SOCIAL SCIENCES

How low can you go? Air pollution affects mortality at very low levels

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The World Health Organization (WHO) recently released new guidelines for outdoor fine particulate air pollution ($PM_{2.5}$) recommending an annual average concentration of 5 μg/m^3. Yet, our understanding of the concentration-response relationship between outdoor $PM_{2.5}$ and mortality in this range of near-background concentrations remains incomplete. To address this uncertainty, we conducted a population-based cohort study of 7.1 million adults in one of the world's lowest exposure environments. Our findings reveal a supralinear concentration-response relationship between outdoor $PM_{2.5}$ and mortality at very low (<5 μg/m^3) concentrations. Our updated global concentration-response function incorporating this new information suggests an additional 1.5 million deaths globally attributable to outdoor $PM_{2.5}$ annually compared to previous estimates. The global health benefits of meeting the new WHO guideline for outdoor $PM_{2.5}$ are greater than previously assumed and indicate a need for continued reductions in outdoor air pollution around the world.

INTRODUCTION

In September 2021, the World Health Organization (WHO) released new guidelines for annual average outdoor concentrations of fine particulate air pollution ($PM_{2.5}$, <2.5 μm) and cut its previous guideline value in half from 10 to 5 μg/m^3 (*1*). The current United States Environmental Protection Agency (U.S. EPA) standard of 12 μg/m^3 is now more than double the value recommended by the WHO (*2*). This ambitious new guideline is based on a large body of epidemiological evidence supporting a causal relationship between long-term exposure to outdoor $PM_{2.5}$ and premature mortality, which has been demonstrated around the world (*1*, *3*–*5*). Nevertheless, few cohort studies to date provide a detailed characterization of the shape of the concentration-response relationship between outdoor $PM_{2.5}$ and mortality in the low range of global $PM_{2.5}$ concentrations, the space now occupied by the new WHO guideline (*6*). It is crucial to quantify this relationship to accurately characterize the global health benefits of meeting the ambitious new level set by the WHO.

Numerous challenges must be addressed in estimating the relationship between long-term exposures (i.e., annual average) to outdoor $PM_{2.5}$ and mortality including (i) identifying and enumerating a large population-based cohort that adequately reflects the population of interest and also includes detailed information on the timing and types of mortality outcomes; (ii) accurately and reliably assigning cohort members' exposures to outdoor $PM_{2.5}$ concentrations on a fine spatial scale (i.e., residential location) over broad geographic areas with exposures updated over time for residential mobility and including back-casted exposure to capture historical variations in pollutant concentrations; (iii) collecting detailed information on important confounding factors that may distort the observed relationship between $PM_{2.5}$ and mortality; and (iv) combining this information in a flexible statistical framework to estimate the relationship between outdoor $PM_{2.5}$ and mortality risk to inform future regulatory interventions. The functional form of the $PM_{2.5}$-mortality relationship can be modeled as linear (i.e., a linear relationship between outdoor $PM_{2.5}$ concentrations and logarithm of the mortality rate) or more complex nonlinear functional forms as needed. The Canadian Census Health and Environment Cohort (CanCHEC) was developed to address these challenges. Specifically, this national population-representative cohort was created by linking people who completed the mandatory Long-Form Census questionnaire (including multiple cycles in the years 1991, 1996, and 2001) to income tax files and mortality records across Canada combined with state-of-the-art predictions for outdoor $PM_{2.5}$ concentrations developed and refined using satellite remote sensing, ground-level measurements of $PM_{2.5}$ and aerosol optical depth (AOD), and chemical transport models (*7*).

Here, we use CanCHEC to characterize the shape of the $PM_{2.5}$-mortality function (and associated uncertainty) at $PM_{2.5}$ concentrations < 20 μg/m^3 including values below the latest WHO guideline. Using this new information, we first develop a refined concentration-response function for outdoor $PM_{2.5}$ and mortality to capture health risks on the low end of the global exposure distribution. Next, we apply this revised function to derive updated annual global mortality estimates given this improved understanding of the $PM_{2.5}$-morality relationship. The analysis used to refine the global concentration-response function is based on 7.1 million adults followed between 1991 and 2016 and adjusting for numerous individual-level and neighborhood-level covariates. We also verified these results in an ancillary cohort [the Canadian Community Health Survey (CCHS) cohort, including 450,000 adults] which allowed for additional adjustment for individual-level behavioral factors such as smoking, diet, and obesity on observed relationships between $PM_{2.5}$ and mortality. Our analysis focusses on nonaccidental mortality as this

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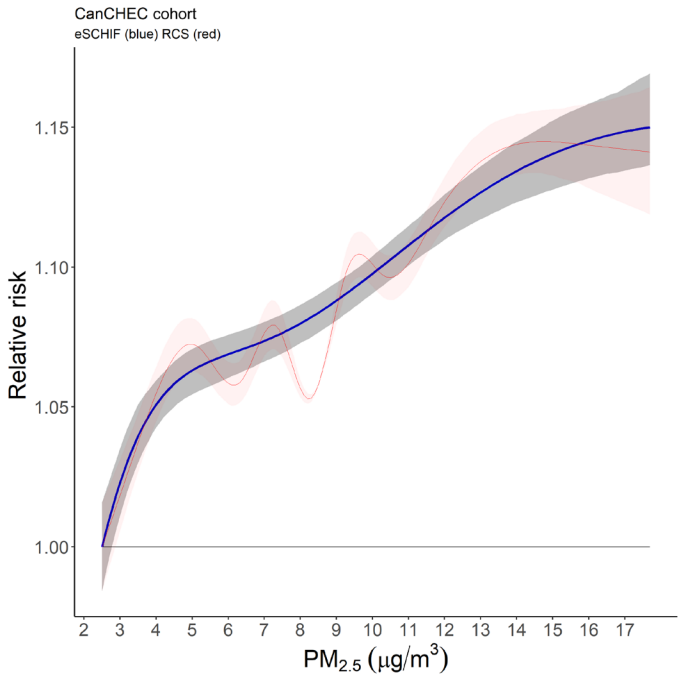

Fig. 1. Fully adjusted restricted cubic spline relative risk predictions for nonaccidental mortality over the CanCHEC $PM_{2.5}$ concentration range (red dashed line, mean; red shaded area, 95% CIs) with associated eSCHIF predictions (blue solid line, mean; gray shaded area, 95% CIs). The green *x*-axis tick marks indicate the nine restricted cubic spline (RCS) knot locations that reflect percentiles of $PM_{2.5}$ (2, 14, 26, 50, 62, 74, 86, and 98%) for person-years of during follow-up (13.3% of person-years had PM2.5 values below 5 μg/m^3, which is indicated by the vertical dotted line).

outcome is most influential in terms of guiding regulatory interventions and associated cost-benefit analyses (*8*). Note that our refined $PM_{2.5}$-mortality function at low concentrations was not used in developing the most recent WHO guideline as our study was completed after this guideline was released.

The main purpose of this study was to (i) derive a new global exposure-response function for outdoor $PM_{2.5}$ and mortality capturing the shape of this relationship at low levels and (ii) to update estimates of annual global mortality attributable to outdoor $PM_{2.5}$ incorporating new knowledge of the shape of this relationship at low $PM_{2.5}$ levels, including values at or below the new WHO guideline. The cohort populations used to support this analysis are the same as recently described (*9*); however, for this application, we combined unique participants from the three CanCHEC cohorts for increased statistical power at low $PM_{2.5}$ concentrations (*10*). Moreover, this analysis uses updated estimates of long-term exposures to outdoor $PM_{2.5}$ concentrations across Canada, which were previously refined using colocated measurements of ground-level $PM_{2.5}$, aerosol scatter, and AOD (V4.NA.02.MAPLE) (*10*, *11*).

