral risk factors not included in CanCHEC, such as smoking habits and diet.
   - Evaluate the impact of adjustment for ground-level O_3, NO_2, or their combined oxidant capacity (O_x).
   - Evaluate the sensitivity of $PM_{2.5}$–mortality associations to the choice of exposure time window (1, 3, and 8 years).
   - Evaluate the sensitivity of $PM_{2.5}$–mortality associations by the spatial scale used for exposure assessment (1, 5, and 10 km^2).
4. Examine risk estimates across strata of age, sex, and immigrant status.

METHODS

Study Population

The investigators used a very large and nationally representative sample of the adult Canadian population to evaluate health effects of air pollution at low ambient concentrations. The study assessed mortality outcomes in the following 4 longitudinal cohorts, representing ~9 million people (after exclusions in accordance with predefined eligibility criteria) with 150 million person-years of follow-up and nearly 1.5 million deaths:

CanCHEC: 1991, 1996, 2001. Data were obtained for 2.5 million (1991) and 3 million (for each of 1996 and 2001) participants, selected randomly, over the age of 25 who completed the mandatory long-form census in the relevant year, which is linked to vital statistics, tax records, and cause of death from census day through December 31, 2016. CanCHEC surveys contain basic individual-level information (including education, occupational class, and income).

Canadian Community Health Survey (CCHS). Data were obtained for 540,900 randomly selected participants who completed one of the annual health surveys (2001, 2003, 2005, 2007, 2008, 2009, 2010, 2011, and 2012); the surveys were linked to vital statistics, tax records, and cause of death from date of interview through December 31, 2016. In addition to the information on individual risk factors for mortality in the CanCHEC long-form census, the CCHS includes information on smoking behavior, body mass index, exercise, alcohol consumption, and diet. In contrast to the CanCHEC census, the CCHS excludes residents living on reserves, Canadian Forces bases, and some remote areas (<3% of the target population of Canada).

Linkage

Statistics Canada linked each study respondent to their income tax records for years near the year of completion of the long-form census or health survey interview in order to obtain their unique social insurance number. This number was then used to link each respondent to Statistics Canada's Social Data Linkage Environment, a relational database consisting of temporally linked information on Canadians. This information includes annual postal codes of each respondent's mailing address, in addition to date and cause of death if it occurred during the cohort follow-up period. Respondents without a postal code history were excluded.

Covariates

The investigators considered individual- and area-level risk factors as well as geographical (contextual) covariates. CanCHEC surveys contain basic individual-level information including education, income, marital status, indigenous identity, occupational class, visible minority status, employment status, and years since immigrating to Canada. CCHS contains rich individual-level data; therefore, analyses in this cohort incorporate additional individual covariates such as fruit and vegetable consumption, leisure exercise frequency, alcohol and smoking consumption, and body mass index. The study used the following four marginalization dimensions as covariates from the Canadian Marginalization Index (CAN-Marg) to characterize respondents' inequalities in health and social well-being predictors: material deprivation, residential instability, dependency, and ethnic concentration (i.e., proportion of recent immigrants and self-reported visible minorities). The geographical areas for CAN-Marg are

defined as census tracts (neighborhoods) in cities and as census subdivisions (municipalities) outside of large urban areas. Geographical covariates include community size, urbanization, and airshed, which is a geographical area with similar air-quality characteristics or dispersion patterns as defined by the Canadian Air Quality Management System.

Ambient Concentration Assessment

$PM_{2.5}$ Model For each year from 1981 to 2016, Brauer and colleagues developed ambient concentration estimates across North America based on a refined-scale $PM_{2.5}$ model of 1 km × 1 km. The method is a sophisticated integration of remote-sensing AOD, chemical transport model (GEOS-Chem), land-use, and ground-monitoring data.

Specifically, geophysical $PM_{2.5}$ exposure estimates were derived by relating daily satellite-based aod retrievals — at a 1 km × 1 km resolution (from the moderate resolution imaging spectroradiometer [MODIS] satellite) — to surface $PM_{2.5}$ concentrations using simulations from GEOS-Chem (van Donkelaar et al. 2015). The GEOS-Chem model uses meteorological and emission inventory observations and algorithms representing chemical and physical atmospheric constituents to solve for the temporal and spatial evolution of aerosol and gaseous compounds (GEOS-Chem; *http://acmg.seas.harvard.edu/geos/index.html*). To evaluate the GEOS-Chem model's conversion of AOD to $PM_{2.5}$ in regions of low PM concentrations, investigators are collecting colocated measurements of $PM_{2.5}$, aerosol scatter, and AOD at five added measurement sites in low-level air pollution areas across Canada (expanding the Surface PARTiculate mAtter Network [SPARTAN]) (Snider et al. 2015). Refinements are ongoing as measurement collection and particle composition analyses are continually underway, which will further inform and validate the relationship between $PM_{2.5}$ and AOD from colocated ground measurement data, to be reported in the Final Phase 2 report. In the interim, existing aerosol scatter and mass data from the Interagency Monitoring of Protected Visual Environments (IMPROVE) network were used to evaluate the satellite estimates between 2000 and 2015 (IMPROVE; *http://vista.cira.colostate.edu/Improve/*).

Geographically weighted regression (GWR) was applied to estimate surface $PM_{2.5}$ measurements by fusing monthly mean measurements from $PM_{2.5}$ monitors (Canadian National Air Pollution Surveillance and United States Air Quality System Data Mart) and the geophysical $PM_{2.5}$ estimates to yield refined hybrid $PM_{2.5}$ estimates for the years 2000 through 2016 (Environment Canada 2013; U.S. EPA 2018). Because limited AOD data were available before 2000, Brauer and colleagues applied a backcasting method to estimate annual average $PM_{2.5}$ concentrations for the years 1981 through 1999 for application to epidemiological analyses, using GEOS-Chem simulations and ground-based measurements of $PM_{2.5}$, PM_{10}, and TSP (Hystad et al. 2011; Meng et al. 2019). Specifically, the satellite-based $PM_{2.5}$ surface (van Donkelaar et al. 2015) was projected to other years using GEOS-Chem simulations, and $PM_{2.5}$ was inferred from ground-based measurements of PM_{10} and TSP. GWR was used to statistically fuse the backcasted data to the ground-based measurements.

