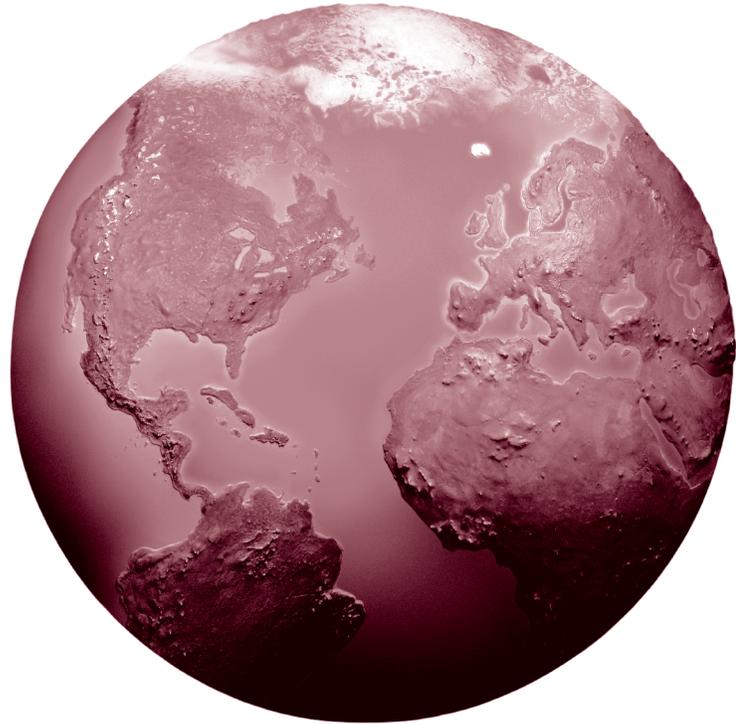


HEI

July 2022



COMMENTARY BY THE HEI LOW-EXPOSURE EPIDEMIOLOGY
STUDIES REVIEW PANEL SUMMARIZING AND EVALUATING
THE INVESTIGATORS' REPORT:

**Mortality–Air Pollution Associations in Low Exposure
Environments (MAPLE): Phase 2**

Brauer et al.

Health Effects Institute

Mortality–Air Pollution Associations in Low Exposure Environments (MAPLE): Phase 2

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

Research Report 212
Health Effects Institute
Boston, Massachusetts

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ABOUT HEI

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

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

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

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. For this study, a special panel — HEI's Low-Exposure Epidemiology Studies Oversight Panel — worked with the Research Committee in project selection and oversight. The Review Committee, which has no role in selecting or overseeing studies, typically 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 — fulfilled this role.

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

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Research Report 212, *Mortality–Air Pollution Associations in Low Exposure Environments (MAPLE): Phase 2*, M. Brauer et al.

INTRODUCTION

Ambient air pollution is an important contributor to the global burden of disease (GBD 2020; HEI 2020). Although levels of air pollution have declined over the past 50 years in many high-income countries, several studies published in the last decade reported associations between risk of mortality and long-term exposure to particulate matter ≤ 2.5 μm in aerodynamic diameter (PM_{2.5}^{*}) at low concentrations (Beelen et al. 2014; Crouse et al. 2012, 2015; Hales et al. 2012; Pinault et al. 2016). To inform future risk assessment and regulation, it is important to confirm whether associations with adverse health effects continue to be observed as air pollution levels decline further. Determining the shape of the concentration–response curve at low concentrations is also key to identifying levels of exposure with minimal health risks. Thus, HEI initiated a research program on health effects at low concentrations.

In 2016, HEI funded three studies under Request for Applications (RFA) 14-3, *Assessing Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution*, to explore the health effects associated with exposures to low concentrations of air pollution using large cohorts and administrative databases (e.g., census, health insurance claims). Dr. Brauer's study, *Mortality–Air Pollution Associations in Low Exposure Environments (MAPLE)*, focused on a nationally representative cohort of approximately nine million people in Canada. Additional information about the RFA and the two other studies that were conducted in the United States and Europe is included in the Preface. It should be noted that all three study teams are conducting additional analyses to harmonize their approaches to the maximum extent possible. Through this

Dr. Michael Brauer's 4-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 April 2016. Total expenditures were \$2,065,564. The draft Phase 2 Investigators' Report from Brauer and colleagues was received for review in December 2020. A second revised report, received in October 2021, was accepted for publication in January 2022. 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.

This document has not been reviewed by public or private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views of these parties, and no endorsements by them should be inferred.

collaboration, the teams aim to (1) evaluate concentration–response thresholds, (2) share analytical techniques and identify common statistical methods (e.g., a common set of covariates across the studies), and (3) determine strengths, weaknesses, and common findings of the three studies. That work is expected to be completed in 2022.

The current MAPLE study is the second of two phases. In November 2019, HEI published *Research Report 203: Mortality–Air Pollution Associations in Low Exposure Environments (MAPLE): Phase 1*, along with a Commentary by HEI's Low-Exposure Epidemiology Studies Review Panel (Brauer et al. 2019). That Report and Commentary summarized and discussed analyses and findings produced through the first half of Dr. Brauer's study. The present Commentary focuses on the research and findings produced during the second phase, recognizing that this work builds on the Phase 1 analyses.

This Commentary was prepared by HEI's Low-Exposure Epidemiology Studies Review Panel, which was convened to review these three HEI-funded studies, and by members of HEI's Scientific Staff. The Commentary includes the scientific and regulatory background for the research, a summary of the study's approach and key results, and the Panel's evaluation of the Investigator's Report. This Commentary is intended to aid HEI sponsors and the public by highlighting the strengths and limitations of the study and by placing the Investigators' Report into scientific and regulatory context.

SCIENTIFIC AND REGULATORY BACKGROUND

Setting ambient air quality standards at levels considered adequate to protect public health is central to programs designed under the U.S. Clean Air Act, the European Union Ambient Air Quality Directives, and similar measures around the world. Although the process for setting such standards varies, 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 public health effects likely to be seen at various levels of the standards

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

- Identifying and setting standards based on risk assessments
- Monitoring air quality to identify areas that do not meet the standards
- Implementing air quality interventions to meet the standards by reducing the concentrations to which people are exposed

In September 2021, the World Health Organization (WHO) updated its 2005 Global Air Quality Guidelines after extensive research and deliberation. The new Air Quality Guidelines set ambitious targets for air pollutants of worldwide importance, including PM_{2.5}, nitrogen dioxide (NO₂), and ozone (O₃). Although the Air Quality Guidelines are not legally binding, they will influence air quality policy across the globe for years to come. The recommended limits for long-term exposure are as follows (WHO 2021):

- PM_{2.5}: annual mean of 5 µg/m³
- NO₂: annual mean of 10 µg/m³
- O₃: peak season 8-hour mean of 60 µg/m³

SETTING AIR QUALITY STANDARDS IN THE UNITED STATES

The U.S. Clean Air Act requires that in setting the National Ambient Air Quality Standards (NAAQS), the U.S. Environmental Protection Agency (U.S. EPA) Administrator reviews all available science and sets the NAAQS for all major (criteria) pollutants (e.g., particulate matter, NO₂, and O₃) at a level “requisite to protect the public health with an adequate margin of safety.” In practice, that review has had two principal steps:

1. Synthesis and evaluation of all available science in what is now called an Integrated Science Assessment. This document reviews the widest range of exposure, dosimetry, toxicological, mechanistic, clinical, and epidemiological evidence. It then—using a predetermined set of criteria (U.S. EPA 2015)—draws on all lines of evidence to determine whether the exposure is causal, likely to be causal, or suggestive of being causal 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 additional analysis draws on the Integrated Science Assessment to identify the strongest evidence—most often from human clinical and epidemiological studies—of the lowest concentrations at which health effects are observed, the likely implications of such concentrations for adverse health outcomes across the population, and the degree to which the newest evidence suggests that there are health effects observed below the then current NAAQS for a particular pollutant.

The Risk and Policy Assessment also examines the uncertainties around estimates of health effects and the shape of the concentration–response curve, especially at concentrations

near and below the then current NAAQS. Although a range of possible shapes for the curve is considered, including whether there is a threshold at a concentration below which effects are not likely, the U.S. EPA’s conclusions in these reviews thus far have not found evidence of such thresholds (although studies to date have not always had the statistical power to detect one) (U.S. EPA 2004, 2013). Also, although the standard is set under the Clean Air Act at “a level requisite to protect public health with an adequate margin of safety,” it has been understood that there are likely additional, albeit more uncertain, health effects of exposure to air pollution concentrations below the NAAQS.