RESULTS AND DISCUSSION

In total, our analyses included more than 128 million person-years of follow-up time with 1.2 million nonaccidental deaths observed between 1991 and 2016 (table S1). The mean outdoor $PM_{2.5}$ concentration during follow-up (assigned as a 10-year moving average at 1-km^2 resolution with a 1-year lag) was 8.5 μg/m^3 (SD = 3.1 μg/m^3) with values ranging from 2.5 to 17.7 μg /m^3. In total, 13.3% of person-years in the cohort had outdoor $PM_{2.5}$ concentrations below 5 μg/m^3. Each 10 μg/m^3 increase in long-term average outdoor

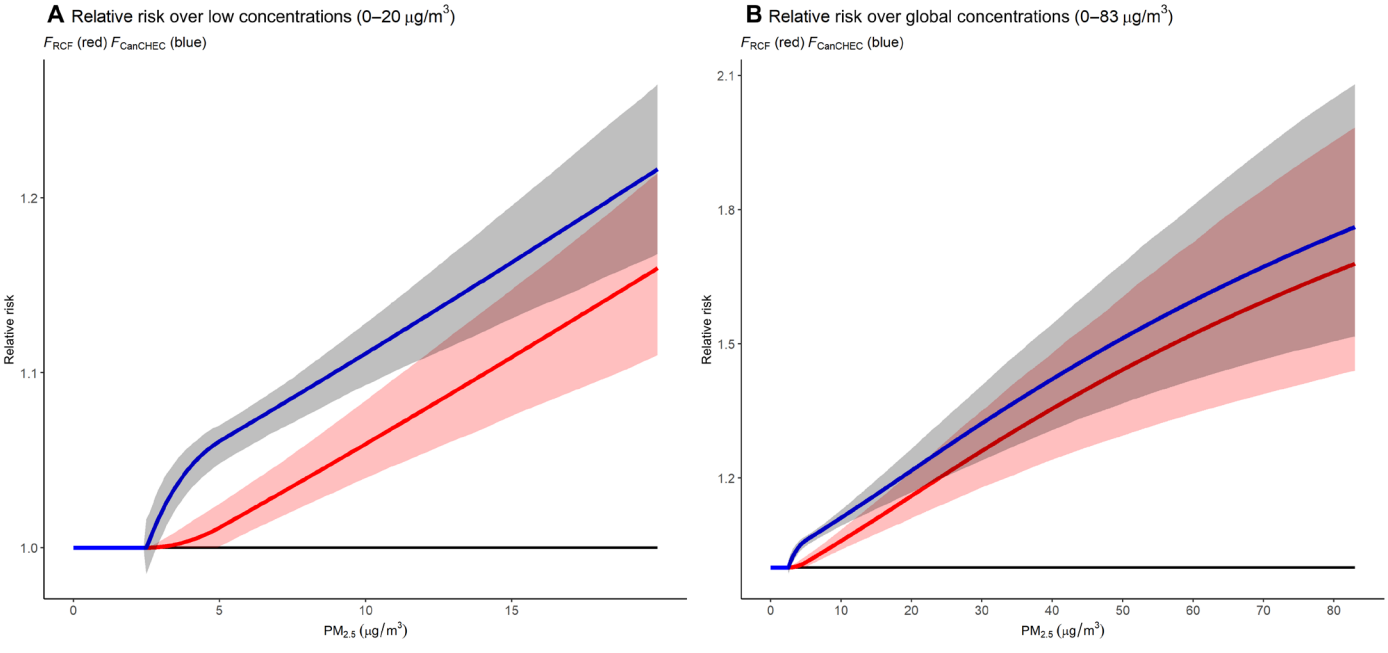

Fig. 2. Concentration-response functions describing the relationship between outdoor $PM_{2.5}$ concentrations and nonaccidental mortality. (**A**) Concentration-response functions on the low end of the global exposure distribution (0 to 20 μg/m^3). The blue line (and shaded 95% CI) indicates the shape of the refined global function that incorporates the supralinear relationship between $PM_{2.5}$ and mortality at low concentrations as characterized by the CanCHEC cohort. The red line (and shaded 95% CI) indicates the shape of the current global concentration-response function for $PM_{2.5}$ and mortality at low concentrations which uses a random counterfactual concentration selected from a uniform distribution between 2.5 and 5 μg/m^3. (**B**) Current (red) and refined (blue) concentration-response functions for $PM_{2.5}$ and mortality over the global $PM_{2.5}$ exposure distribution.

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$PM_{2.5}$ concentration was associated with an 8.0% [95% confidence interval (CI): 7.0, 10.0] increased risk of nonaccidental mortality after adjusting for numerous potential confounding factors including age (5-year categories), sex, recent immigrant status, income, visible minority status, indigenous identity, educational attainment, labor force status, marital status, community size, airshed, urban form, and four dimensions of the Canadian Marginalization Index (CAN-Marg). This estimate is based on a model that assumes a linear relationship between $PM_{2.5}$ and the logarithm of the mortality rate and is equal in magnitude to the estimate obtained from a meta-analysis of cohort studies conducted globally by the WHO [8.0% (95% CI: 6.0, 9.0)] (*12*), thus suggesting that the $PM_{2.5}$-mortality association observed in CanCHEC is similar to that based on the large body of epidemiological evidence globally. Analyses replicated in the ancillary CCHS cohort with additional detailed adjustment for individual-level behavioral covariates including smoking, alcohol consumption, body mass index (BMI), exercise, and fruit and vegetable intake confirmed these results (9.0% increase; 95% CI: 2.0, 16) (table S2).

Using our population-based cohort, we characterized the shape of the concentration-response relationship between outdoor $PM_{2.5}$ and nonaccidental mortality at the low end of the global exposure distribution (down to 2.5 $\mu g/m^3$) and refined the global concentration-response function over the concentration range from 2.5 to 5 $\mu g/m^3$ to incorporate this improved understanding of $PM_{2.5}$ health risks at low concentrations. Next, we updated global estimates of annual deaths attributable to outdoor $PM_{2.5}$ using this refined concentration-response relationship which explicitly models the nonlinear relationship (and uncertainty) between $PM_{2.5}$ and nonaccidental mortality at levels below the current WHO guideline (i.e., 5 $\mu g/m^3$) while also incorporating existing epidemiological evidence across the global exposure distribution (table S3).