Copollutant Models (NO_2 and O_3) NO_2 and O_3 concentrations were estimated using models developed earlier to enable copollutant adjustment in the main $PM_{2.5}$ health model; those pollutant concentrations were not primarily used to independently assess their association with mortality. Ambient annual NO_2 concentrations were estimated at each postal code based on a national land-use regression model that estimated ground-level concentrations for the year 2006, utilizing satellite data, ground monitor data, and land-use data at a high spatial resolution (100 m^2) (Hystad et al. 2011). Eight-hour average daily maximum concentrations of O_3 were estimated based on chemical transport modeling of surface observations in the warm season from 2002 to 2015 (Environment and Climate Change Canada). From 2002 to 2009 the spatial resolution of the O_3 model was 21 km^2; subsequently, this was improved to 10 km^2. Hourly O_3 model output was fused with ground monitor data (Robichaud et al. 2016; Robichaud and Ménard 2014) as part of the routine Canadian air quality forecast modeling system. These hourly data were then processed into warm season (May–September) 8-hour daily maximum concentrations and interpolated to Canadian six-digit postal codes by the Canadian Urban Environmental Health Research Consortium (CANUE) (Additional Materials 2, Appendix C in Pappin et al. 2019). Backcasting procedures were applied to NO_2 and O_3 using ground-based time-series measurements obtained in 24 of Canada's largest cities. Annual time series were constructed in each of the 24 cities based on the available ground data. Postal code estimates of NO_2 and O_3 estimates were spatially and temporally scaled to the geographically closest time-series data. Finally, O_x (combined oxidant capacity, or redox potential) was calculated as a weighted average of O_3 and NO_2 using the following (Weichenthal et al. 2017):

$$\left[\left(1.07 \times NO_2\right) + \left(2.075 \times O_3\right)\right] / 3.14$$

Exposure Assignment to Cohorts

For each year from 1981 to 2016, $PM_{2.5}$ exposure estimates were assigned to respondents in each cohort based

on residential, geocoded postal codes — taking into account residential mobility. Canadian urban postal codes often correspond to one side of a city block or to a single apartment building and fall within a single 1 km^2 raster of $PM_{2.5}$ concentration, while rural postal codes are often much larger. Since there may be a greater potential for exposure misclassification among respondents with rural postal codes, investigators considered models using the 1-km^2 buffer for urban residences and 10-km^2 buffer for rural residences. Missing postal code data were imputed for 2.1% of the person-years using an approach described by Finès and colleagues (2017).

To ensure the exposure preceded follow-up, the exposure time window for both $PM_{2.5}$ and oxidant gas concentrations was assigned using a 3-year moving average, with a 1-year lag. Additional exposure time windows were explored in sensitivity analyses.

Health Assessment

To assess the relationship of mortality with $PM_{2.5}$ exposure, main analyses were conducted on each of the four cohorts separately (the three CanCHEC cohorts and CCHS). Cohort respondents had to be at least 25 years of age at cohort commencement and were censored if they reached 90 years of age anytime during follow-up. Age censoring was based on the concern that assigned postal codes for these very elderly respondents might not represent those of the respondent but rather of someone else who completed their tax returns. The investigators fit Cox proportional hazards models for all individuals ages 25–89 with year of follow-up as the time axis and stratified the baseline hazard function by age (5-year groups), sex, and immigrant status (yes/no).

Hazard ratios (HR) (per 10-$\mu g/m^3$ $PM_{2.5}$ exposure) were computed for each of the three CanCHEC cohorts and then pooled for a single summary HR using meta-analytic methods. The investigators fit two primary covariate adjustment models, based on their conceptual model of the relationships between outdoor $PM_{2.5}$ and mortality as outlined in a directed acyclical graph (DAG):

1. *The DAG-based model* includes only geographically based predictors and ecological variables (i.e., CANMarg, airshed, urban form, and community size) and no individual-level risk factors.
2. *The full model* includes all DAG-based covariates plus individual-level risk factors available in CanCHEC (income, education, occupational class, indigenous status, visible minority status, employment status, and marital status). Since CCHS includes a richer set of behavioral covariates for each participant, Brauer and colleagues developed additional models to allow for a direct comparison with CanCHEC.

In addition, the investigators conducted several stratified analyses, examining the relationship by categories of age during follow-up (<65, 65–74, or ≥75 years), sex, and immigrant status, and they explored the association between $PM_{2.5}$ and mortality while adjusting for O_3, NO_2, or O_x (see *Sensitivity Analyses* section).

Concentration–Response Function

Brauer and colleagues examined the shape of the association between $PM_{2.5}$ and mortality by fitting two different models of shape characterization to the data — the RCS and the SCHIF. RCS methods are relatively common in the field, whereas SCHIFs, which are flexible nonlinear sigmoidal functions, are more recently developed. The investigators note that an important feature of SCHIFs is that they are "constrained to produce functions that increase monotonically with concentration and in forms that are biologically plausible" and can be readily applied in risk and burden assessments (see the Investigators' Report). However, because of computational limitations, they borrowed information from the RCS to inform the SCHIF. Specifically, an RCS was fit with 15 knots to characterize the shape of the PM–mortality relationship and enable visual inspection of patterns in the HR estimates over the exposure range. Next, for each cohort, a SCHIF was fit to the resulting RCS predictions (logarithm of the RCS HRs and standard errors) at 500 equally spaced concentrations. The uncertainty in the RCS predictions is captured at each concentration and applied to the SCHIF model predictions. The SCHIFs resulting from each individual CanCHEC cohort were pooled in a meta-analytic summary (parameter estimates are provided in Table 1 of the Investigators' Report).

Sensitivity Analyses

Brauer and colleagues conducted several subanalyses using the 2001 CanCHEC cohort to examine the sensitivity of the associations between $PM_{2.5}$ and mortality to the following factors: missing individual or behavioral risk covariates, which are only available in the CCHS cohort; temporal and spatial scales of the exposure assessment, including characterization of coexposure to gaseous pollutants (i.e., O_3, NO_2, or O_x); and immigrant effect. Results from these subanalyses informed the approach for the main analyses.

Indirect Adjustment Since important individual risk factors for mortality such as smoking, alcohol use, exercise, and diet are not included in the CanCHEC census long form, the investigators assessed whether these individual-level

risk factors, available in the CCHS cohort, would influence the air pollution risk estimates in the CanCHEC cohorts. To this end, Brauer and colleagues applied and evaluated a newly developed method of *indirect adjustment* for these individual-level risk factors (Shin et al. 2014) and used estimated associations between $PM_{2.5}$ and these risk factors in CCHS to indirectly adjust the HR in the 2001 CanCHEC cohort. The evaluation methodology comprises three steps. First, analyses were conducted to assess whether the 2001 CCHS respondent data set (n = 130,000), in which these individual risk factors are available, could serve as the representative matching data set to the primary data set (CanCHEC 2001, n = 2.4 million). Next, an internal validation step assessed the degree of bias in adjusted HRs when indirect adjustment is applied to nonlinear Cox proportional hazards models. A *gold-standard* approach was applied in which two variables available in both data sets (income and education) were excluded from CanCHEC analyses (partial model), and then indirectly adjusted for using the coefficients and standard errors from the true model containing both variables, with results compared to those of the true model. Finally, an external validation step assessed the bias of using the CCHS as the matching data set to indirectly adjust CanCHEC (i.e., CanCHEC data were replaced with data from CCHS) and employed a static as well as a time-varying $PM_{2.5}$ exposure value (Erickson et al. 2019).