Both documents are subjected to extensive public comments and review by the Clean Air Scientific Advisory Committee, which was established under the U.S. Clean Air Act. The Committee is charged with peer reviewing the documents, which includes advising the Administrator on the strength and uncertainties in the science and making the decision whether to retain or change the NAAQS. The current NAAQS for long-term exposure to PM_{2.5}, NO₂, and O₃ are as follows (<https://www.epa.gov/criteria-air-pollutants/naaqs-table>):

- PM_{2.5}: annual mean averaged over 3 years of 12 µg/m³
- NO₂: annual mean of 53 ppb (approximately 100 µg/m³)
- O₃: 3-year average peak season 8-hour mean of 70 ppb (approximately 140 µg/m³)

SETTING AIR QUALITY STANDARDS IN CANADA

Air quality policy in Canada is broadly directed by the Canadian Environmental Protection Act of 1999, a federal regulation that aims to prevent pollution and protect the environment and human health. However, multiple levels of government collectively share responsibility in developing specific policies and managing air pollution. They are led by the Canadian Council of Ministers of the Environment (CCME), an intergovernmental organization of Ministers from federal, provincial, and territorial governments (Health Canada 2016).

In 2012, the CCME collaborated with industry, nongovernmental, and Indigenous organizations to develop and implement an Air Quality Management System. As part of this system, new Canadian Ambient Air Quality Standards (CAAQS) replaced the older Canada Wide Standards for several ambient air pollutants. The CAAQS were adopted across Canada, except for Quebec, with decreasing target concentrations set for 2015, 2020, and 2025. Risk of adverse health effects is the primary consideration in setting CAAQS, but technology, economics, and societal concerns are also considered (Health Canada 2016). The current 2020 CAAQS for long-term exposure to PM_{2.5}, NO₂, and O₃ are as follows (CCME 2021):

- PM_{2.5}: annual mean averaged over 3 years of 8.8 µg/m³
- NO₂: annual mean of 17 ppb (approximately 33 µg/m³)

- O₃: 3-year average peak season 8-hour mean of 62 ppb (approximately 124 µg/m³)

Although CAAQS are nonlegally binding goals, air quality is actively managed. Local governments within individual *air zones* and regional *airsheds* monitor air quality with four management levels—green, yellow, orange, and red. Each level corresponds to increasing pollutant concentration targets up to the CAAQS at the red level. The four levels also have increasingly strict mitigation strategies, ranging from industrial and mobile emissions controls to individual consumer incentives, with the goal of discouraging emissions so ambient concentrations remain below the CAAQS (CCME 2021).

EVALUATING ASSOCIATIONS BELOW CURRENT AIR QUALITY STANDARDS AND GUIDELINES

As the quality and availability of data on air pollution concentrations improved over the first decade of this century, emerging research from Canada and New Zealand suggested that associations between PM and mortality could be observed down to concentrations well below the NAAQS of 12 µg/m³ (Crouse et al. 2012; Hales et al. 2012). Using standard statistical methods, these studies found robust associations, with some evidence of larger effects at the lowest concentrations of PM_{2.5}. However, neither study examined associations with NO₂ or O₃ exposure, and some potential individual-level confounding variables were unavailable. If replicated in other populations and by other investigators, such findings could change the basis for future determinations of the levels to set the NAAQS and other air quality standards.

At the same time, the findings of these previous studies from Canada and New Zealand suggested several questions:

- Would the results be robust to the application of more sophisticated statistical methods, including nonlinear and causal inference models?
- Could other important determinants of population health not accounted for in prior studies—including lifestyle factors such as smoking, health status, access to medical care, and differences in air pollution sources and time–activity patterns—modify or confound the associations?
- What might be the effects of co-occurring pollutants on health effect associations at low ambient concentrations?

As described in the Preface, these important questions were the basis for RFA 14–3. After a rigorous selection process, the Research Committee recommended the study by Brauer and colleagues for funding because it used a large representative sample of the Canadian population, aimed to develop new methods for concentration–response modeling in health assessments, and built on prior work by an experienced research team.

SUMMARY OF APPROACH AND METHODS

The overall objective of the MAPLE study was to characterize the relationship between long-term exposure to low ambient concentrations of PM_{2.5} and nonaccidental mortality in a representative sample of the adult Canadian population. The investigators developed fine-scale satellite-based PM_{2.5} exposure estimates for North America from 1981 to 2016. They then applied epidemiological analyses to estimate the shape of the concentration–response relationship and the lowest PM_{2.5} concentration of detectable health effects. Here we describe the overall approach and methods of the MAPLE study.

STUDY OBJECTIVES

To estimate ambient PM_{2.5} concentrations, the investigators proposed to

1. Develop and apply annual average satellite-derived PM_{2.5} estimates for North America at 1 km × 1 km spatial resolution for years 2000–2016
2. Evaluate PM_{2.5} estimates using insight gained from comparisons of colocated measurements of PM_{2.5} and aerosol optical depth (AOD) with chemical transport model (GEOS–Chem) simulations of that relationship
3. Use a combination of geophysical and statistical methods, together with land use information, to further refine the above PM_{2.5} estimates
4. Use available PM_{2.5}, PM₁₀, and total suspended PM monitoring data in Canada from 1981–1999, to scale the 1 km × 1 km exposure estimates back in time annually from 1981–1999 and produce high-resolution exposure estimates over the entire 1981–2016 study period
5. Make the above refined PM_{2.5} estimates available to other studies that cover Canada and the United States for incorporation into their analyses

To examine the concentration–response relationship between PM_{2.5} exposure and risk of nonaccidental mortality, investigators proposed to:

1. Use five cohorts linked to mortality, vital statistics, and tax records through December 31, 2016
 - a. Three Canadian Census Health and Environment Cohort (CanCHEC) cycles (1991, 1996, and 2001)
 - b. A CanCHEC cohort combining all three cycles
 - c. A pooled Canadian Community Health Survey (CCHS) cohort that contained detailed information on health behaviors
2. Examine the shape of the association between long-term exposure to ambient concentrations of PM_{2.5} and mortality in all five cohorts by using
 - a. Restricted cubic splines (RCS)
 - b. A standard threshold approach

- c. An extended version of the Shape Constrained Health Impact Functions (SCHIF) to identify the lowest concentration for which there is evidence of a positive association with mortality

The study was completed in two phases, with the Phase 1 Report (Brauer et al. 2019) providing interim results to inform ongoing review of the NAAQS for $PM_{2.5}$. In Phase 2, the investigators refined some of their methods, tackled additional aspects of the analysis, and omitted methods shown to be insufficiently robust during Phase 1 (Commentary Table).

METHODS AND STUDY DESIGN

Study Population

The investigators used a nationally representative sample of the adult Canadian population, ages 25–89 years, and followed them for up to 25 years. They created four census-based