We observed strong evidence of a supralinear concentration-response relationship between outdoor $PM_{2.5}$ concentrations and mortality in CanCHEC (Fig. 1), resulting in a refined global concentration-response function (Fig. 2). This refined understanding of the concentration-response relationship between outdoor $PM_{2.5}$ and mortality at low concentrations suggests a large increase in the

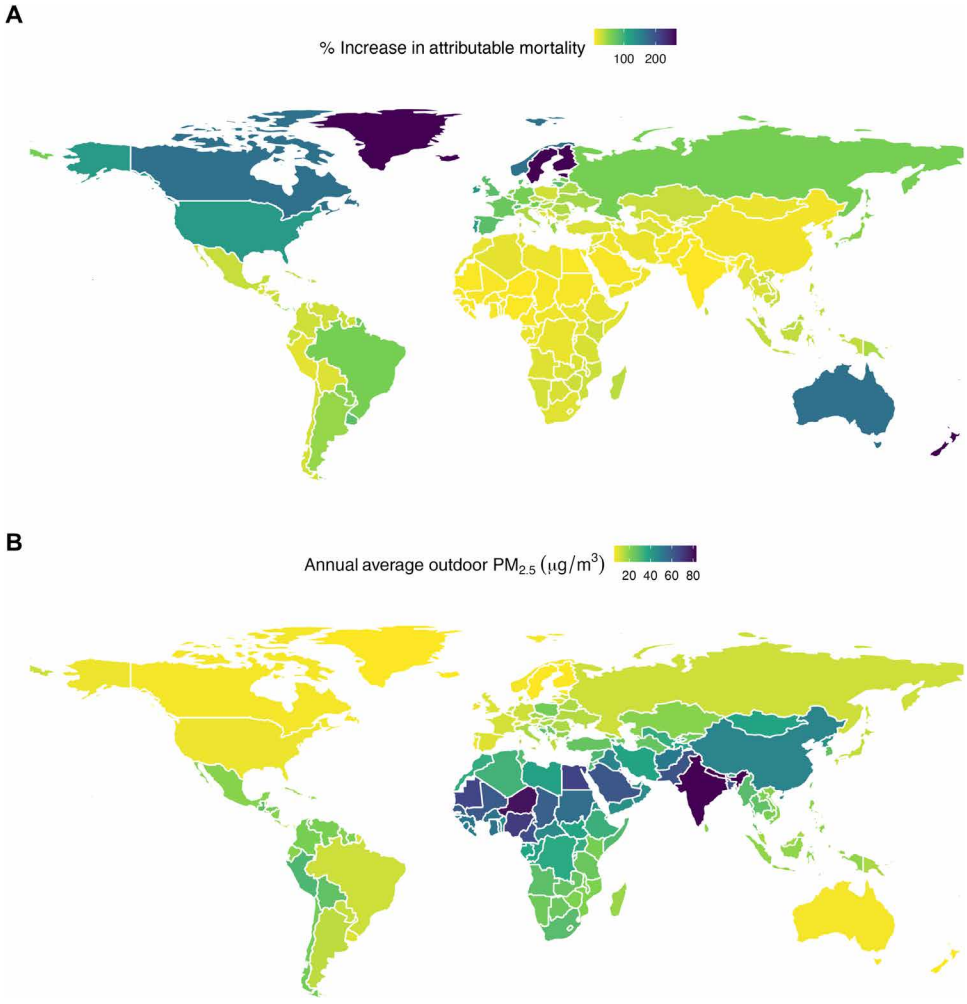

Fig. 3. Percent increase in annual mortality attributable to outdoor $PM_{2.5}$ on a global scale and global variations in annual average outdoor $PM_{2.5}$. (**A**) Percent increase in annual attributable mortality comparing deaths predicted using our refined global exposure-response function for outdoor $PM_{2.5}$ and mortality to a function which uses a random counterfactual concentration selected from a uniform distribution between 2.5 and 5 $\mu g/m^3$. (**B**) Global distribution of annual average outdoor $PM_{2.5}$ concentrations.

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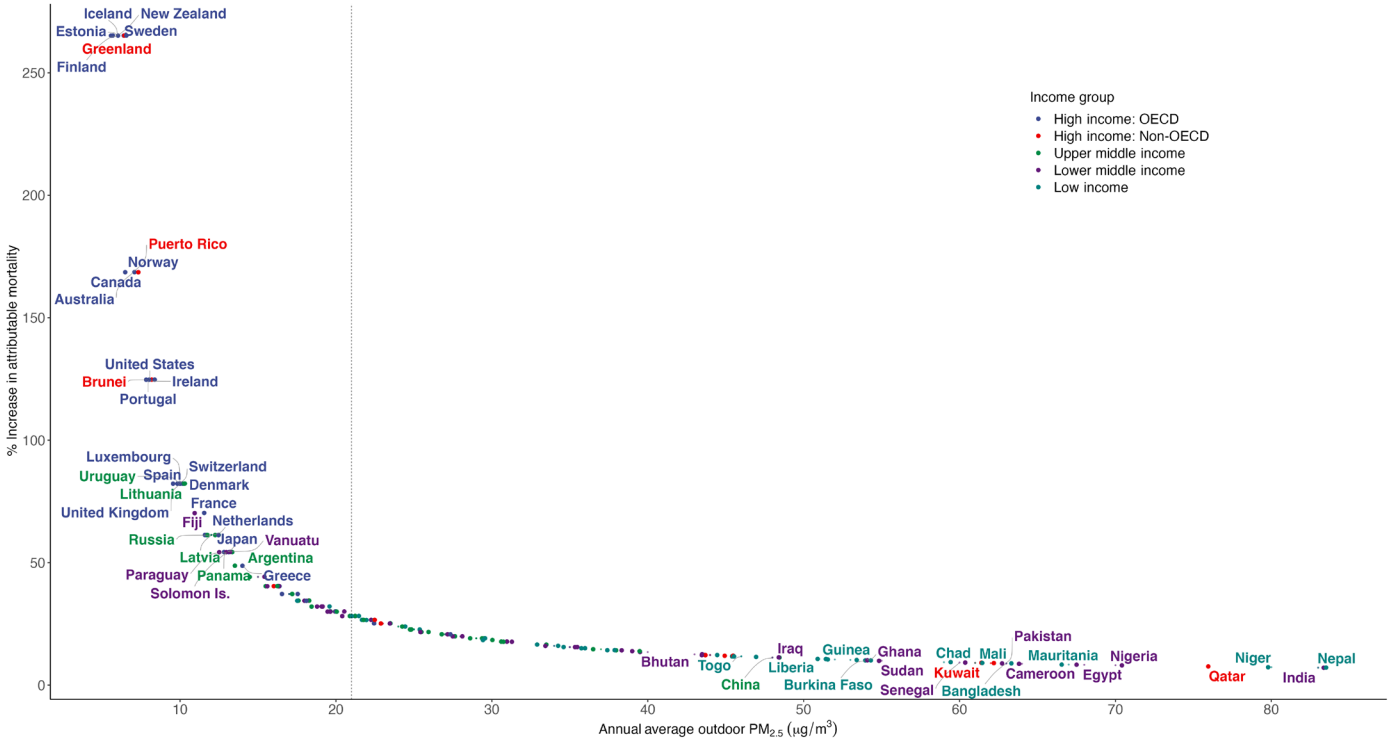

Fig. 4. Percent increase in annual mortality attributable to outdoor $PM_{2.5}$ by income group and annual average outdoor $PM_{2.5}$. OECD, Organization for Economic Co-operation and Development.

number of annual global deaths attributable to outdoor $PM_{2.5}$, particularly in "low pollution" settings (Figs. 3 and 4). Specifically, we estimate an additional 1.55 million deaths (95% CI: 1.53 million, 1.57 million) annually on a global scale [i.e., 10.8 million (95% CI: 10.7 million, 10.9 million) compared to 9.24 million (95% CI: 9.17 million, 9.31 million)], with larger underestimation of attributable mortality occurring in countries with lower $PM_{2.5}$ concentrations and higher incomes (Fig. 4). This pattern is illustrated in Fig. 5 for attributable mortality estimates in locations above (i.e., >12 μg/m^3) and below (≤12 μg/m^3) the current U.S. EPA standard for annual average outdoor $PM_{2.5}$. On an absolute scale, the number of deaths underestimated in regions above 12 μg/m^3 was larger [i.e., 1.15 million (95% CI: 1.14 million, 1.17 million) compared to 403,000 (95% CI: 407,500, 398,500)] as most of the world's population lives in areas above the current EPA standard.