Exposure Assessment The investigators further assessed the sensitivity to the temporal exposure assignment scale of a 3-year moving average used in the main analysis by developing survival models employing 1-, 3-, and 8-year moving averages for comparison. Similarly, various spatial scales of exposure assignment (i.e., 5-km^2 and 10-km^2 buffers) were also examined and compared with 1 km^2 in the base model, holding the temporal scale constant.

Copollutant $PM_{2.5}$ Models Sensitivity of the main $PM_{2.5}$ estimates to ambient O_3, NO_2, and O_x coexposure was assessed by adjusting for each of these oxidant gases using 3- and 8-year moving average windows.

Immigrant Effect Brauer and colleagues also conducted subanalyses to assess the association of long-term $PM_{2.5}$ exposure and mortality in the Canadian immigrant population, which constitutes nearly 20% of the nation's population, for comparison with nonimmigrant Canadians. Immigrant-specific covariates, such as duration of residence in Canada, country of birth, age at immigration, and neighborhood ethnic concentration were examined.

SUMMARY OF KEY RESULTS

EXPOSURE ASSESSMENT AND ASSIGNMENT

Brauer and colleagues reported that the prediction model performed well, and satellite-derived $PM_{2.5}$ estimates for 2004–2008 at a 1-km^2 resolution were in good agreement with ground-based monitors across Canada and the northern United States (R^2 = 0.82; root mean square difference [RMSD] = 1.5 $\mu g/m^3$ across 721 sites). Constraining the model to lower concentrations (<8 and ≤10 $\mu g/m^3$) did not influence its performance; absolute error even decreased slightly (i.e., RMSD = 1.3 $\mu g/m^3$) when values were restricted to 8 $\mu g/m^3$ and below (248 sites).

The historical backcasted $PM_{2.5}$ exposure estimates improved when all ground-based measurement sites (i.e., $PM_{2.5}$, PM_{10}, and TSP) were used for adjustment, compared with when only ground-based sites for $PM_{2.5}$ were used (R^2 = 0.77 vs. 0.52; RMSD = 1.9 vs. 3.1, respectively). When satellite remote sensing information was removed from the models, the performance of the estimated prediction decreased. Thus, the investigators noted the importance of including satellite data in the exposure estimation. The agreement between satellite-derived and ground-based estimates decreased after 2008 as $PM_{2.5}$ ambient concentrations and spatial variability declined. It should be noted that backcasted estimates are most relevant to the 1991 and 1996 cohorts, since the 3-year moving average window for the 2001 cohort started in 1998.

Across Canada, the mean $PM_{2.5}$ concentration was 7.1 $\mu g/m^3$ for 2004–2008, with a low mean concentration of 2.6 $\mu g/m^3$ in the Yukon Territory to a high of 8.5 $\mu g/m^3$ in Ontario. Overall, the population-weighted annual average $PM_{2.5}$ in all of North America decreased from 22 $\mu g/m^3$ in 1981 to 8 $\mu g/m^3$ in 2016.

Similar to the decreasing trend of the overall population-weighted annual average $PM_{2.5}$ concentrations over the past 35 years across North America, assigned mean $PM_{2.5}$ estimates were highest in the 1991 CanCHEC cohort (8.10 $\mu g/m^3$, standard deviation: 3.44) and lowest in the more recent 2001 CanCHEC cohort (6.68 $\mu g/m^3$, standard deviation: 2.24), with greater declines of $PM_{2.5}$ concentrations in locations with previously higher concentrations. $PM_{2.5}$ levels for CCHS cohort participants were consistently 1.8 to 2.0 $\mu g/m^3$ lower compared with CanCHEC respondents. This is likely due to the different sampling protocols of the two types of cohorts. The CCHS was designed to produce stable estimates at the health unit level (often defined by census divisions). They thus oversampled health units with proportionally lower population counts, and undersampled in high population health

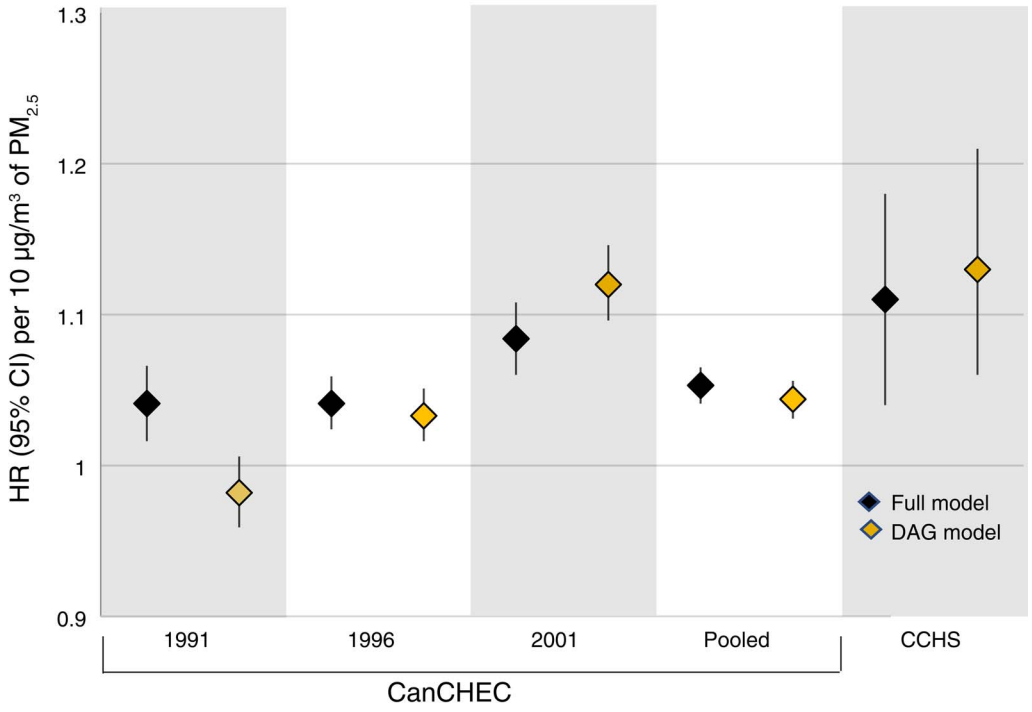
units. However, CanCHEC was sampled strictly proportional to population (i.e., one in every five households). This resulted in proportionally higher counts in larger cities, and lower counts in less populated areas, for CanCHEC compared with the CCHS. These differences in sampling strategies resulted in higher assigned concentrations in CanCHEC compared with CCHS.