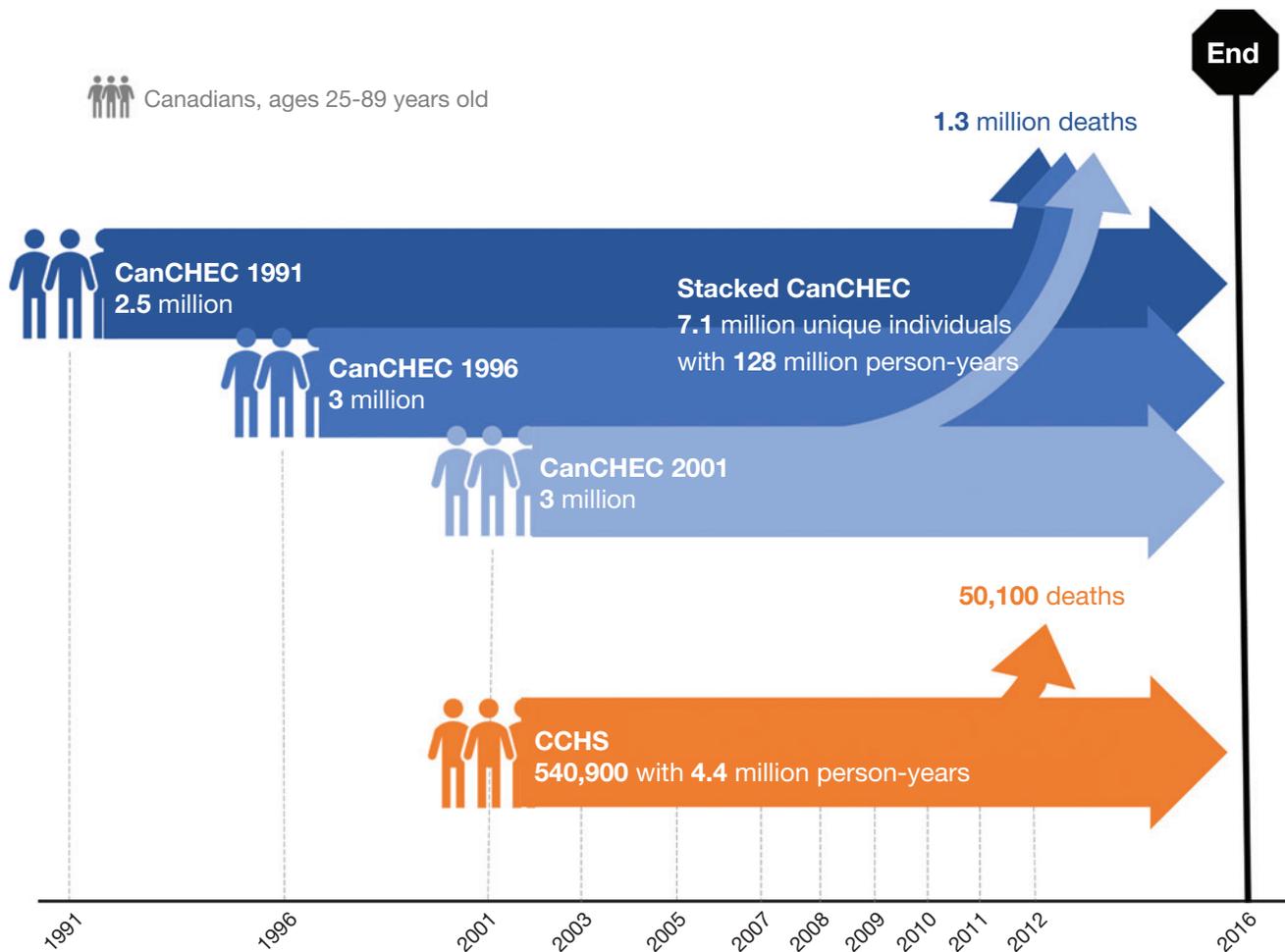
cohorts and one survey-based cohort, including approximately 7.6 million people, and recorded nearly 1.4 million deaths (Commentary Figure 1). Three CanCHEC cohorts comprised randomly selected participants who completed the mandatory long-form census. This census contains detailed individual-level sociodemographic information, such as education, income, and ethnicity. A Stacked CanCHEC cohort merged all CanCHEC cycles into a single cohort with duplicate respondents removed. The survey-based CCHS cohort comprised randomly selected participants to complete one of the CCHS health surveys between 2001 and 2012. In addition to the sociodemographic information in CanCHEC, the CCHS includes information on health status and behaviors such as smoking.

Survey data were linked to Statistics Canada's Social Data Linkage Environment from survey date through December 31, 2016, which provided residential histories via annual tax records and dates and causes of death. Participants were

Commentary Table. Analytic Approaches in the MAPLE Study

	Phase 1	Phase 2
Use of CanCHEC Cohorts for Overall Analysis	Cohort-specific analyses and meta-analyses	Cohort-specific and pooled cohort analyses with duplicates removed (see Commentary Figure 1)
Linking CanCHEC and CCHS Participants to Death Records	Probabilistic and deterministic linkage	Deterministic only linkage
$PM_{2.5}$ Exposure Modeling	Developed a high-resolution exposure model using single daily satellite observations	Improved the model with multiple daily satellite observations and colocated ground measurements
$PM_{2.5}$ Exposure Windows and Lag Time	1-, 3-, and 8-year moving average with a 1-year lag	10-year moving average with a 1-year lag based on analysis showing larger effect estimates for longer moving averages
$PM_{2.5}$ Exposure Assignment for Person-Years with Missing Postal Codes	Imputed as the national population-weighted average exposure	Imputed based on the population-weighted average exposure from nearby postal codes
Covariate Adjustment	Directed Acyclic Graph informed (group-level covariates only), fully adjusted (included group- and individual-level covariates), and indirectly adjusted for health behaviors	Fully adjusted only
Evaluation of the Concentration-Response Shape	RCS, SCHIF	RCS, extended SCHIF, and threshold
Copollutant Analysis	Linear HR models adjusted for NO_2 , O_3 , and O_x	Linear HR models adjusted for O_3 and O_x , stratified by O_3 and O_x tertiles and nonlinear model adjustment for linear O_3 and O_x
Additional Sensitivity Analyses	With and without immigrants included	Exclusion of person-years with $PM_{2.5}$ exposure >U.S. and Canadian air quality standards, and mortality risk by regional airshed

O_x = gaseous pollutant oxidant capacity.



Commentary Figure 1. MAPLE study cohorts. The five cohorts included CanCHEC 1991, CanCHEC 1996, CanCHEC 2001, Stacked CanCHEC, and CCHS. The Stacked CanCHEC and CCHS cohorts included groups of respondents that entered the study in different census or survey years (dashed lines). Participants were followed until death or the end of the study.

excluded if they had immigrated less than 10 years prior, turned 90 years old during follow-up, or had no recorded postal code with which to assign exposure. Due to these exclusions and the noninstitutionalized representation of CanCHEC, the study sample was slightly healthier than Canada's general population as evidenced by lower mortality rates, particularly for older individuals (Tjepkema et al. 2019). All data linkages and analyses were conducted at Statistics Canada's secure Research Data Centers by approved researchers with government security clearance.

Exposure Assessment

$PM_{2.5}$ Model Brauer and colleagues developed high resolution (1 km²) annual average ambient $PM_{2.5}$ concentration estimates for North America for 1981 to 2016. The method combined remote sensing of AOD with the GEOS-Chem

chemical transport model, land use information, and ground-monitoring data. First, multiple daily satellite measurements of AOD from the moderate resolution imaging spectroradiometer (MODIS) were inversely weighted by error, then converted to geophysical $PM_{2.5}$ concentrations using GEOS-Chem model simulations (van Donkelaar et al. 2019). To evaluate the conversion in regions of low $PM_{2.5}$ concentrations, the investigators collected colocated ground measurements of $PM_{2.5}$, aerosol scatter, and AOD at five sites (in five different airsheds) with low concentrations of air pollution across Canada. Sites included Halifax, Nova Scotia; Sherbrooke, Quebec; Downsview, Ontario; Lethbridge, Alberta; and Kelowna, British Columbia, and were added to the Surface Particulate Matter Network (SPARTAN).

Next, they used geographically weighted regression to merge the satellite-derived geophysical estimates with average monthly ground monitoring measurements (Canadian

National Air Pollution Surveillance and U.S. EPA Air Quality System Data Mart) to produce hybrid PM_{2.5} estimates for the years 2000 through 2016. Because few AOD data exist before 2000, the investigators used historic ground measurements of PM_{2.5}, PM₁₀, and total suspended PM to *backcast*, or simulate, satellite-based estimates from 1981 through 1999 (Meng et al. 2019).

Copollutant Models To estimate the effect of PM_{2.5} on mortality in the presence of important copollutants, the investigators estimated ambient NO₂, O₃, and gaseous pollutant oxidant capacity (O_x) concentrations. One hundred m²-resolution NO₂ concentrations for 2006 were previously derived via land use regression modeling that incorporated ground monitoring, satellite (10 km²), and land use data (Hystad et al. 2011). Warm season (May–September) 8-hour daily maximum O₃ concentrations were estimated using chemical transport modeling of monitoring data at spatial resolutions of 21 km² (2002–2009) and 10 km² (2010–2015) (Pappin et al. 2019; Robichaud and Ménard 2014; Robichaud et al. 2016). NO₂ and O₃ concentrations were backcasted to all study years using time-series analysis of ground monitoring measurements obtained in 24 large cities (Weichenthal et al. 2017). O_x was calculated as a weighted average of O₃ and NO₂ following a formula used by Weichenthal and colleagues (2017).

Exposure Assignment For each study year (1981–2016), individual residential, geocoded postal codes were assigned to the nearest 1 km² grid of estimated ambient concentration of PM_{2.5}. NO₂ and O₃ exposure was assigned to postal codes based on the geographically nearest time-series data point. Brauer and colleagues accounted for changes in postal codes over time and for residential mobility. Exposure assignment to urban postal codes provided locational accuracy within about 150 meters, whereas greater uncertainty existed when assigning exposure to rural postal codes, which are accurate within a 1–5 kilometer range (Khan et al. 2018). Missing postal codes were imputed for 2.1% of the person-years, with exposure assigned based on the population-weighted average of postal codes that had at least two characters in common with the postal codes of adjacent nonmissing person-years. To assess long-term exposure, the investigators used a 10-year moving average with a 1-year lag. The lag ensured that exposure temporally preceded recorded deaths.