The supralinear concentration-response relationship identified between outdoor $PM_{2.5}$ and mortality at low concentrations has a marked impact on global estimates of annual mortality attributable to $PM_{2.5}$ compared to models using a random counterfactual concentration selected from a uniform distribution between 2.5 and 5 μg/m^3 (*1*). While the reason for this supralinear shape at low concentrations has yet to be fully elucidated, other studies examining the impact of outdoor $PM_{2.5}$ on mortality risk have reported similar shapes including both time series studies and cohort studies (*5*, *12*–*14*). Recent evidence related to $PM_{2.5}$ chemical composition suggests one possible explanation for the observed pattern of steeper slopes at lower $PM_{2.5}$ concentrations. Specifically, a recent study of $PM_{2.5}$ and acute cardiovascular events reported an interaction between the transition metal and sulfur content of $PM_{2.5}$, with stronger associations observed when the mass fractions of both these components are elevated (*15*). Since the mass fraction of sulfur increases as $PM_{2.5}$ decreases (*15*), the biological availability of metals in $PM_{2.5}$ may be higher at lower $PM_{2.5}$ mass concentrations, thus increasing the slope of concentration-response functions in this range. The validity of our results depends on the global generalizability of risk estimates from Canada, which is supported by the fact that the hazard ratio observed in CanCHEC was nearly identical to the estimate obtained in a meta-analysis of global studies of outdoor $PM_{2.5}$ (*12*). Moreover, other large cohort studies conducted in the United States (*4*) and Europe (*5*) also reported clear and consistent relationships between outdoor $PM_{2.5}$ and mortality at low concentrations, supporting the notion that this relationship is not limited to Canada. In the United States, Di *et al.* (*4*) also conducted analyses separately for person-years above and below the current U.S. EPA standard for annual average outdoor $PM_{2.5}$ (12 μg/m^3) and reported stronger associations at lower $PM_{2.5}$ mass concentrations, which is again consistent with a supralinear concentration response relationship. Likewise, Strak *et al.* (*5*) performed a similar analysis in Europe by removing person-years above various $PM_{2.5}$ concentrations between 10 and 25 μg/m^3 and reported stronger associations at lower concentrations. Collectively, recent evidence from large cohort studies of outdoor $PM_{2.5}$ and mortality suggests important health risks below existing standards for annual average $PM_{2.5}$.

In summary, refining the shape of the global concentration-response function for outdoor $PM_{2.5}$ and mortality at the low end of the exposure distribution results in more than 1.5 million additional attributable deaths each year globally. This finding may be used to strengthen support for air quality management globally as our results suggest that country-specific burden estimates vary substantially depending on how the $PM_{2.5}$-mortality association is characterized.

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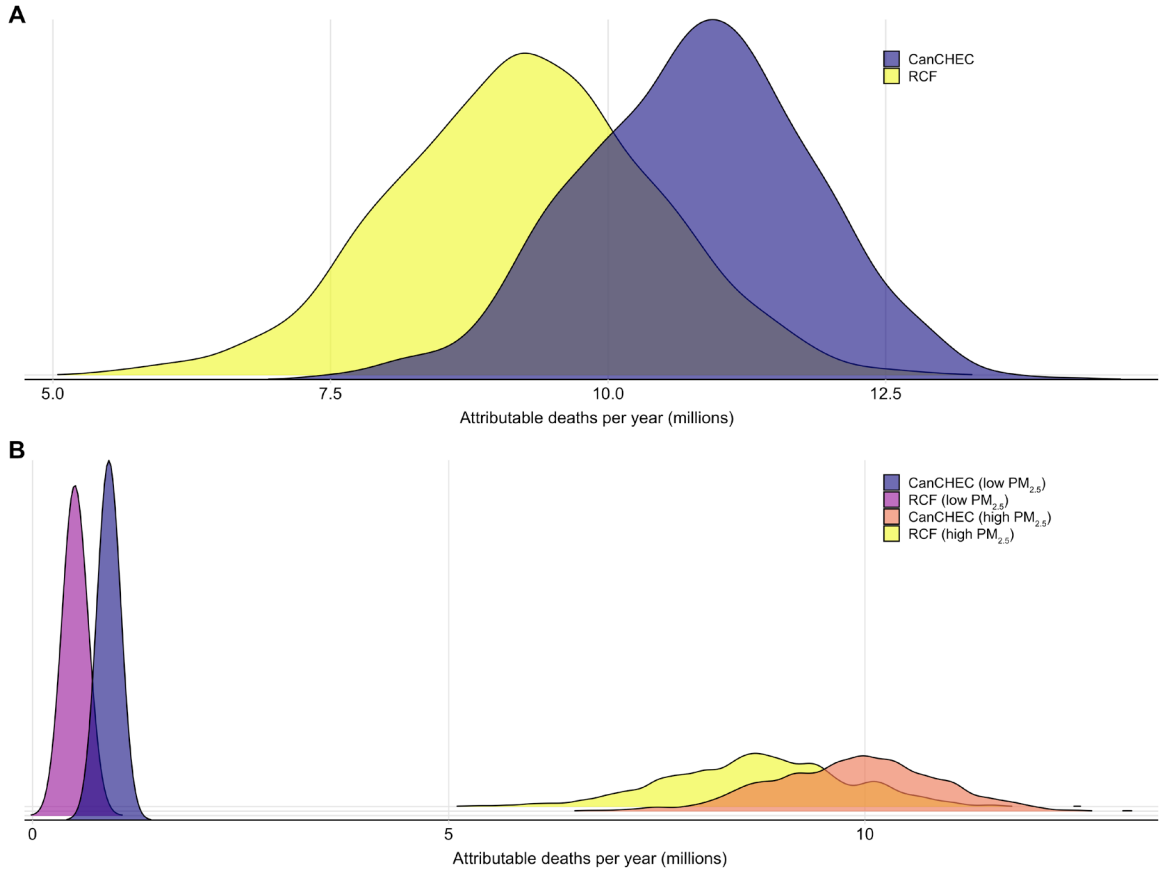

Fig. 5. Density plots comparing estimated annual global mortality attributable to outdoor $PM_{2.5}$. (**A**) Distributions of attributable mortality per year predicted by the current global exposure-response function [random counterfactual distribution (RCF)] and our new refined function incorporating the supralinear relationship between $PM_{2.5}$ and mortality at low concentrations (CanCHEC). (**B**) Distributions of attributable mortality per year predicted above [>12 μg/m^3 (high $PM_{2.5}$)] and below [≤12 μg/m^3 (low $PM_{2.5}$)] the current U.S. EPA standard by the RCF model and our new CanCHEC model. Percent underestimation of attributable deaths by the RCF model is greater at lower $PM_{2.5}$ concentrations.

Refinement of this function comes at a crucial time given that increasing evidence of $PM_{2.5}$ health affects below existing regulatory standards. The results of this analysis suggest that global efforts to meet the new WHO guideline of 5 μg/m^3 for annual average outdoor $PM_{2.5}$ mass concentrations will have much larger benefits than previously anticipated, even in regions of the world with relatively low outdoor air pollution concentrations.