HEALTH ASSESSMENT

Mortality–Air Pollution Association

Based on pooled estimates of the three CanCHEC cohorts, Brauer and colleagues found that a 10-μg/m^3 increment in long-term average $PM_{2.5}$ was associated with a 5% increase in the risk of nonaccidental mortality (HR = 1.05, 95% confidence interval [CI]: 1.04–1.07, the full model). Consistent results, though generally smaller than the full model effect estimates, were also found in the DAG-adjusted model. For both adjustment sets, the $PM_{2.5}$–mortality risk was slightly lower in the 1991 and 1996 cohorts as compared with the 2001 CanCHEC cohort (see Commentary Figure 2). In the pooled CanCHEC results, male populations consistently had stronger associations than female populations. Consistently across all CanCHEC cohorts, HRs declined with increasing age across the three categories (i.e., <65 years, 65–74 years and ≥75 years). Given lower Akaike Information Criterion (AIC) and Schwarz Bayesian Criterion (SBC) statistics under the full models versus the DAG-based models (see Table 8 in the Investigators' Report), the investigators focused their interpretation of results on the full models.

In the full model for the CCHS cohort, with extensive adjustment for socioeconomic, contextual ecological, and behavioral covariates (only available for this cohort), $PM_{2.5}$ exposure was associated with an 11% increase in nonaccidental mortality (HR: 1.11, 95% CI: 1.04–1.18). Although this was a larger HR than was observed in the three CanCHEC cohorts, the simpler DAG-based model (adjusted for socioeconomic and contextual ecological covariates, but not behavioral factors) in this cohort resulted in a similar risk of mortality (HR = 1.13, 95% CI: 1.06–1.21), suggesting that inclusion of behavioral covariates only slightly affected the $PM_{2.5}$–mortality association.



Commentary Figure 2. Hazard ratio estimates and 95% confidence intervals for the association between $PM_{2.5}$ and nonaccidental mortality for Full and DAG-informed models across the CanCHEC and CCHS cohorts.

Consistent with the 1991 and 1996 CanCHEC cohorts, higher $PM_{2.5}$–mortality associations were observed in the CCHS survey for males, nonimmigrants, and — similar to all CanCHEC cohorts — younger respondents. The finding that immigrants had smaller $PM_{2.5}$ HRs compared with nonimmigrants in 1991 and 1996 was possibly attributable to the healthy immigrant effect, as noted by the investigators (Beiser 2005; Ng 2011; Omariba et al. 2014), and by immigrants' selective settlement in larger cities where $PM_{2.5}$ levels were higher.

Concentration–Response Function

For each cohort, the investigators graphically depicted the shapes of the association between $PM_{2.5}$ and mortality using the nonlinear RCS model and the SCHIF, as described earlier (see Figures 12 and 13 in the Investigators' Report). They caution that these nonlinear HRs should not be directly compared with the linear estimates derived from the Cox proportional hazards model. While the marginal change in the linear model is constant (i.e., constant change in HR per 10-μg/m^3 change in concentration), the marginal change in risk for a nonlinear model will vary by concentration and is relative to an HR of 1 at a counterfactual concentration of 0.4 μg/m^3 (the lowest observed concentration in the data). For comparability to other studies, the investigators estimated the HR for a 5- to 15-μg/m^3 change in concentration from the SCHIF as 1.06 (95% CI: 1.05–1.07). Overall, both the RCS and the SCHIF show a supralinear association in the CanCHEC cohorts, with a steep increase in the spline predictions across lower concentrations (i.e., <5 μg/m^3), followed by a leveling off or a smaller increase after ~10 μg/m^3. The investigators suggest that there is no evidence of a threshold or sublinear association at very low concentrations. A similar supralinear curve with a steep increase in the RCS at low concentrations was observed in the CCHS cohort, and the SCHIF displayed a similar pattern. However, because of the wide CIs, the investigators caution against over-interpretation of the SCHIF. Both the splines and the SCHIFs are for $PM_{2.5}$ models only and do not incorporate copollutant effects of O_3 or NO_2.

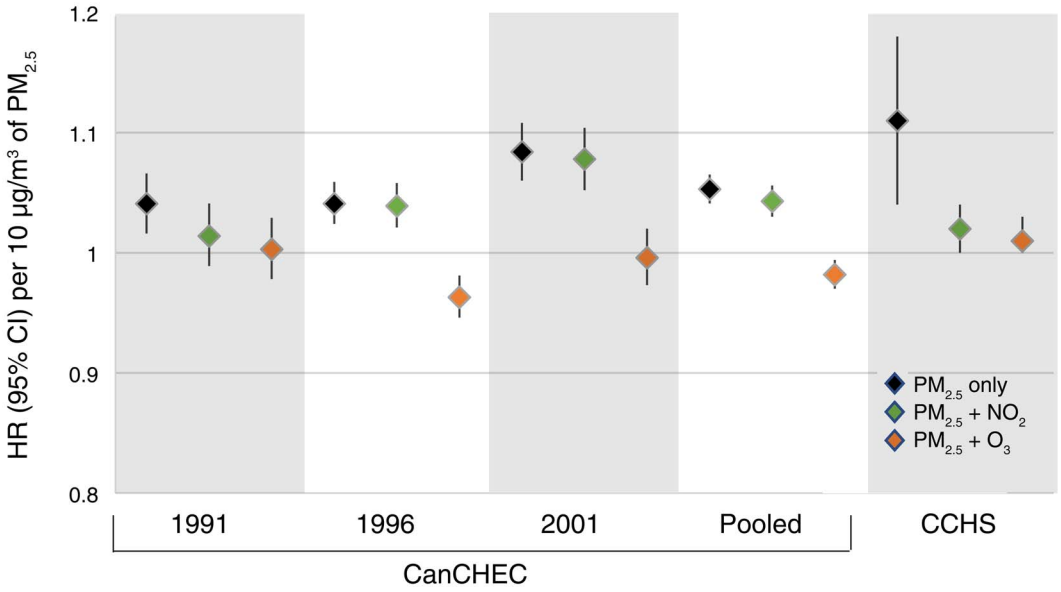
Sensitivity Analyses

Indirect Adjustment In evaluating the indirect adjustment methodology where secondary ancillary data from the CCHS were used to adjust for missing covariates in a primary data set (namely, CanCHEC 2001), Brauer and colleagues found that the two data sets (2001 CCHS and 2001 CanCHEC) were similar across the individual variables but slightly different across the ecological variables, with a greater proportion of CCHS respondents having lived in rural areas compared with those in CanCHEC. A weighting procedure was applied to correct for this (Erickson et al. 2019). The validation test comparing the partial and true models resulted in an adjustment bias ranging from 1.7% in the static model to 3.0% in the time-varying model for nonaccidental mortality (Figure 16 in the Investigators' Report). The internal and external validation models performed well and found only small adjustment biases both in the static and time-varying $PM_{2.5}$ exposure models for all-cause mortality (<1% and <2%, respectively). Investigators also found that the adjustment correction from the indirectly adjusted models were comparable to equivalent models that directly adjusted for these risk factors (i.e., smoking, alcohol use, exercise, and diet) using the CCHS cohort. Based on their modeling — which included multiple covariates and indirect adjustment and a representative ancillary data set — the investigators concluded that missing data on these behavioral covariates were unlikely to significantly confound the $PM_{2.5}$–mortality relationship in the Canadian population.