Health Assessment

Associations with Mortality To assess PM_{2.5} exposure with the rate of nonaccidental total- and cause-specific mortality, the investigators conducted Cox proportional hazards regression on all five cohorts. This linear modeling method calculates a hazard ratio (HR), which describes the risk of mortality associated with PM_{2.5} exposure, compared with the

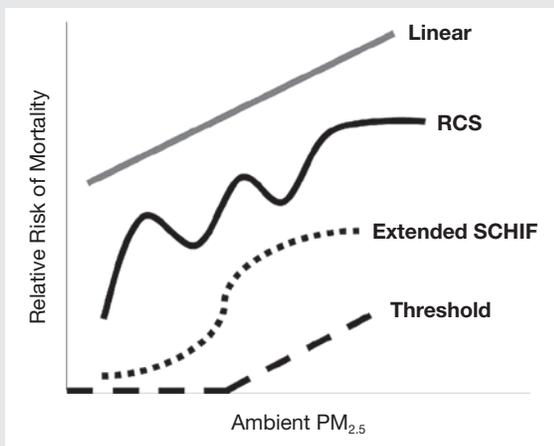
baseline risk in the study population, while controlling for potential individual- and area-level confounding characteristics. In this Commentary, HRs were reported per interquartile range (IQR), or 75th versus 25th percentile, increase in PM_{2.5} exposure with 95% confidence intervals (CI). Person-years before the census and after year of death were excluded from the analysis.

Cause-specific outcomes were selected partly based on similar studies (e.g., Global Burden of Disease project) to facilitate comparison and determined using International Classification of Disease, 10th edition (ICD–10) codes. Selected outcomes were cardiovascular mortality, cerebrovascular mortality, heart failure, ischemic heart disease, diabetes (types 1 and 2), nonmalignant respiratory disease, chronic obstructive pulmonary disease (COPD), pneumonia, lung cancer, and kidney failure. Models were adjusted for numerous individual-level variables (e.g., income, minority [not white], Indigenous identity, education, marital status, employment, and occupation) and community-level variables (community size, airshed, urban form, and four Canadian Marginalization Index dimensions). Models were stratified by 5-year age groups, sex, and immigrant status. Analyses of the CCHS cohort were further adjusted for individual-level health behavior variables (smoking, alcohol consumption, fruit and vegetable consumption, body mass index, and exercise behavior). Given the multiple years that participants could enter the Stacked CanCHEC and CCHS cohorts, analyses of these were also stratified by census or survey year.

Concentration–Response Function To examine the shape of the association, and to identify the lowest PM_{2.5} concentration at which a positive association with mortality was observed, Brauer and colleagues applied three nonlinear modeling approaches—RCS, extended SCHIF, and standard threshold (see Sidebar). In RCS modeling (Harrell 2015), the investigators tested 3 to 18 knots (i.e., 16 models) and selected the model with the lowest Bayesian Information Criterion, a measure of fit. Next, the investigators applied a novel extension of the SCHIF model (Burnett et al. 2018; Nasari et al. 2016), which they deemed more suitable for health impact assessments. For the RCS and extended SCHIF, the HR was fixed to one (e.g., no association) at the minimum PM_{2.5} concentration of 2.5 µg/m³, meaning that the risk of mortality associated with all higher concentrations was compared with the risk at the minimum concentration. The 95% CIs for RCS and extended SCHIF were computed to reflect the uncertainty in high- and low-level exposure estimates relative to the mean PM_{2.5} concentration, becoming wider as PM_{2.5} concentrations deviated from the mean. Finally, the standard threshold model was applied to identify levels of exposure with no detectible health effects. They evaluated threshold values ranging from 2.5 to 10 µg/m³ and identified the most probable thresholds using a weighted

Modeling the Shape of the Concentration–Response Function

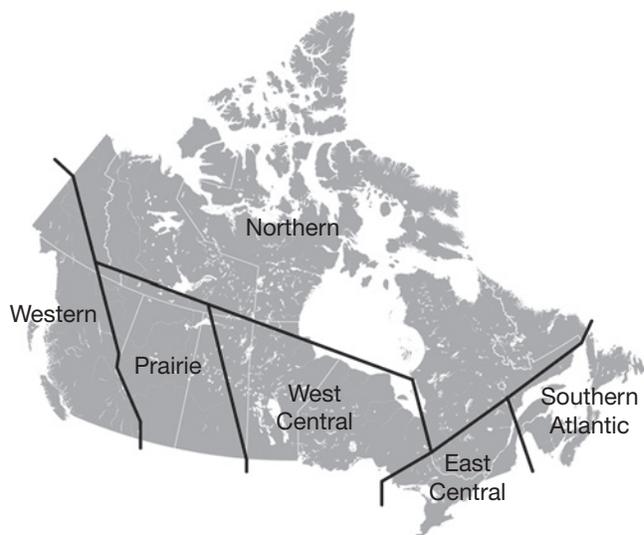
Brauer and colleagues used three nonlinear modeling approaches to evaluate the shape of the association between ambient $PM_{2.5}$ exposure and nonaccidental mortality. Unlike a *linear* model where the change in risk of mortality for a unit increase in $PM_{2.5}$ is constant across all exposure concentrations, nonlinear models allow the association to fluctuate. Allowing fluctuation is important because many biological responses to toxicants do not follow a linear relationship outside of narrow concentration ranges (Klassen 2019). The Sidebar Figure shows hypothetical example curves derived from the models described here.



- **RCS** allows for highly complex curves. Splines represent smoothly connected piecewise polynomials and take on different shapes over different intervals of $PM_{2.5}$ exposure; they are connected by knots, or points where the curve changes shape. A disadvantage of RCS is that the curve can become so complex that it is biologically implausible or exceedingly difficult to interpret.
- The **extended SCHIF** incorporates RCS predictions, but places constraints on the shape so that it is consistent with known biological concentration–response curves. Therefore, error-prone data that produce highly complex, or wiggly, RCS curves would be smoothed into a near-linear, sublinear (e.g., U-shaped), supralinear (e.g., inverted U-shaped), sigmoidal (e.g., S-shaped), or simpler non-monotonic (e.g., areas of decreasing response) curve. This approach ensures that public health risks can be interpreted and communicated.
- **Threshold** models assume that there is a level of $PM_{2.5}$ exposure between 0 and the threshold value where mortality is not affected. Above the threshold value, $PM_{2.5}$ is associated with mortality and the concentration–response curve can take on a variety of shapes. The MAPLE study applied a linear model beyond the threshold. These models are commonly used in toxicology (and pharmacology) where a specific concentration of toxicant (or drug) is required to elicit a target effect.

ensemble method. Under all three modeling scenarios, they reported the lowest $PM_{2.5}$ concentration for which the HR 95% CI lower limit was greater than or equal to one; this concentration was defined as the lowest concentration with observed adverse health effects.

Sensitivity Analyses The investigators assessed the association between $PM_{2.5}$ and mortality and restricted the analysis to person-years with <10 and $<12 \mu\text{g}/\text{m}^3$ of exposure to evaluate whether the association persisted below these concentrations. The cutoff value of $10 \mu\text{g}/\text{m}^3$ corresponded to the CAAQS and WHO Air Quality Guidelines prior to 2020 and 2021, respectively. The cutoff value of $12 \mu\text{g}/\text{m}^3$ corresponded to the current U.S. NAAQS. They also examined associations controlling for, and stratified by tertiles of, copollutants O_3 and O_x . Finally, they examined the association and shape of the concentration–response function across six geographic regions with distinct atmospheric conditions known as airsheds: Northern, Western, Prairie, West Central, East Central, and Southern Atlantic (Commentary Figure 2). Population density is highest in the East Central, and lowest in the West Central and Northern airsheds.



Commentary Figure 2. Airsheds of Canada. The associations between $PM_{2.5}$ and mortality were also examined by airshed because regional geographical features and weather conditions influence ambient air quality.

SUMMARY OF FINDINGS

EXPOSURE ESTIMATION RESULTS

Between 1981 and 2015, average annual $PM_{2.5}$ concentrations ranged from 8 to 16 $\mu\text{g}/\text{m}^3$ in Canada's largest cities, but only from 2 to 6 $\mu\text{g}/\text{m}^3$ in rural areas. The highest annual $PM_{2.5}$ concentration, 18 $\mu\text{g}/\text{m}^3$, was observed in the cities of Toronto, Hamilton, Quebec, and Vancouver between 1981 and 1990. Over the next 25 years, $PM_{2.5}$ concentrations declined. For example, in the Stacked CanCHEC cohort, the 10-year average assigned exposure was 12.2 $\mu\text{g}/\text{m}^3$ in 1991, but just 6.8 $\mu\text{g}/\text{m}^3$ in 2016. Similarly, the average assigned exposure for CanCHEC 1991, 1996, and 2001, and CCHS were 9.0, 8.3, 7.7, and 6.8 $\mu\text{g}/\text{m}^3$, respectively. The highest and lowest assigned exposure concentrations for the Stacked CanCHEC overall were 17.7 and 2.5 $\mu\text{g}/\text{m}^3$, respectively, with similar high and low concentrations among all individual cohorts (see Investigators' Report Table 4 for complete descriptive statistics).