MATERIALS AND METHODS

Cohort study populations

Our primary study cohort pooled all individuals from three waves (1991, 1996, and 2001) of CanCHEC which comprises subjects responding to the long-form Census questionnaire, capturing individual and household sociodemographic data on census day, and linking them to longitudinal vital statistics and tax records (*16*). To create the cohorts, respondents were linked to death records and residential history through Statistics Canada's Social Data Linkage Environment. Linkage was approved by Statistics Canada and is governed by the Directive on Microdata Linkage. A list of linked unique individuals was created through linkages that were either deterministic (matching records based on unique identifiers) or probabilistic (matching records based on nonunique identifiers such as names, sex, date of birth, and postal code and estimating the likelihood that records are referring to the same entity).

Minimum ages in the original CanCHECs differed between waves but were standardized for this study to include adults older than 25 years, including 2.5 million individuals from the 1991 Census (4 June 1991), 3 million individuals from the 1996 Census (14 May 1996), and 3 million individuals from the 2001 Census (15 May 2001). After pooling the three waves and removing duplicate subjects across waves, we applied additional exclusion criteria to person-years to obtain the final pooled cohort. First, since postal code history was not available for each person in every year of follow-up (e.g., because respondents did not file a tax return), missing postal codes were imputed (using the Statistic Canada Postal Code Conversion File Plus) (*17*) fully or partially based on postal codes reported in adjacent years using a method where the probability of imputation varied depending on the number of adjacent years missing (*18*). In Canadian urban areas, six-digit postal codes typically represent one side of a city block or the center of an apartment building with a positional accuracy of approximately 150 m. Location uncertainty is greater for rural postal codes that are typically accurate to within 1 to 5 km (*19*). In total, 89.9% of all person-years had a valid postal code after imputation. Additional person-years were excluded if respondents immigrated to Canada less than 10 years before the survey

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date (9,364,400 person-years excluded), age during the follow-up exceeded 89 years (7,357,200 person-years excluded), or postal codes could not be matched to an air pollution estimate (17,814,400 person-years excluded), a CAN-Marg value (25,613,100 person-years excluded), or airshed (25,545,500 person-years excluded) (note that these exclusion numbers overlapped for many person-years so percentages are not informative as they are not mutually exclusive). Last, since air pollution exposures were based on a 10-year moving average with a 1-year lag, person-years were excluded if fewer than 7 of 10 years of data were available (21,751,800 person-years excluded). After applying these criteria, a total of 128,371,800 person-years (7.1 million subjects) were available for analysis.

We used a secondary cohort to estimate possible confounding by health behaviors and health status: the CCHS—mortality cohort. The CCHS includes 540,900 subjects over the age of 25 years who completed one of the CCHS panels between 2001 and 2012, linked to longitudinal vital statistics and tax records from the date of survey to 31 December 2016 (*20*). We applied the same exclusion criteria as with the CanCHEC; the total available person-years for analyses were 4,405,000 (450,000 subjects) after all exclusions.

Individual-level covariates captured at baseline in both the CanCHEC and CCHS included income, educational attainment, marital status, indigenous identity, employment status, occupational class, and visible minority status. Furthermore, CCHS analyses included additional covariates describing fruit and vegetable consumption, leisure exercise frequency, alcohol consumption behavior, smoking behavior, and BMI categories. We also considered area-based contextual measures to capture neighborhood characteristics in both cohorts including community size, urban form (a designation of population density and transportation characteristics) (*21*), and airshed (large geographic areas with similar air quality characteristics and dispersion patterns) (*22*). We used the CAN-Marg to describe inequalities across four dimensions of marginalization: material deprivation, residential instability, dependency, and ethnic concentration (*23*). Additional details on cohort composition and methodology are available elsewhere (*10*).

Outdoor $PM_{2.5}$ concentrations

Our epidemiological analysis applied the most recent estimates of outdoor $PM_{2.5}$ mass concentrations across Canada over the follow-up period (V4.NA.02.MAPLE) (*7*, *11*, *24*–*26*). Briefly, daily satellite retrievals of AOD at 1-km^2 resolution were combined with simulations of the daily AOD-to-$PM_{2.5}$ relationship using GEOS-Chem (a chemical transport model) to produce ground-level estimates of $PM_{2.5}$ mass concentrations (*24*). This most recent model incorporates improvements based on collocated measurements of aerosol scatter and $PM_{2.5}$ mass across North America and uses geographically weighted regression to fuse monthly mean measurements from $PM_{2.5}$ monitors with the geophysical $PM_{2.5}$ estimates (*7*, *24*–*25*).

Statistical analysis

We first used Cox proportional hazards models to estimate the linear relationship between outdoor $PM_{2.5}$ concentrations and the logarithm of the mortality rate. Individuals were followed from census or survey date until either the age of 89 years, the year of death, or the end of follow-up in 2016. We considered nonaccidental mortality as the primary outcome, and all models were stratified by age (5-year age groups), sex, immigrant status, and CanCHEC/CCHS cycle. All Cox models were adjusted for the individual and contextual variables listed in table S1 (fig. S1). CCHS analyses were additionally adjusted for the behavioral covariates of fruit and vegetable consumption, exercise frequency, alcohol consumption, smoking, and BMI. Smoking was defined as never/former/occasional smokers and, for regular smokers, by the number of cigarettes smoked per day. All $PM_{2.5}$ exposures were assigned as a 10-year moving average with a 1-year lag. The 10-year moving average exposure used in our analyses was selected on the basis of a previous evaluation of the impact of exposure time window on $PM_{2.5}$-mortality associations (*27*).

Shape of the association between outdoor $PM_{2.5}$ and mortality in CanCHEC

We developed a two-stage method to characterize the shape (nonlinear) of the association between outdoor $PM_{2.5}$ concentrations and mortality in CanCHEC. In the first stage, a spline of $PM_{2.5}$ is fit within the Cox survival model. We selected restricted cubic splines (RCS) to flexibly model the association between outdoor concentrations of $PM_{2.5}$ and mortality (*28*). These regression-based splines require fewer computing resources compared with smoothing splines, a restriction that is necessary within the computing environment at Statistics Canada. The RCS has the form

$$\mathrm{RCS}(z) = \beta_0(z - \bar{z}) + \sum_{l=1}^{K-2} \beta_l(\, s_l(z) - s_l(\bar{z}))$$

for $K \geq 3$ with

$$s_l(z) = \left(\max\left(0, \frac{z-\lambda_l}{(\lambda_K-\lambda_1)^{2/3}}\right)\right)^3 - \left(\frac{\lambda_K-\lambda_l}{\lambda_K-\lambda_{K-1}}\right)\left(\max\left(0, \frac{z-\lambda_{K-1}}{(\lambda_K-\lambda_1)^{2/3}}\right)\right)^3 + \left(\frac{\lambda_{K-1}-\lambda_l}{\lambda_k-\lambda_{k-1}}\right)\left(\max\left(0, \frac{z-\lambda_K}{(\lambda_K-\lambda_1)^{2/3}}\right)\right)^3$$

and K knot concentrations ($\lambda_1, \ldots, \lambda_K$). The RCS is linear below λ_1 and above λ_K with continuous second derivatives at the K knots. The $K - 1$ unknown parameters ($\beta_0, \ldots, \beta_{K-2}$) are estimated within the Cox survival model framework by including ($z, s_1(z), \ldots, s_K(z)$) as $K - 1$ variables in the survival model. The analyst must specify the number and location of the knots. Knot locations were based on percentiles of the $PM_{2.5}$ person-year distribution.

