HEALTH EFFECTS INSTITUTE

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

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 μg/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.

studies are based in 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 10–21 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 (10–21 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.
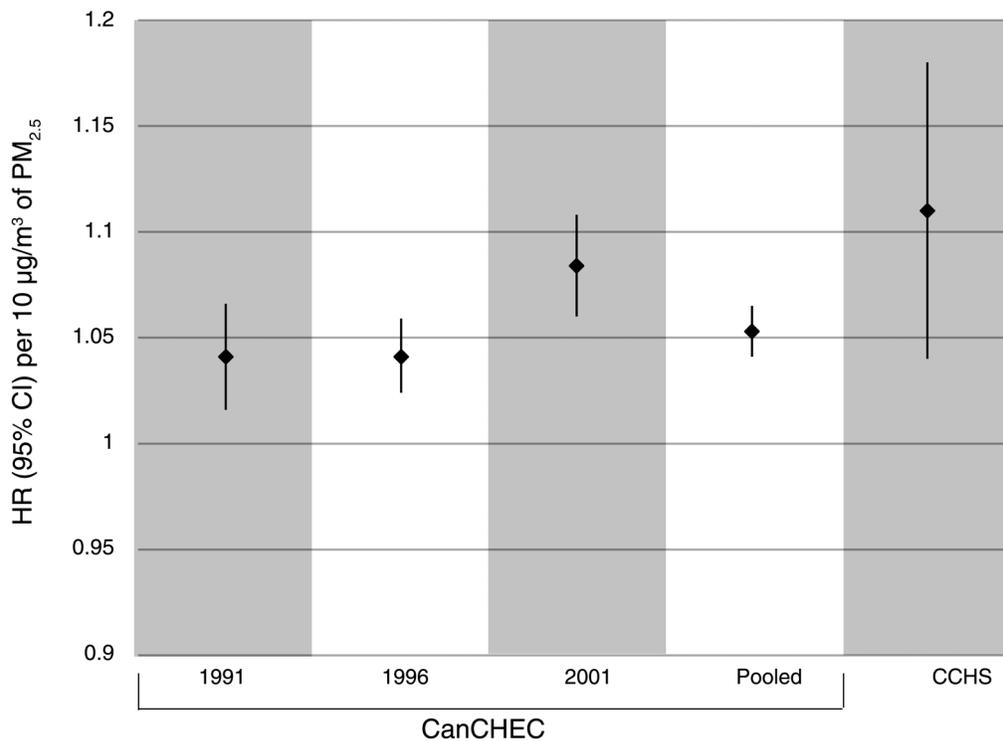
RESULTS

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.

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

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 µg/m³), followed by a leveling off or a smaller increase after ~10 µg/m³. The investigators suggest that there is no evidence of a threshold or sublinear association at very low concentrations. They caution against over-interpretation of the SCHIF results due to wide confidence intervals, and state that these nonlinear hazard ratios 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 km² vs. 10 km²), 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 km² 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.

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 10–21 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.

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