The chemical composition of $PM_{2.5}$ varied widely across the colocated sampling sites in the five different regional airsheds. The $PM_{2.5}$ composition variability reflected differences in natural and anthropogenic sources of PM. O_3 and O_x concentrations also varied by regional airshed and were highest in southern areas. Compared with Phase 1, Brauer and colleagues noted improved performance using the refined Phase 2 exposure models. For example, when comparing $PM_{2.5}$ concentrations estimated from the model with those measured at ground monitors across the North America, a higher R^2 (0.81 vs. 0.71) and lower root mean square deviation (1.5 vs. 1.9 $\mu\text{g}/\text{m}^3$) were achieved in Phase 2.

HEALTH ASSESSMENT RESULTS

$PM_{2.5}$ was Associated with Increased Mortality in Linear Models Ambient long-term $PM_{2.5}$ exposure was associated with increased nonaccidental mortality. The investigators observed similar results across all five cohorts. In the CCHS cohort, adjustment for individual-level health behaviors elicited similar, but attenuated associations. The investigators theorized that after adjusting for the numerous individual- and community-level variables, health behaviors might not be important confounders at the low $PM_{2.5}$ exposure concentrations observed in this study population. Therefore, health assessment results presented here will focus primarily on the Stacked CanCHEC cohort given that it had the largest sample size and longest follow-up.

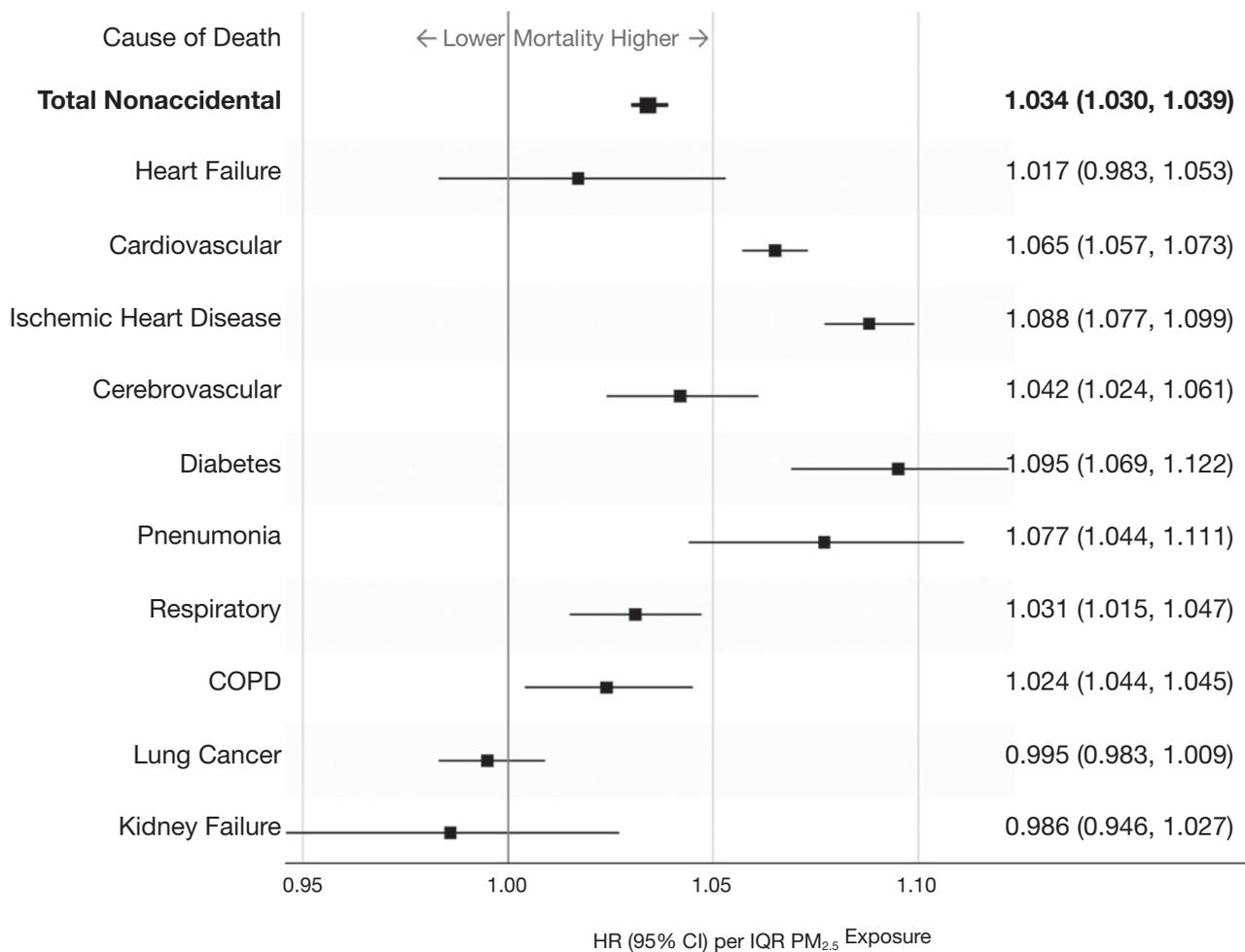
In the Stacked CanCHEC cohort an IQR increase (4.16 $\mu\text{g}/\text{m}^3$) in $PM_{2.5}$ exposure was associated with a 3% rise in the total nonaccidental mortality rate (HR per IQR: 1.034; 95% CI: 1.030–1.039) (Commentary Figure 3). When scaled to the average annual total nonaccidental mortality rate over the entire 25-year study period (1991–2016), this HR corresponded to

about 32 additional deaths for every 100,000 people each year with a 4.16- $\mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ exposure. In reference to the 2016 Canadian population, this was equivalent to 7,848 additional deaths annually. In cause-specific analyses, ambient long-term $PM_{2.5}$ exposure was associated with increased mortality due to cardiovascular, ischemic heart, and cerebrovascular diseases, diabetes, pneumonia, respiratory disease, and COPD (Commentary Figure 3), with the largest association for diabetes. The associations with kidney failure and lung cancer were consistent with the null; these two causes of death were less common in the population. The association with heart failure was also consistent with the null given the confidence interval.

Nonlinear Concentration–Response Function The RCS models suggested that the shape of the association between $PM_{2.5}$ and total nonaccidental mortality was nonlinear, with a statistically significantly better fit than the linear model. In the Stacked CanCHEC cohort the RCS with 9 knots was selected and showed that the relative risk of mortality increased rapidly with increasing $PM_{2.5}$ concentration from the minimum observed concentration of 2.5 until about 5 $\mu\text{g}/\text{m}^3$, plateaued with undulations to about 8 $\mu\text{g}/\text{m}^3$, and increased again at higher concentrations (Commentary Figure 4). In other words, although the HR (e.g., a single point on the curve) is generally higher for any given higher concentration of $PM_{2.5}$ when compared with the minimum exposure, the largest increases in the HR (e.g., change in the curve) occurs at lower concentration ranges. In the RCS curve, the lowest $PM_{2.5}$ concentration for which the 95% CI lower limit of the HR was ≥ 1 was 2.8 $\mu\text{g}/\text{m}^3$.

The extended SCHIF model showed a similar but smoothed concentration–response curve compared with the RCS in the Stacked CanCHEC cohort, demonstrating a rapid increase from $PM_{2.5}$ of 2.5 to 5 $\mu\text{g}/\text{m}^3$, and then increasing approximately linearly at an intermediate rate thereafter (Commentary Figure 4). Results for the threshold analysis in the Stacked CanCHEC were not conclusive. Specifically, the HR was greater than one even at the lowest level exposure of 2.5 $\mu\text{g}/\text{m}^3$, but the 95% CI lower limit did not exceed one until a threshold of 8 $\mu\text{g}/\text{m}^3$ was reached. Above 8 $\mu\text{g}/\text{m}^3$, the slope was steeper for the threshold model compared with the RCS and extended SCHIF. Model fit (using the likelihood statistic) was equal for models with thresholds of 2.5 and 8 $\mu\text{g}/\text{m}^3$, and all threshold models demonstrated inferior fit compared with the RCS model. Overall, the three nonlinear modeling approaches all suggested that there may be no safe level of $PM_{2.5}$ exposure given the minimum observed exposure concentration in this study of 2.5 $\mu\text{g}/\text{m}^3$.