Let $\hat{\beta} = (\hat{\beta}_0, \ldots \hat{\beta}_{K-2})'$ be a $K - 1$ by 1 vector of parameter estimates with corresponding covariance matrix $\hat{V}$ and let $s(z) = (z, s_1(z), \ldots, s_{K-2}(z))'$. The estimate of the lnRCS(z) prediction is given by $\ln\widehat{\mathrm{RCS}}(z) = \hat{\beta}'(s(z) - s(\bar{z}))$, where $\bar{z}$ is the person-year–based mean concentration, with uncertainty in the estimate given by $\hat{\sigma}(z) = (s(z) - s(\hat{z}))'\hat{V}(s(z) - s(\hat{z}))$. We summarize the information obtained from the fitted RCS model by its mean prediction at any concentration z, $\widehat{\mathrm{RCS}}(z)$, and its 95% CI: $\exp(\ln\widehat{\mathrm{RCS}}(z) \mp 1.96 \times \hat{\sigma}(z))$. For all nonaccidental causes of death, we fit 16 RCS models based on 3 to 18 knots and selected the model that minimized the BIC (Bayesian Information Criterion) (the best fitting model included nine knots). We then incorporated a counterfactual concentration, z_{cf}, such that our prediction of relative risk at z_{cf} is equal to one by calculating $\widehat{\mathrm{RCS}}(z)/\widehat{\mathrm{RCS}}(z_{cf})$. As described below, z_{cf} was set to the minimum observed concentration (2.5 $\mu g/m^3$).

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In some cases, RCS predictions may not be suitable for health benefits analysis as they may not be monotonically increasing in concentration or may have "wiggles" in the predictions. Therefore, to ensure a relative risk function that is suitable for benefits analysis, in the second stage, we fit an algebraic function specifically designed for benefits analysis to the RCS predictions. Our aim was to estimate a function that can take a variety of shapes including linear, sub/supralinear, and sigmodal. We also require a function whose statistical certainty is such that prediction uncertainty limits increase as concentrations deviate from their mean, a property of spline predictions.

The shape constrained health impact function (SCHIF) (*29*) has been proposed to model concentration-mortality associations within a cohort using an algebraic from suitable for benefits analysis: $\mathrm{SCHIF}(z) = \exp\left\{\theta \ln\left(\frac{(z - z_{cf})}{\alpha} + 1\right)/(1 + \exp\left(-\frac{z - z_{cf-\mu}}{\nu}\right)\right\}$, with parameters (θ, α, μ, and ν) estimated from the cohort data. Although this function can take near linear, sub/supralinear, and sigmodal forms, it cannot capture the property of spline predictions with uncertainty limits increasing as concentrations deviate from their mean. To incorporate this property, we added a term to the SCHIF(z) of the form $\exp\left\{\gamma \ln\left(\frac{(z - z_{cf})}{\delta} + 1\right)\right\}$ with two additional parameters (γ and δ) and denote our new model as eSCHIF(z) for our extension of the SCHIF.

To fit the eSCHIF, we first generate 1000 sets of RCS predictions over the concentration range by simulating 1000 sets of RCS regression coefficients $\hat{r}_i = \mathrm{MVN}(\hat{\beta}, \hat{V})$, where MVN is the multivariate normal distribution and calculating $\widehat{\mathrm{RCS}}_i(z) = \exp\{\hat{r}_i' s(z)\}$ over a sequence of J concentrations (z_{cf}, z_1, …, z_J) with z_J defined as the maximum concentration and $i = 1, \ldots, 1000$. These 1000 sets of predictions capture both the shape and uncertainty of splines over the concentration range. We then fit the eSCHIF functional form to each of the 1000 sets of predictions $\widehat{\mathrm{RCS}}_i(z_j)/\widehat{\mathrm{RCS}}_i(z_{cf})$. We denote our relative risk model as CanCHEC(z). It has been defined such that $\mathrm{CanCHEC}(z_{cf}) = 1$, where z_{cf} is the minimum observed concentration in the cohort (2.5 μg/m^3).

Relative risk model covering the global concentration range

WHO identified a set of cohort studies examining the association between long-term average outdoor $PM_{2.5}$ concentrations and mortality from all nonaccidental causes (*12*). Burnett and colleagues (*30*) used these studies to develop a new model, Fusion, to characterize the magnitude and shape of the association over the global concentration range. We note that the Fusion model was developed as an alternative to the Global Exposure Mortality Model (GEMM) (*14*). Both these models characterize the potentially nonlinear relationship between outdoor $PM_{2.5}$ concentrations and nonaccidental mortality over the range of exposures reported by cohort studies. However, the GEMM requires a detailed examination of the concentration response within each cohort, while the Fusion model only relies on meta-data from each cohort to fit the model parameters, such as that provided by Chen and Hoek (*12*). A detailed comparison between the global burden estimates provided by these two models suggests that the mean burden estimates are similar; however, the Fusion model has less uncertainty at high global concentrations (*30*).

The algebraic form of the Fusion model is given by

$$F(z) = \exp\left\{\gamma \times (\min(z, \mu) + \int_{\mu}^{z} \left(1 + \frac{1-\rho}{\rho}\left(\frac{x-\mu}{\theta-\mu}\right)^{\frac{\theta-\mu}{\theta(1-\rho)}}\right)^{-1} dx + \rho\theta \ln(\max(z, \theta)/\theta))\right\}$$

Estimates of the parameters (γ, μ, ρ, and θ) were derived from results reported in the literature for each cohort, including the slope estimate based on a linear association between the logarithm of the mortality and $PM_{2.5}$, its standard error, and the 5th and 95th percentiles of the $PM_{2.5}$ exposure distribution. Hence, the model cannot identify the shape of the association at very low concentrations (i.e., below the fifth percentile of $PM_{2.5}$ concentrations from available cohorts). To address this limitation, we considered two different characterizations of the shape and uncertainty of the $PM_{2.5}$-mortality relationship at these low concentrations. The first function, F_{RCF}, incorporates guidance from WHO that a positive association exists between outdoor concentrations of $PM_{2.5}$ and mortality when concentrations are greater than 5.0 μg/m^3. However, it is uncertain whether such associations exist below 5.0 μg/m^3. We incorporate this guidance mathematically into the Fusion model by creating a random counterfactual distribution (RCF), defined as a uniform distribution between 2.5 and 5.0 μg/m^3. Then, F_{RCF} is defined such that

$$\begin{aligned} F_{RCF}(z) &= 1 && \text{if } z < 2.5\ \mu g/m^3 \\ F_{RCF}(z) &= 1 && \text{if } z \le \mathrm{RCF} \sim U(2.5\ \mu g/m^3, 5.0\ \mu g/m^3) \\ F_{RCF}(z) &= F(z)/F(\mathrm{CF}) && \text{if } z > \mathrm{RCF} \sim U(2.5\ \mu g/m^3, 5.0\ \mu g/m^3) \end{aligned}$$

This formulation stochastically models uncertainty regarding the value of the true counterfactual concentration in this range. Such RCFs have also been used by GBD (Global Burden of Disease) (*3*).