Exposure Assessment To assess how various temporal and spatial scales may affect the magnitude of the $PM_{2.5}$–mortality associations, the investigators compared the $PM_{2.5}$ exposure estimates for the 2001 CanCHEC cohort across three different moving averages (1 year, 3 years, and 8 years) and spatial scales (1 km^2, 5 km^2, and 10 km^2). The best fitting models, based on the largest HRs and lowest AIC values, were models with longer moving averages (up to 8 years) and smaller spatial scales (1 km^2 vs. 10 km^2).

Copollutant $PM_{2.5}$ Models When gaseous copollutants (NO_2, O_3, and O_x) were included in the $PM_{2.5}$–mortality models, the crude positive HRs were either attenuated slightly, when adjusted for NO_2, or eliminated entirely, as with adjustment for O_3 or O_x. This blunting or elimination of the HRs after copollutant adjustment was consistently observed across all three CanCHEC cohorts, as well as the pooled results (see Commentary Figure 3). Similarly, in the CCHS cohort, the $PM_{2.5}$–mortality HRs were smaller in all three copollutant-adjusted $PM_{2.5}$ models (NO_2, O_3, and O_x) (see Commentary Figure 3).

Immigrant Effect Analysis The investigators analyzed $PM_{2.5}$–mortality impacts specifically on the immigrant population of the 2001 CanCHEC cohort and found that estimated concentrations of ambient $PM_{2.5}$ were 20% higher in immigrants compared with nonimmigrants (9.3 vs. 7.5 μg/m^3, respectively). With regard to demographic characteristics, recent immigrants (1980 onward) tended to live in the Western (including Vancouver) and East Central airsheds, and had a disproportionately large



Commentary Figure 3. Hazard ratio estimates and 95% confidence intervals for the association between $PM_{2.5}$ and nonaccidental mortality with and without adjustment for NO_2 and O_3 (full models) in the CanCHEC and CCHS cohorts. Since the $PM_{2.5}$ model results including O_x are similar to those adjusted for O_3, O_x-adjusted results are not included in this figure.

number of women, younger people, married people, and people with a higher-level education. However, they also tended to have lower income and higher unemployment rates. In this subanalysis — and unlike with the 1991 and 1996 CanCHEC cohorts — Brauer and colleagues found that immigrants had increased risks for nonaccidental mortality; however, the difference in risk was small.

EVALUATION BY HEI'S LOW-EXPOSURE EPIDEMIOLOGY STUDIES REVIEW PANEL

In its independent review of the study, HEI's Low-Exposure Epidemiology Studies Review Panel noted that Brauer and colleagues have conducted an impressive and innovative study on a very large population-based cohort using advanced methods for both exposure and health assessment, including the derivation of the concentration–response functions. This research contributes to the body of evidence regarding health effects at low ambient $PM_{2.5}$ concentrations and advances the science considerably. Notable strengths of the study include the sheer sample size (~9 million adults) in four nationally representative cohorts in Canada that make this study uniquely generalizable to the entire population, as well as the highly detailed and refined spatial resolution (1 km × 1 km) of the $PM_{2.5}$ exposure predictions through the novel integration of multiple inputs that include satellite measurements, ground-level monitoring data, GEOS-Chem atmospheric modeling data, and geographical covariates. Additionally, the investigators' plan to make these refined exposure estimates publicly available creates a valuable asset for future research studies.

EVALUATION OF STUDY DESIGN AND APPROACH

Exposure Models

The $PM_{2.5}$ exposure model is an impressive undertaking, drawing from state-of-the-art techniques that combine ground measurements, land-use modeling, satellite data, and simulations from GEOS-Chem, to allow a spatial resolution of 1 km × 1 km over the entire area of Canada and the United States. The current model represents a 100-fold higher resolution than the previously used resolution of 10 km × 10 km in earlier work by these investigators (Crouse et al. 2012). Similarly, the NO_2 model has a very fine spatial resolution, obtained through satellite inputs (10 km × 10 km) and downscaled to 100 m × 100 m using land-use regression modeling, while the exposure estimates for O_3 and O_x have a coarser resolution (21 km × 21 km for 2002–2009, and subsequently 10 km × 10 km) compared with the $PM_{2.5}$ model. The different spatial resolutions of

the three pollutants is a notable issue in this work, given the sensitivity of the $PM_{2.5}$ epidemiological findings for copollutants in the multipollutant models. Thus, the overall impact of using different spatial resolutions presents some challenges and is an important future research topic.

While the 1 km × 1 km spatial resolution of the $PM_{2.5}$ exposure model is a laudable improvement, this model inherently cannot fully capture very fine-scale $PM_{2.5}$ spatial gradients near sources such as roadways and local point emission sources, producing some degree of exposure measurement error.

The investigators backcasted $PM_{2.5}$ estimates from 1981 to 1999 using inputs from GEOS-Chem simulations and $PM_{2.5}$, PM_{10}, and TSP measurements. While the backcasting methods used to assign exposure predictions are relevant mainly for the 1991 and 1996 CanCHEC cohorts (since the main results are calculated using a 3-year exposure lag), the performance of the predictions over time and associated error are important considerations in the pooled results from this study, as well as in the potential application of this methodology in other studies. Overall, the inclusion of satellite remote sensing information — which became available in 1998 — improved the exposure prediction. As expected, the more recent estimates are more stable and accurate (i.e., the R^2 value for all sites increased from 0.52 to 0.77). However, the investigators observed a decrease in R^2 in the $PM_{2.5}$ base estimates after 2008 due to weaker spatial $PM_{2.5}$ gradients from declining $PM_{2.5}$ levels. Another potential source of error could be introduced by the fact that the exposure models seem to be highly reliant on data from the United States, where pollution levels and ground monitor density are generally higher than in Canada. The Review Panel would be interested in seeing Canada-specific data and performance measures; the investigators have indicated such analyses are currently planned for inclusion in the Final Phase 2 report.

Health Models

The health analyses were conducted in repeated, large, nationally representative samples of the adult Canadian population, using rich data sets with individual-level and regional covariates. Complete annual residential history data for all cohort members, based on unique permission for linkage to postal codes in tax records, allowed for detailed spatial characterization and time-varying exposures, a particularly useful feature of this study.