Cause-specific analyses of the concentration–response curve in the Stacked CanCHEC cohort using RCS generally showed increased risk of mortality across the observed $PM_{2.5}$ concentration ranges (see Investigators' Report Figure 16). However, this was not the case for heart failure, lung cancer, or diabetes. The concentration–response curve for heart



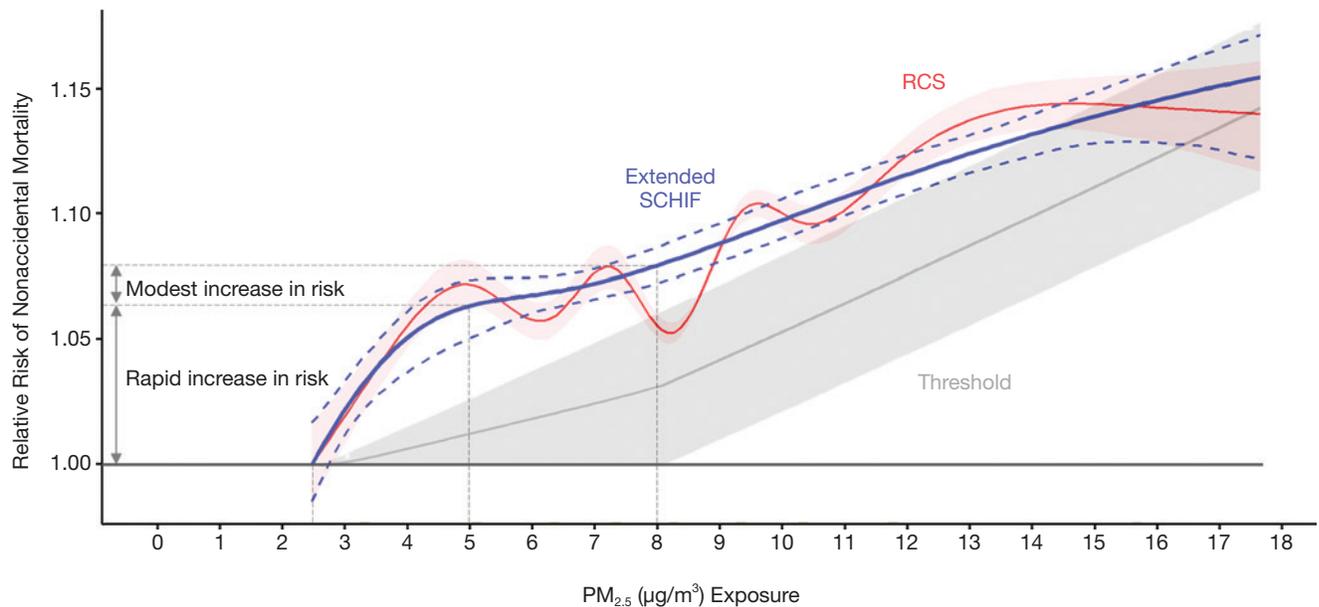
Commentary Figure 3. Ambient PM_{2.5} exposure and nonaccidental mortality in the Stacked CanCHEC cohort. Ambient PM_{2.5} exposure with a 10-year moving average and 1-year lag was associated with higher total nonaccidental and select cause-specific mortality rates using a linear model and controlling for individual- and community-level sociodemographic variables.

failure hovered near the null, and for lung cancer showed an increased risk until a peak at 8 $\mu\text{g}/\text{m}^3$, and then decreased. The concentration–response curve for diabetes demonstrated a decreased risk until 8 $\mu\text{g}/\text{m}^3$, and then increased.

Associations Below U.S. NAAQS When restricting the analyses of the Stacked CanCHEC to person-years with exposure below the U.S. NAAQS for annual average PM_{2.5} exposure of 12 $\mu\text{g}/\text{m}^3$, similar results were observed when compared with the full cohort. Specifically, the linear model showed that PM_{2.5} exposure was associated with total nonaccidental mortality, although the HR was slightly smaller compared with the full cohort. The concentration–response curve using RCS showed a nearly identical relative risk of mortality with the full cohort for PM_{2.5} concentrations from 2.5 to 8 $\mu\text{g}/\text{m}^3$, and a slightly lower relative risk through <12 $\mu\text{g}/\text{m}^3$ (see Investigators' Report Table 19 and Figure 25). However, when restricting the analyses of the Stacked CanCHEC to person-years with

exposure below the previous CAAQS of 10 $\mu\text{g}/\text{m}^3$, PM_{2.5} was not significantly associated with total nonaccidental mortality. The concentration–response curve using RCS showed a similar rapid increase in the relative risk of mortality for PM_{2.5} concentrations from 2.5 to 4 $\mu\text{g}/\text{m}^3$, but no further increased relative risk from 4 to <10 $\mu\text{g}/\text{m}^3$. The investigators suggested that higher PM_{2.5} concentrations contributed to the observed positive associations with mortality. They also noted that the interpretation of these results was challenging because the restrictions compromised the representativeness of the cohorts. Specifically, the <12 and <10 cutoffs excluded 13% and 30% of person-years and 10% and 28% of deaths, respectively. Therefore, these restricted cohorts were not representative of the original Stacked CanCHEC and thus not representative of the Canadian adult population.

Copollutants Weaken the Association Inclusion of copollutants O₃ or O_x in two-pollutant models with PM_{2.5} weakened



Commentary Figure 4. Concentration–response curves for ambient $PM_{2.5}$ exposure and relative risk of nonaccidental mortality in the Stacked CanCHEC cohort. The RCS and extended SCHIF 95% CIs are wider at low and high $PM_{2.5}$ levels to reflect greater uncertainty in the hazard ratio at these levels of exposure relative to the mean concentration. (Adapted from Investigators' Report Figures 20 and 29.)

the associations between $PM_{2.5}$ exposure and total nonaccidental mortality in the Stacked CanCHEC cohort (O_3 -adjusted HR per IQR: 1.016; 95% CI: 1.011–1.021; O_x -adjusted HR per IQR: 1.096; 95% CI: 1.091–1.101). Two-pollutant nonlinear models that included O_3 or O_x flattened the concentration–response curves for $PM_{2.5}$ exposure and total nonaccidental mortality in the Stacked CanCHEC cohort.

Airsheds and Copollutants Modify the Association Analyses of different regional airsheds across Canada revealed considerable variation in the association and shape of the concentration–response curve by place. In the Stacked CanCHEC, $PM_{2.5}$ concentration–response curves using RCS for the East Central, Southern Atlantic, Western, and Northern airsheds varied in shape but generally showed increases in total nonaccidental mortality across $PM_{2.5}$ concentrations. In contrast, the Prairie and West Central airsheds showed minimal increased mortality for $PM_{2.5}$ concentrations from 2.5 to 5 $\mu g/m^3$ and then an inverse association with mortality for $PM_{2.5}$ concentrations from 5 to 8 $\mu g/m^3$ (see Investigators' Report Table 16 and Figure 21). Further sensitivity analyses that adjusted for proximity to healthcare resources or excluded immigrants, Indigenous people, or older age groups suggested that the variation was not due to differences in population characteristics or healthcare access by regional airshed. Instead, Brauer and colleagues hypothesized that the regional variation in the $PM_{2.5}$ –mortality relationship could be due to differences in PM chemical composition and pollutant mixtures, including copollutants O_3 and O_x , which are known

to vary over space and time. In addition, stratified analyses found larger associations between $PM_{2.5}$ and nonaccidental mortality in the highest O_3 or O_x exposure terciles. As such, they recommended that future studies evaluate interactions between mixtures of $PM_{2.5}$ chemical constituents and $PM_{2.5}$ with other copollutants.

EVALUATION BY THE HEI LOW-EXPOSURE EPIDEMIOLOGY STUDIES REVIEW PANEL

EVALUATION OF STUDY DESIGN AND APPROACH

The MAPLE Study examined whether long-term low-level air pollution exposure was associated with nonaccidental death among five population-based cohorts comprising 7.6 million Canadian adults. The investigators combined information from satellites, ground monitors, and models to estimate fine-scale $PM_{2.5}$ concentrations across Canada between 1981 and 2016. They assigned 10-year moving average exposure with a 1-year lag using complete residential histories and followed people for up to 25 years. Long-term $PM_{2.5}$ exposure was associated with increased risk of total nonaccidental mortality, including deaths caused by several cardiovascular and respiratory-related diseases and by diabetes. The MAPLE cohort included 20% of noninstitutionalized adults and was geographically representative of the Canadian population. Overall, the collection and analysis of such high-quality and comprehensive data over more than two decades was a major accomplishment.