Alternatively, we define the function $F_{CanCHEC}$ by directly modeling the shape and uncertainty over this concentration interval (2.5,5.0 μg/m^3) based on the CanCHEC(z) model identified using the CanCHEC cohort. Under $F_{CanCHEC}$, the shape of the $PM_{2.5}$-mortality function is defined by CanCHEC(z) when $PM_{2.5}$ concentrations are below 5 μg/m^3 and by F when $PM_{2.5}$ concentrations are ≥5 μg/m^3. This is represented as

$$\begin{aligned} F_{CanCHEC}(z) &= 1 && \text{if } z \le 2.5\ \mu g/m^3 \\ F_{CanCHEC}(z) &= \mathrm{CanCHEC}(z) && \text{if } 2.5\ \mu g/m^3 < z < 5.0\ \mu g/m^3 \\ F_{CanCHEC}(z) &= F(z)/\mathrm{CanCHEC}(z) && \text{if } z \ge 5.0\ \mu g/m^3 \end{aligned}$$

To calculate excess deaths (i.e., all nonaccidental causes of death) attributable to outdoor $PM_{2.5}$ mass concentrations, the total number of country-specific deaths for population greater than 25 years of age (*31*) was multiplied by the population attributable fraction, defined by one minus the inverse of the relative risk evaluated at the population-weighted country-specific average. Counterfactual concentrations (i.e., when RR = 1) for $F_{CanCHEC}$ and F_{RCF} are defined above. All country-specific data for nonaccidental mortality were obtained from the Institute of Health Metrics and Evaluation (IHME) at the University of Washington (https://vizhub.healthdata.org/gbd-compare/). Country-level $PM_{2.5}$ data were also obtained from IHME (https://ghdx.healthdata.org/record/global-burden-disease-study-2019-gbd-2019-air-pollution-exposure-estimates-1990-2019) (*32*). Data and code needed to replicate the burden estimates are available in the Supplementary Materials.