Confounding Adjustment

During the review process, the Panel had requested that the investigators use a directed acyclic graph (DAG) as an advantageous method for selecting and identifying covariates that could contribute to both outdoor $PM_{2.5}$ concentrations and mortality. This represents a transparent epidemiological approach to confounder selection that graphically depicts (suspected) causal and non-causal relationships between covariates. DAGs are especially helpful in clarifying whether bias is reduced or increased as variables are introduced into the model (Arnold et al. 2019; Greenland et al. 1999). In response to the Panel comments, the investigators created two DAGs that can be found in Figure 3 of the Investigators' Report. They then proposed a *DAG-informed model*, one for the CanCHEC cohorts and one for the CCHS cohort, that includes only contextual geographically based predictors (i.e., airshed, community size, neighborhood dependence and deprivation, ethnic concentration, neighborhood instability, and urban/rural category) and one *full model*, which additionally includes individual-level risk factors (i.e., income, education, employment status, and marital status, as well as indigenous and visible minority status).

Although the Panel was very pleased to see the investigators' efforts to produce DAGs for this research, they had questions surrounding some of the causal pathways assumed and found the application of these DAGs to the specification of the full model to be unclear. For example, the DAGs developed by the investigators seem to more closely reflect the various covariates available from the surveys, rather than the full set of factors that may potentially affect the health outcomes (e.g., age is likely to correlate with place of residence as well as risk of mortality). The Panel also felt that the construct of "personal $PM_{2.5}$" should be replaced by "$PM_{2.5}$ of ambient origin" to better reflect the relationships being estimated. This would change the conceptual relationships, and thus there would be a need to control for factors such as "individual-level smoking" that may not be associated with "$PM_{2.5}$ of ambient origin." Given this feedback, the Review Panel suggests that the investigators revisit the assumptions of their DAG for the Final Phase 2 report. The Panel similarly encouraged the use of their revised DAG to select the most parsimonious set of covariates to minimize the inclusion of multiple overlapping contextual covariates in the same model (e.g., airshed, given the other geographical covariates).

The investigators ultimately chose to focus on the full model. While the Panel agreed with this choice based on the covariates included, they did not agree with the justification of this choice based on the AIC and SBC statistics. Although lower scores in the full model suggest that additional covariates in the full model improve model fit, it does not follow that the inclusion of all the covariates in

the full model will reduce bias in the all-cause mortality estimate of $PM_{2.5}$. Similarly, the Panel did not understand the investigators' statement that moving from a DAG-informed model to a more inclusive full model would address the possible bias in the HRs introduced by an "imbalance of individual-level mortality risk factors" across the $PM_{2.5}$ concentrations due to the observational nature of the study. In principle, the DAG should account for all potential confounders that should be included in the model. If there are additional measured variables that are imbalanced but are not confounders, then there would be no reason to include them for the purpose of reducing bias, and their inclusion could in fact in some circumstances actually increase bias. Hence, the Panel encourages the investigators to consider a broader and more comprehensive approach to their DAG-based efforts for the final phase of the project.

Although the Panel did not agree with the investigators' methods for selecting their primary model, they were ultimately comfortable with the final model selected. The Panel commends the investigators on their thorough investigation into the sensitivity of their findings to various methodological choices. These sensitivity analyses demonstrated that the results from the DAG and full models are not substantially different, as differences between the two models range from <1% to 6% (calculated from estimates listed in Tables 7 and 11 in the Investigators' Report). This increases the confidence in their findings.

In additional subanalyses, the investigators applied an indirect adjustment methodology (Shin et al. 2014) to assess how much bias is introduced by adjusting for missing behavioral risk factors (i.e., smoking, alcohol use, exercise, and diet) in the 2001 CanCHEC cohort, using an available representative data set from the CCHS cohort (Erickson et al. 2019). Overall, the sensitivity analyses showed a minimal downward bias adjustment in the $PM_{2.5}$–nonaccidental mortality HR in the CanCHEC model of 2%–3.5% (see Table 15 in the Investigators' Report). The internal (i.e., using CanCHEC 2001) and external (i.e., using CCHS) validation models results show minimal downward bias in $PM_{2.5}$ and all-cause mortality HRs using both static and time-varying exposures (see Figure 16 in the Investigators' Report). The Panel was concerned that the development of the indirect adjustment method of Shin and colleagues (2014) lacks critical details regarding the statistical justification for its use with Cox models, but did feel that the validation provided some assurance that the three-step modeling process served its intended purpose. As the investigators move forward in Phase 2, the Panel recommends a more formal and rigorous assessment of these methods.

Concentration–Response Curve and SCHIF

Because of computational constraints, the authors used a stepwise approach to estimate the nonlinear association of $PM_{2.5}$ exposure and mortality, first fitting an RCS function of exposure in the Cox model and then using predictions from that spline function to fit the SCHIF models. Uncertainty estimates for the SCHIF models were then matched to the spline function uncertainty via a two-stage approach, resulting in pointwise uncertainty bands. While taking this stepwise approach is understandable from a practical perspective, given the computational limitations it is difficult to assess the degree to which the seemingly nonstandard approach produces results (including uncertainty) that are consistent with what would be obtained by fitting the nonlinear association directly in the Cox model. In addition, the pointwise nature of the uncertainty estimates necessarily makes it difficult to adequately assess the shape of the relationship, an important aim in this study.

In presenting the fitted spline curves and making spline predictions for fitting the SCHIF models, the investigators chose the minimum exposure as the reference exposure. An alternative would be to use the mean (or median) exposure as the reference. Since uncertainty at the reference exposure is necessarily zero by construction, using this alternative approach would result in increasing uncertainty as one approaches very low exposures, rather than the decreasing uncertainty at low levels, as shown in the results (see Figures 12 and 13 in the Investigators' Report). This raises the concern that readers may incorrectly interpret the spline results as being quite certain of a steep increase in the HR at low exposures. Yet intuitively we must have less information about the relationship at low- and high-exposure levels where the data are necessarily sparser. Choosing the reference in the middle of the observed exposure range should also have the benefit of much lower uncertainty for the HR in the middle of the exposure distribution, where most of the data are. Furthermore, this choice of reference affects the SCHIF model-fitting estimates and uncertainty because the SCHIF models are fit to the spline predictions and their uncertainty. The Panel recommends that sensitivity of the results to the choice of reference exposure be carefully addressed in the Final Phase 2 report. Finally, we note that the investigators do not use predictions above the 99th percentile because of the boundary effects of the RCS. Given this, it is not clear why they do include predictions below the 1st percentile and how this affects the resulting SCHIF model estimates and uncertainty.