This study addressed important research gaps in understanding the health effects of low-level ambient air pollution. Regulators want to know whether tightening PM_{2.5} standards below current levels might benefit public health. The U.S. EPA's 2019 Integrated Science Assessment asserted that the scientific evidence supported a nonthreshold, linear association between PM_{2.5} and adverse health effects, with limited and uncertain evidence of a supralinear shape at lower PM_{2.5} concentrations (U.S. EPA 2019). Consequently, the U.S. EPA invited information on the shape of the concentration–response curve, particularly at concentrations below 8 µg/m³. Because Canada boasts some of the cleanest ambient air quality globally with a large proportion of the population who experience low exposures (HEI 2017), it was an ideal setting to address these research questions. Indeed, half of all person-years in the Stacked CanCHEC cohort were estimated to have PM_{2.5} exposures at concentrations less than 8.26 µg/m³ averaged over the entire study period, and a quarter were below 6.26 µg/m³. These exposures were lower than those seen in most prior studies (Chen and Hoek 2020), enabling Brauer and colleagues to evaluate the lower end of the concentration–response curve.

Evaluation of Air Pollution Models and Exposure Estimation

The investigators developed highly detailed PM_{2.5} exposure models that incorporated information from ensemble satellite measurements, atmospheric modeling, government and supplemental ground monitor measurements, and land use. Phase 2 refinements to the exposure models demonstrably improved the exposure estimation. Although the investigators incorporated new colocated measurements at five sites with lower ambient air pollution, data remained sparse across rural, less polluted areas. The Panel appreciated that the investigators acknowledged this potential measurement error given the MAPLE study's emphasis on capturing low PM_{2.5} exposure concentrations. Favorably, the epidemiological analyses were weighted more toward highly populated areas in cities and near the U.S. border with less exposure measurement error. Yet it is uncertain how exposure measurement error may have affected analyses that focused on the lower observed exposure ranges, particularly in mostly rural regional airsheds with no major cities.

Evaluation of Epidemiological Analysis

A major strength of this study was the thorough epidemiological analysis. The analysis of the concentration–response curve was impressive, using three different nonlinear modeling techniques. The investigators assessed cause-specific mortality, adjusted for copollutants O₃ and O_x, and analyzed findings by regional airshed. They also conducted sensitivity analyses that restricted the cohort to people with PM_{2.5} exposures below the current U.S. and former Canadian standards of 12 and 10 µg/m³, respectively. Analyses were applied to

the five cohorts, allowing them to compare results across different time periods, length of follow-up, and with different covariate adjustments.

Although all methods consistently showed associations of increased mortality with greater PM_{2.5} levels, the Panel was unclear about how to interpret findings from some of the statistical methods, including the lowest PM_{2.5} concentration at which the lower confidence limit of the HR was greater than or equal to one, and uncertainty estimates for the extended SCHIF. For the former, it is unclear how statistically appropriate and robust this approach is for estimating a potential threshold, as discussed further below. For the latter, the RCS simulations used as input for the extended SCHIF model were not clearly frequentist or Bayesian, thus the statistical properties of the uncertainty estimates and how they relate to standard approaches is unclear. Further details on the rationale and limitations of these methods would have improved the report. Despite this, the standard statistical approaches that were used reached similar substantive conclusions.

DISCUSSION OF THE FINDINGS AND INTERPRETATION

Brauer and colleagues found that long-term low-level ambient PM_{2.5} exposures averaged over ten years, with a 1-year lag were associated with an increased risk of total nonaccidental mortality, as well as for several specific causes. The increased risk for total, respiratory-, and cardiovascular-related mortality is consistent with a recent meta-analysis (Chen and Hoek 2020), and the increased risk for diabetes mortality was recently reported in large U.S.-based cohort studies (Bowe et al. 2019; Lim et al. 2018). However, the lack of an association between PM_{2.5} and lung cancer conflicts with prior research that demonstrated relatively consistent positive associations (Ciabattini et al. 2021; Pope et al. 2002).

Shape of the Concentration–Response Function

The investigators observed a rapid increase in mortality risk for person-years exposed to long-term PM_{2.5} concentrations between 2.5 µg/m³ and 5 µg/m³ in both the RCS and extended SCHIF curves. Between PM_{2.5} concentrations of 5 and 8 µg/m³, the RCS concentration–response curve demonstrated only a modest increase in the mortality risk where the slope of the curve was shallower. Mortality risk increased at an intermediate rate and was approximately linear for the RCS and extended SCHIF models above 8 and 5 µg/m³, respectively. The supralinear curve at low concentrations and near linearity at higher concentrations is consistent with concentration–response curves estimated in a recent study of over 325,000 Europeans with average PM_{2.5} exposures below 25 µg/m³ (Brunekreef et al. 2021; Strafoggia et al. 2022; Strak et al. 2021) and in a study that combined

41 cohorts with varying levels of exposure from across the globe (Burnett et al. 2018).

The immediate rise in mortality risk from the minimum $PM_{2.5}$ concentration of $2.5 \mu\text{g}/\text{m}^3$ suggests that there is no threshold for adverse health effects given the observed data. This is consistent with the investigators' threshold model analysis in which a conclusive threshold value could not be determined. The investigators approximated a threshold value by reporting the $PM_{2.5}$ concentration ($2.8 \mu\text{g}/\text{m}^3$) at which the 95% CI lower limit exceeded one in the RCS curve. However, the Panel was unclear on how to interpret this metric. The approach as implemented does not account for the uncertainty in the HR at the minimum exposure concentration. Therefore, it does not estimate the uncertainty for the difference in the mortality risk at a given exposure concentration compared with the minimum exposure concentration, thereby preventing a robust statistical assessment with regard to the presence of a threshold. The absence of evidence for a threshold is consistent with most prior studies that evaluated thresholds (Chen and Hoek 2020). This reinforces that we currently have no evidence of a $PM_{2.5}$ concentration below which there is no association with health effects. Further, the investigators' health impact analysis projected that $PM_{2.5}$ reductions within the 2.5 to $5 \mu\text{g}/\text{m}^3$ range would benefit the largest proportion of the sample population. Overall, evidence from this study supports the 2021 WHO Air Quality Guidelines of $5 \mu\text{g}/\text{m}^3$ and suggests that achieving ambient $PM_{2.5}$ concentrations below $5 \mu\text{g}/\text{m}^3$ where the curve demonstrates supralinearity could prevent premature mortality.

The segment of the RCS concentration–response curve in the middle $PM_{2.5}$ concentration range between 5 and $8 \mu\text{g}/\text{m}^3$ demonstrated a shallower slope relative to segments of the curve in lower and higher concentration ranges. The RCS curve also demonstrated up-and-down undulations in this middle concentration range. These results imply that incremental reductions within this middle range may not yield substantial health benefits. However, this segment of the RCS curve must be interpreted cautiously due to its inconsistency with prior evidence and lack of biological plausibility. The investigators concluded that the undulations in the RCS curves were partly due to the large sample size which statistically favored many knots, resulting in an RCS curve that is likely under-smoothed relative to the true unknown curve. Due to different results for the individual cohorts, which can serve as a proxy for different results over time, the investigators also suggested that undulations in the curve may be due to lower data quality prior to 2001. The Panel noted that it is possible that the undulating portion of the RCS curve is a true reflection of the data and potentially due to complex features such as exposure measurement error and aggregation of heterogeneous responses to air pollution across different populations and spatial regions. When evaluating potential sources of error, the study's large

sample size and concomitant statistical power also imply that bias, more so than precision, should be considered when interpreting these results.