SUPPLEMENTARY MATERIALS

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REFERENCES AND NOTES

1. World Health Organization, *WHO Global Air Quality Guidelines: Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide And Carbon Monoxide* (World Health Organization, 2021); https://apps.who.int/iris/handle/10665/345329, License: CC BY-NC-SA 3.0 IGO.
2. U.S. Environmental Protection Agency, *National Ambient Air Quality Standards (NAAQS) for PM* (U.S. Environmental Protection Agency, 2021); www.epa.gov/pm-pollution/national-ambient-air-quality-standards-naaqs-pm.
3. GBD 2019 Risk Factors Collaborators, Global burden of 87 risk factors in 204 countries and territories, 1990-2019: A systematic analysis for the global burden of disease study 2019. *Lancet* **396**, 1223–1249 (2020).
4. Q. Di, Y. Wang, A. Zanobetti, Y. Wang, P. Koutrakis, C. Choirat, F. Dominici, J. D. Schwartz, Air pollution and mortality in the Medicare population. *N. Engl. J. Med.* **376**, 2513–2522 (2017).
5. M. Strak, G. Weinmayr, S. Rodopoulou, J. Chen, K. de Hoogh, Z. J. Andersen, R. Atkinson, M. Bauwelinck, T. Bekkevold, T. Bellander, M. C. Boutron-Ruault, J. Brandt, G. Cesaroni, H. Concin, D. Fecht, F. Forastiere, J. Gulliver, O. Hertel, B. Hoffman, U. A. Hvidtfeldt, N. A. H. Janssen, K. H. Jockel, J. T. Jorgensen, M. Ketzel, J. O. Klompmaker, A. Lager, K. Leander, G. Nagel, B. Oftedal, G. Pershagen, A. Peters, O. Raaschou-Nielsen, M. Renzi, D. Rizzuto, Y. T. van der Schouw, S. Schramm, G. Severi, T. Sigsgaard, M. Sorensen, M. Stafoggia, A. Tjonneland, W. M. M. S. Schramm, G. Severi, T. Sigsgaard, M. Sorensen, M. Stafoggia, A. Tjonneland, W. M. M. Verschuren, D. Vienneau, K. Wolf, K. Katsouyannni, B. Brunekreef, G. Hoek, E. Samoli, Long term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: Pooled analysis. *BMJ* **374**, n1904 (2021).
6. M. Stafoggia, B. Oftedal, J. Chen, S. Rodopoulou, M. Renzi, R. W. Atkinson, M. Bauwelinck, J. O. Klompmaker, A. Mehta, D. Vienneau, Z. J. Andersen, T. Bellander, J. Brandt, G. Cesaroni, K. de Hoogh, D. Fecht, J. Gulliver, O. Hertel, B. Hoffmann, U. A. Hvidtfeldt, K. H. Jöckel, J. T. Jørgensen, K. Katsouyanni, M. Ketzel, D. T. Kristoffersen, A. Lager, K. Leander, S. Liu, P. L. S. Ljungman, G. Nagel, G. Pershagen, A. Peters, O. Raaschou-Nielsen, D. Rizzuto, S. Schramm, P. E. Schwarze, G. Severi, T. Sigsgaard, M. Strak, Y. T. van der Schouw, M. Verschuren, G. Weinmayr, K. Wolf, E. Zitt, E. Samoli, F. Forastiere, B. Brunekreef, G. Hoek, N. A. H. Janssen, Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: Results from seven large European cohorts within the ELAPSE project. *Lancet Planet. Health* **6**, E9–E18 (2022).
7. J. Meng, C. Li, R. V. Martin, A. van Donkelaar, P. Hystad, M. Brauer, 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 (2019).
8. J. K. Hammit, P. Morfeld, J. T. Tuomisto, T. C. Erren, Premature deaths, statistical lives, and years of life lost: Identification, quantification, and valuation of mortality risks. *Risk Anal.* **40**, 674–695 (2020).
9. M. Brauer, J. R. Brook, T. Christidis, Y. Chu, D. L. Crouse, A. Erickson, P. Hystad, C. Li, R. V. Martin, J. Meng, A. J. Pappin, L. L. Pinault, M. Tjepkema, A. van Donkelaar, S. Weichenthal, R. T. Burnett, Mortality-air pollution associations in low-exposure environments (MAPLE): Phase 1. *Res. Rep. Health Eff. Inst.* **203**, 1–87 (2019).
10. M. Brauer, J. R. Brook, T. Christidis, Y. Chu, D. L. Crouse, A. Erickson, P. Hystad, C. Li, R. V. Martin, J. Meng, A. J. Pappin, L. L. Pinault, M. Tjepkema, A. van Donkelaar, S. Weichenthal, R. T. Burnett, "Mortality-air pollution associations in low exposure environments (MAPLE): Phase 2," (Research Report 212, Health Effects Institute, Boston, MA, 2012); www.healtheffects.org/publication/mortality-air-pollution-associations-low-exposure-environments-maple-phase-2. [accessed 18 July 2022].
11. R. V. Martin, North American Regional Estimates (V4.NA.02.MAPLE) (Dalhousie University); fizz.phys.dal.ca/~atmos/martin/?page_id=140#v4.NA.02.MAPLE
12. J. Chen, G. Hoek, Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. *Environ. Int.* **143**, 105974 (2020).
13. C. Liu, R. Chen, F. Sera, A. M. Vicedo-Cabrera, Y. Guo, S. Tong, M. S. Z. S. Coelho, P. H. N. Saldiva, E. Lavigne, P. Matus, N. V. Ortega, S. O. Garcia, M. Pascal, M. Stafoggia, M. Scortichini, M. Hashizume, Y. Honda, M. Hurtado-Díaz, J. Cruz, B. Nunes, J. P. Teixeira, H. Kim, A. Tobias, C. Íñiguez, B. Forsberg, C. Åström, M. S. Ragettli, Y.-L. Guo, B.-Y. Chen, M. L. Bell, C. Y. Wright, N. Scovronick, R. M. Garland, A. Milojevic, J. Kyselý, A. Urban, H. Orru, E. Indermitte, J. J. K. Jaakkola, N. R. I. Ryti, K. Katsouyanni, A. Analitis, A. Zanobetti, J. Schwartz, J. Chen, T. Wu, A. Cohen, A. Gasparrini, H. Kan, Ambient particulate air pollution and daily mortality in 652 cites. *N. Engl. J. Med.* **381**, 705–715 (2019).
14. R. Burnett, H. Chen, M. Szyszkowicza, N. Fann, B. Hubbell, C. A. Pope III, J. S. Apte, M. Brauer, A. Cohen, S. Weichenthal, J. Coggins, Q. Di, B. Brunekreef, J. Frostad, S. S. Lim, H. Kan, K. D. Walker, G. D. Thurstonp, R. B. Hayes, C. C. Lim, M. C. Turner, M. Jerrett, D. Krewski, S. M. Gapstur, W. R. Diver, B. Ostro, D. Goldberg, D. L. Crouse, R. V. Martin, P. Peters, L. Pinault, M. Tjepkema, A. van Donkelaar, P. J. Villeneuve, A. B. Miller, P. Yin, M. Zhou, L. Wang, N. A. H. Janssen, M. Marra, R. W. Atkinson, H. Tsang, T. Q. Thach, J. B. Cannon, R. T. Allen, J. E. Hart, F. Laden, G. Cesaroni, F. Forastiere, G. Weinmayr, A. Jaensch, G. Nagel, H. Concin, J. V. Spadaro, Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc. Natl. Acad. Sci. U.S.A.* **115**, 9592–9597 (2018).
15. S. Weichenthal, E. Lavigne, A. Traub, H. You, K. Pollitt, T. Shin, R. Kulka, D. M. Stieb, J. Korsiak, B. Jessiman, J. R. Brook, M. Hatzopoulou, G. Evans, R. T. Burnett, Association of sulfur, transition metals, and the oxidative potential of outdoor $PM_{2.5}$ with acute cardiovascular events: A case-crossover study of Canadian adults. *Environ. Health Perspect.* **129**, 107005 (2021).
16. M. Tjepkema, T. Christidis, T. Bushnik, L. Pinault, Cohort profile: The Canadian census health and environment cohorts (CanCHECs). *Health Rep.* **30**, 18–26 (2020).
17. Statistics Canada, *Postal Code Conversion File Plus (PCCF+) Version 6D, Reference Guide: August 2015 Postal Codes* (Statistics Canada, 2017).
18. P. Finès, L. Pinault, M. Tjepkema, "Imputing Postal Codes to Analyze Ecological Variables in Longitudinal Cohorts: Exposure to Particulate Matter in the Canadian Census Health and Environment Cohort database" Anal. Studies: Methods. Ref. No. 11-633-X.no.003 (Statistics Canada, 2017).
19. S. Khan, L. Pinault, M. Tjepkema, R. Wilkins, Positional accuracy of geocoding from residential postal codes versus full street addresses. *Health Rep.* **29**, 3–9 (2018).
20. T. Christidis, A. C. Erickson, A. J. Pappin, D. L. Crouse, L. Pinault, S. Weichenthal, J. R. Brook, A. van Donkelaar, P. Hystad, R. V. Martin, M. Tjepkema, R. T. Burnett, M. Brauer, Low concentrations of fine particle air pollution and mortality in the canadian community health survey cohort. *Environ. Health* **18**, 84 (2019).
21. D. L. Gordon, M. Janzen, Suburban nation? Estimating the size of Canada's suburban population. *J. Archit. Plan Res.* **30**, 197–220 (2013).
22. D. L. Crouse, S. Philip, A. van Donkelaar, R. V. Martin, B. Jessiman, P. A. Peters, S. Weichenthal, J. R. Brook, B. Hubbell, R. T. Burnett, A new method to jointly estimate the mortality risk of long-term exposure to fine particulate matter and its components. *Sci. Rep.* **6**, 18916 (2016).
23. F. I. Matheson, J. R. Dunn, K. L. W. Smith, R. Moineddin, R. H. Glazier, Development of the Canadian Marginalization Index: A new tool for the study of inequality. *Can. J. Public Health* **103**, S12–S16 (2012).
24. A. van Donkelaar, R. V. Martin, C. Li, R. T. Burnett, Regional estimates of chemical composition of fine particulate matter using a combined geoscience-statistical method with information from satellites, models, and monitors. *Environ. Sci. Technol.* **53**, 2595–2611 (2019).
25. R. N. C. Latimer, R. V. Martin, Interpretation of measured aerosol mass scattering efficiency over North America using a chemical transport model. *Atmos. Chem. Phys.* **19**, 2635–2653 (2019).
26. G. Snider, C. L. Weagle, R. V. Martin, A. van Donkelaar, K. Conrad, D. Cunningham, C. Gordon, M. Zwicker, C. Akoshile, P. Artaxo, N. X. Anh, J. Brook, J. Dong, R. M. Garland, R. Greenwald, D. Griffith, K. He, B. N. Holben, R. Kahn, I. Koren, N. Lagrosas, P. Lestari, Z. Ma, J. V. Martins, E. J. Quel, Y. Rudich, A. Salam, S. N. Tripathi, C. Yu, Q. Zhang, Y. Zhang, M. Brauer, A. Cohen, M. D. Gibson, Y. Liu, SPARTAN: A global network to evaluate and enhance satellite-based estimates of ground-level particulate matter for global health applications. *Atmos. Meas. Tech. Discuss.* **7**, 505–521 (2015).
27. D. L. Crouse, A. C. Erickson, T. Christidis, L. Pinault, A. van Donkelaar, L. Chi, J. Meng, R. V. Martin, M. Tjepkema, P. Hystad, R. Burnett, A. Pappin, M. Brauer, S. Weichenthal, Evaluating the sensitivity of PM2.5-mortality associations to the spatial and temporal scale of exposure assessment. *Epidemiology* **31**, 168–176 (2020).
28. J. F. E. Harrel Jr., in *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis* (New York, 2015); https://link.springer.com/book/10.1007%2F978-3-319-19425-7.
29. M. M. Nasari, M. Szyszkowicz, H. Chen, D. Crouse, M. C. Turner, M. Jerrett, C. A. Pope III, B. Hubbel, N. Fann, A. Cohen, M. Gapstur, R. W. Driver, D. Stieb, M. H. Forouzanfar, S.-Y. Kim, C. Olives, D. Krewski, R. T. Burnett, A class of non-linear exposure-response models suitable for health impact assessment applicable to large cohort studies of ambient air pollution. *Air Qual. Atmos. Health* **9**, 961–972 (2016).
30. R. T. Burnett, J. V. Spadaro, G. R. Garcia, C. A. Pope, Designing health impact functions to assess marginal changes in outdoor fine particulate matter. *Environ. Res.* **204**, 112245 (2022).
31. GBD Compare 2021, GBD Compare | IHME Viz Hub, www.healthdata.org [accessed 12 February 2021].
32. GBD 2019 Air Pollution Exposure Estimates 1990–2019, https://ghdx.healthdata.org/record/global-burden-disease-study-2019-gbd-2019-air-pollution-exposure-estimates-1990-2019 [accessed 12 February 2021].

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