Brauer and colleagues used a meta-analytic approach to pool the SCHIF curves across the three CanCHEC cohorts. The pooled estimate corresponds to a fixed-effects meta-analysis, which is generally interpreted as assuming a

constant effect across the studies (or cohorts) — estimated in this case as an appropriately weighted average of the within-cohort effects. This assumption could be questioned in this context, but it is worth noting that Rice and colleagues (2017) show that the fixed effects estimate also corresponds with estimating an effect for a population formed by amalgamating the individual study populations, which may be a reasonable interpretation here. Regardless, it is not clear how the investigators derive their estimator for the variance of the pooled estimate, in which they try to account for both the sampling uncertainty and the variability among the cohorts. The estimator does not appear to correspond to the variance estimator under either the usual fixed-effects or the random-effects meta-analysis approaches, so it is not clear that the resulting variance estimates are valid. The Panel recommends that these issues be better addressed in the Final Phase 2 report.

DISCUSSION OF THE FINDINGS AND INTERPRETATION

Although the study's analyses provide evidence for associations between low-level $PM_{2.5}$ concentration and mortality, important uncertainties still remain at this stage that preclude drawing firm conclusions, as detailed in the sections that follow.

Concentration–Response Curve

The evaluation of the concentration–response curve at low exposures was another strength of this study. The methodological concerns regarding the analysis of the shape of the association between $PM_{2.5}$ and mortality discussed earlier, however, suggest that the current version of these results should be interpreted cautiously. This is especially true given that there is not yet any information provided to assess whether and how the shape of the exposure–mortality relationship may be affected by the adjustment for copollutants. Relatedly, in their primary analyses the authors pooled the HRs across studies, but they did not clarify how this was accomplished. Presumably, the methodology is the same as that used in the meta-analytic approach to pooling the SCHIF models and shares the same statistical concerns that were stated earlier.

Sensitivity Analyses

The Panel appreciates the comprehensive sensitivity analyses to assess the range of possible effects from varying temporal and spatial scales, the indirect adjustment method, and the immigrant effects.

Exposure Assessment Regarding the temporal influence on the point estimates, specifically the increased HR in nonaccidental mortality in the longer moving 8-year average compared with shorter 1- and 3-year windows, the Panel recommends that, in addition to the AIC figures (Investigators' Report Figure 14), the investigators include validation statistics (RMSD, R^2) in the Final Phase 2 report. These statistics and related interpretation could help determine whether this finding is due simply to better stability of the exposure estimates at a longer time window or provides evidence for a longer time window of $PM_{2.5}$ pathophysiological effects.

Copollutant $PM_{2.5}$ Models The focus of the current study was on $PM_{2.5}$, although the investigators used exposure models developed earlier for NO_2, O_3, and O_x to investigate the extent to which those pollutants might influence the $PM_{2.5}$–mortality association. While the estimated HRs showed general consistency of a positive relationship between long-term exposure to low-level $PM_{2.5}$ exposure and nonaccidental mortality across models, a distinct exception was the sensitivity of the findings to the inclusion of O_3 or O_x as covariates in the multipollutant $PM_{2.5}$ models. For example, the CanCHEC pooled $PM_{2.5}$–mortality effect estimate decreased from an HR of 1.05 (95% CI: 1.04–1.07) to 0.98 (95% CI: 0.97–0.99) with adjustment for O_3 and to an HR of 0.96 (95% CI: 0.94–0.97) when adjusting for O_x (per 10-μg/m^3 increment in $PM_{2.5}$). Thus, the inclusion of these gaseous copollutants in the study resulted in associations that did not demonstrate increasing risk of mortality with increasing $PM_{2.5}$ exposures in all CCHS and CanCHEC cohorts.

Recalling the relatively coarse spatial resolution of the O_3 predictions (10- or 21-km^2), it is difficult to know how to interpret these findings. On the face of it, the $PM_{2.5}$ effects seem to be strongly influenced by O_3. However, while the coarse O_3 predictions capture the regional gradients in O_3 concentration, they fail to capture the smaller-scale gradients caused by the scavenging of O_3 by nitrogen oxides that occurs in urban centers and along roadways. One must, therefore, suspect that there is substantial O_3 exposure measurement error. The ability, then, of a confounder (in this case O_3) that is measured with substantial error to adequately control for confounding can be strongly questioned. It must be concluded that it is not known whether the $PM_{2.5}$ effect is completely, or partially, confounded by the gaseous oxidant pollutants. However, given the findings reported here, there is nevertheless concern that there may be important confounding by O_3. Additionally, the differing spatial scales of the three-pollutant exposure prediction models (i.e., $PM_{2.5}$ at 1 km^2, NO_2 at 100 m^2, and O_3 at 10- or 21-km^2) hinder drawing conclusions on how these pollutants correlate over space (e.g., NO_2 and O_3 are unexpectedly positively correlated in this study).

Although Brauer and colleagues state that attenuated results following adjustment for O_x and O_3 (combined with NO_2) are consistent with previous work (Weichenthal et al 2017; Crouse et al. 2015, respectively), they also suggest that measurement error may prevent them from capturing the complex interaction between oxidative gases and $PM_{2.5}$, as their previous work suggests that the redox potential of O_3 and O_x enhances the toxicity of $PM_{2.5}$ mass (Weichenthal et al. 2017). Alternatively, they state that spatial variations in oxidant gases could act as surrogates of air pollution sources or particle components with differing health impacts, in which case adjustment for regional O_3 could serve to adjust for aspects of $PM_{2.5}$ itself, thereby attenuating the effect of $PM_{2.5}$.

While the $PM_{2.5}$ models are sensitive to the inclusion of O_3 and O_x, conclusions cannot be drawn at this point about whether the attenuated HRs result from some or all of the following: (1) the confounding effect of O_3; (2) the impacts of O_3 measurement error and the different spatial scales of the pollutant predictions; (3) poorly captured interactions between oxidant pollution and $PM_{2.5}$; and/or (4) the confounding role of O_3 as a measure of urban pollution, more generally, or as a measure of $PM_{2.5}$ characteristics. The exposure measurement error correction methodology for spatially varying pollutants in multipollutant research is in its infancy (e.g., Bergen et al. 2016), thus it is not surprising that Brauer and colleagues were not able to fully address this issue in their extensive work. The Panel looks forward to eventually seeing results from health models that employ $PM_{2.5}$ and gaseous pollutant (especially O_3) concentration predictions at a very fine spatial scale.

Immigrant Effect Analysis The immigrant subanalyses found larger $PM_{2.5}$ mortality HRs for nonimmigrants when compared with immigrants in the CCHS and 1991 and 1996 CanCHEC cohorts; however, the reverse was observed in the 2001 CanCHEC cohort, though differences were smaller. Previous cohorts had excluded immigrants altogether or limited their inclusion to a minimum of 20 years in Canada because of the difficulty in constructing exposure history and other unknown differences. In this study, since immigrants in Canada comprise ~20% of the population, investigators included all immigrant respondents living in Canada for 10 years before the cohort index year. It is not clear to the Panel whether the stronger associations in nonimmigrants could be due to exposure misclassification during key time periods, the healthy immigrant effect (given Canadian policies on health status when admitting immigrants into the country), or other reasons.