In analyses restricting the cohort to 10-year $PM_{2.5}$ exposure below the current NAAQS ($12 \mu\text{g}/\text{m}^3$) and the former CAAQS and WHO Air Quality Guidelines ($10 \mu\text{g}/\text{m}^3$), the investigators found that compared with the full cohort, there were lower associations for person-years below $12 \mu\text{g}/\text{m}^3$, and that there was no evidence of a positive association below $10 \mu\text{g}/\text{m}^3$ when using linear models. However, the concentration–response curves for the $<10 \mu\text{g}/\text{m}^3$, $<12 \mu\text{g}/\text{m}^3$, and full cohorts all demonstrated similar steep increases in mortality for exposure concentrations $<5 \mu\text{g}/\text{m}^3$. The investigators suggested that the observed associations at low to moderate concentrations in the full cohort were strongly influenced by the inclusion of person-years with higher $PM_{2.5}$ exposure. The Panel disagreed with this interpretation given the use of flexible RCS models in which adjacent segments of the curve generally do not overly influence each other. The investigators noted that restricting the analyses to person-years with these lower exposure concentrations changed the cohort composition, raising potential concerns about differences in associations across populations or locations. Therefore, the actual health benefits of achieving lower $PM_{2.5}$ exposures across the entire country remain uncertain, although likely beneficial. The linear model results in this study were inconsistent with a recent study that analyzed a subsample of older U.S. adults with 1-year $PM_{2.5}$ exposures below $12 \mu\text{g}/\text{m}^3$ (Dominici et al. 2022) and with a meta-analysis that evaluated results for groups of studies with successively lower mean exposure (Chen and Hoek 2020); those studies showed larger effect estimates among people with lower exposures. A possible explanation for this discrepancy is the flatter slope segment of the concentration–response curve in the current study, which spanned concentrations 5 to $8 \mu\text{g}/\text{m}^3$. If analyses restricted person-years to below $5 \mu\text{g}/\text{m}^3$, the steeper slope portion of the concentration–response curve might have resulted in a larger effect estimate in the linear model.

Differences in Associations Due to PM Composition and Pollutant Mixtures

The RCS concentration–response curves generally increased across $PM_{2.5}$ concentrations for four of the airsheds. In contrast, the concentration–response curves for the Prairie and West Central airsheds showed only small increased mortality risk with subtle undulations for low $PM_{2.5}$ concentrations, followed by decreased risk near $8 \mu\text{g}/\text{m}^3$. These results were mirrored in the linear models where $PM_{2.5}$ was associated with lower risk of mortality in the Prairie and West Central airshed. Thus, it is possible that the Prairie and West Central airsheds were responsible for driving the low slope and undulating segment in the overall curve for Canada. Although the investigators adjusted for a wide range

of individual level and spatial covariates and performed sensitivity analyses to control for disparate demographic makeup and healthcare access, residual confounding could be responsible for the regional variation. Regional heterogeneity across North America, but not in Europe, has previously been reported in a meta-analysis of long-term PM_{2.5} exposure and mortality (Chen and Hoek 2020). Consequently, aggregating data across certain geographic regions might have limitations unless the underlying cause of the heterogeneity can be determined. In the end, the investigators hypothesized that regional variation may partly be attributed to regional differences in PM_{2.5} composition. This notion is supported by the varied chemical composition of the colocated sampling measurements in five of the airsheds. It is also supported by prior research indicating that individual PM_{2.5} chemical components vary by geography and in elicited adverse health effects (Dai et al. 2014; Davis et al. 2011; Lippmann et al. 2013). In this study the colocated measurements only served as a supplemental input to the exposure modeling and were not used in the health analysis directly. Note also that the regional variation is unlikely to be solely due to differences in the concentrations of copollutants O₃ and O_x as the Prairie and West Central airsheds had distributions of these pollutants similar to the other airsheds.

Although the effects of PM_{2.5} chemical composition in the MAPLE study were speculative, the results showed that adjusting for copollutants O₃ and O_x attenuated the association between PM_{2.5} and mortality, and inclusion of these copollutants in the nonlinear models flattened the RCS concentration–response curves. This result is consistent with the findings from numerous previous studies (Dominici et al. 2022; U.S. EPA 2019). In stratified analyses, the largest effect sizes were observed for PM_{2.5} and mortality in the highest O₃ and O_x tertiles, suggesting that these gases play an important role in determining the adverse health effects of PM_{2.5}. Recent studies in Europe and the United States indicated that NO₂ was also an important copollutant (Brunekreef et al. 2021; Dominici et al. 2022). Brauer and colleagues assessed NO₂ exposure but did not evaluate it in the MAPLE study Phase 2, given the Phase 1 results demonstrating minimal effect of adjusting for NO₂ on the association between PM_{2.5} and mortality. Note that these multipollutant results must be interpreted in light of the fact that O₃, O_x, and NO₂ were estimated at coarser spatial resolutions than PM_{2.5}. Given the sensitivity of the association between PM_{2.5} and mortality to copollutants O₃ and O_x, it will be important to investigate this issue in future studies.

Generalizability of the Findings

The size of the study populations was unprecedented and allowed detailed investigations for the questions at hand. The Panel noted that despite the large size of the MAPLE cohort, the results might not be generalizable to

the Canadian population as a whole. Although the response and data linkage rates were high for both the CanCHEC and CCHS cohorts, successive steps in assembling cohort data incrementally reduced inclusivity and generalizability. Census quality reports indicate that 4% of the Canadian population are not enumerated in CanCHEC and tend to be younger, mobile, low income, homeless, or Indigenous peoples (Tjepkema et al. 2019). After imputation, 90% of person-years were linked to a valid postal code. Because this linkage is based on tax records, unlinked person-years are presumably associated with lower income. Explicit exclusion criteria was more likely to remove immigrants and older individuals, and implicit exclusion criteria by way of missing data were more likely to remove minorities, Indigenous peoples, and individuals who were unemployed or lived in rural and Northern communities. Because socioeconomically disadvantaged subsets of the population might be more susceptible to both exposure and the adverse health effects of poor ambient air quality (Deguen and Zmirou-Navier 2010; Hajat et al. 2015), it is important to keep in mind that results from this study might portray a more optimistic scenario than the reality.

CONCLUSIONS

The MAPLE study aimed to characterize the association between nonaccidental mortality and long-term exposure to ambient PM_{2.5} concentrations lower than most of the world. Brauer and colleagues developed fine-scale satellite-, monitor-, and model-based PM_{2.5} exposure estimates across North America from 1981 to 2016. They applied comprehensive epidemiological analyses in a large representative sample of Canadian adults to identify the shape of the concentration–response curve and the lowest PM_{2.5} concentration at which associations with health effects could be detected.

The study demonstrated that 10-year PM_{2.5} exposures were associated with increased total and cause-specific mortality. Given the minimum observed exposure of 2.5 µg/m³, the findings support a nonthreshold, supralinear concentration–response curve.

The Panel commended the investigators' impressive accomplishments and agree that the results show a positive association with mortality even at PM_{2.5} concentrations below the current U.S. ambient air quality standard of 12 µg/m³. Yet they noted that uncertainty remains in how to interpret some of the results, including the low-slope segment of the RCS concentration–response curve for middle concentration ranges and differences by regional airshed. The influence of individual PM chemical components, copollutants, and residual confounding on the results remains uncertain. Further interpretation of findings and further description for some of the nonstandard statistical methods would have enhanced the report. Future work is warranted to build on

the MAPLE study findings, including analyses of PM composition, multipollutant models, and further refinement of concentration–response curve methods.

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ABBREVIATIONS AND OTHER TERMS

AERONET	Aerosol Robotic Network	mCCHS	CCHS mortality cohort
AIC	Akaike information criterion	MSE	mass scattering efficiency
AOD	aerosol optical depth	NAAQS	National Ambient Air Quality Standards
BIC	Bayesian information criterion	NAPS	National Air Pollution Surveillance
BMI	body mass index	NO ₂	nitrogen dioxide
CA	census agglomeration	O ₃	ozone
CAAQS	Canadian Ambient Air Quality Standards	O _x	gaseous pollutant oxidant capacity
CAN-Marg	Canadian Marginalization Index	PAF	population attributable fraction
CanCHEC	Canadian Census Health and Environment Cohort	PCCF+	Postal Code Conversion File Plus
CCHS	Canadian Community Health Survey	PM	particulate matter
CCME	Canadian Council of Ministers of the Environment	PM _{2.5}	particulate matter ≤2.5 µm in aerodynamic diameter
CI	confidence interval	R ²	coefficient of determination
CMA	census metropolitan area	RCS	restricted cubic splines
COPD	chronic obstructive pulmonary disease	RFA	request for applications
ESCAPE	European Study of Cohorts for Air Pollution Effects	RMSD	room mean square difference
eSCHIF	extended shape constrained health impact function	SCHIF	shape constrained health impact function
GBD	global burden of disease	SD	standard deviation
GEMM	Global Mortality Exposure Model	SE	standard error
GEOS-Chem	GEOS-Chem chemical transport model	SIA	secondary inorganic aerosol
HR	hazard ratio	SO ₂	sulfur dioxide
ICD	International Classification of Disease	SPARTAN	Surface PARTiculate mAtter Network
IQR	interquartile range	TSP	total suspended particulate matter
MAPLE	Mortality–Air Pollution Associations in Low Exposure Environments	U.S. EPA	U.S. Environmental Protection Agency
		WHO	World Health Organization

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