CONCLUSIONS

Brauer and colleagues have conducted a thorough and state-of-the-art study, and this Phase 1 report constitutes a significant contribution to elucidating the associations between low-level exposures to air pollution and mortality. The MAPLE study greatly advances the investigators' previous work by (1) increasing the cohort size and follow-up time (to 2016), (2) employing deterministic (vs. probabilistic) linkage of participants to mortality records using individual identifiers, (3) refining spatial resolution (1 km × 1 km) of the $PM_{2.5}$ exposure models, (4) including residential mobility at follow-up, (5) using year-adjusted exposure estimates from 1981 onward, employing a sophisticated backcasting approach, (6) including behavioral covariate adjustment, and (7) expanding analyses to include all immigrants who have been in Canada for more than 10 years.

The investigators reported that exposure to $PM_{2.5}$ was associated with a 5% increase in nonaccidental mortality per 10 $\mu g/m^3$ (HR = 1.05, 95% CI: 1.04–1.07, using the full model for pooled data of the three CanCHEC cohorts). Across all cohorts, Brauer and colleagues showed evidence of associations between $PM_{2.5}$ and nonaccidental mortality at concentrations below current health standards. Finally, secondary analyses using more detailed covariate information from the CCHS data set suggested that adjustment for additional covariates (i.e., smoking and diet) appeared to be largely unnecessary after adjustment for the available covariates in the CanCHEC data.

Although the study's analyses had a number of important advantages over previous cohort studies and earlier studies by these investigators, the Panel raised several limitations that prevent drawing firm conclusions from this interim Phase 1 report. As noted earlier, the observed associations between PM and mortality were weaker with adjustment for O_3, and the investigators only provided concentration–response functions for single-pollutant models. In addition, it remains unclear how robust the SCHIF method is, given that the reference concentration was set at 0.4 $\mu g/m^3$, artificially reducing the level of uncertainty at low concentrations. This Phase 1 report does of course present work in progress, and the authors will explore many of the issues discussed here in their Final Phase 2 report. However, in the absence of those further analyses these initial conclusions on associations and concentration–response relationships should be treated with appropriate caution.

The Panel looks forward to the further examination of these and many other questions in the final phase of the project. Specifically, the investigators plan to conduct the following analyses that will be included in their Final Phase 2 report:

Ground-Based Monitoring Sample collection and analysis are continuing at all five additional SPARTAN sites. Filter sample analyses are ongoing for PM mass, black carbon, ions, and elements. Organic composition of PM collected on filters will also be evaluated. This is anticipated to improve the validation method by yielding valuable information for constraining the GEOS-Chem simulation that is used to relate AOD to contemporary $PM_{2.5}$ concentrations.

Cause-Specific Mortality The investigators present important preliminary cause-specific mortality subanalyses in this Phase 1 report in an attempt to identify more specific causes of death related to low-level PM exposure. They plan to complete main analyses in the CanCHEC and CCHS cohorts of six specific causes of mortality, including cardiovascular disease with and without diabetes, ischemic heart disease, cerebrovascular disease, nonmalignant respiratory causes, chronic obstructive pulmonary disease, and lung cancer. Since the main cause-specific mortality analyses will be conducted in the second phase of the study, the Panel's evaluation has focused solely on nonaccidental mortality outcomes from long-term exposure to $PM_{2.5}$ and gaseous copollutants (NO_2, O_3, and O_x).

Low Concentrations Further analyses will be conducted in which the data set will be restricted to cohort participants that were only exposed to concentrations below certain levels (that is, below 12, 10, 8, and 6 $\mu g/m^3$).

Shape of the Concentration–Response Curve Investigators will refine the selection of knots to focus modeling of the shape of the curve at both the low and high ends of concentrations, as well as to evaluate the validity of the standard error derivation. The investigators plan to examine the shape of the association with $PM_{2.5}$ and mortality in locations with varying levels of O_x to further explore whether $PM_{2.5}$ mass toxicity is enhanced in the presence of the redox potential (O_x) of NO_2 and O_3 (Weichenthal et al. 2017). They also plan to study effect modification in the CanCHEC cohorts to evaluate the shape of $PM_{2.5}$–mortality associations across strata of oxidant gases (i.e., O_3, NO_2, and O_x), both for all-cause and cause-specific mortality.

Thus, these initial results find that $PM_{2.5}$ exposure at low ambient concentrations is associated with nonaccidental mortality, but further work is expected to shed light on the robustness of the association and the concentration–response curve. Importantly, $PM_{2.5}$ exposure estimates have been made publicly available (Dalhousie University Atmospheric Composition Analysis Group, *http://fizz.phys.dal.ca/~atmos/martin/?page_id=140#V4.NA.01*), and this approach could be extended to other geographical regions to support air pollution–health research worldwide.

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ABBREVIATIONS AND OTHER TERMS

AIC	Akaike information criterion
AOD	aerosol optical depth
AOE	adjusted optimal estimates
BMI	body mass index
CA	census agglomeration
CanCHEC	Canadian Census Health and Environment Cohort
CAN-Marg	Canadian Marginalization (index)
CASAC	Clean Air Scientific Advisory Committee
CCHS	Canadian Community Health Survey
CI	confidence interval
CMA	census metropolitan area
DAG	directed acyclic graph
ESCAPE	European Study of Cohorts for Air Pollution Effects
GEOS-Chem	Goddard Earth Observing System chemical transport model
GWR	geographically weighted regression
HR	hazard ratio
IMPROVE	Interagency Monitoring of PRotected Visual Environments
logRCS	logarithm of the RCS hazard ratio
MAPLE	Mortality–Air Pollution associations in Low-Exposure environments
MB	mean bias
mCCHS	CCHS mortality cohort
MODIS	moderate resolution imaging spectro-radiometer
NAAQS	National Ambient Air Quality Standards
NO_2	nitrogen dioxide
O_3	ozone
O_x	combined oxidant capacity
PCCF+	Postal Code Conversion File Plus
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
PM_{10}	particulate matter ≤10 μm in aerodynamic diameter
R^2	coefficient of determination
RCS	restricted cubic splines
RMSD	root mean square difference
RR	relative risk
SBC	Schwarz Bayesian criterion
SCHIF	shape-constrained health impact function
SD	standard deviation
SE	standard error
SPARTAN	Surface PARTiculate mAtter Network
TSP	total suspended particulate matter
U.S. CAA	U.S. Clean Air Act
U.S. EPA	U.S. Environmental Protection Agency

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