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$_{2.5}$-mortality 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 focuses on nonaccidental mortality as this

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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 $\mu$g/m$^3$ (SD = 3.1 $\mu$g/m$^3$) with values ranging from 2.5 to 17.7 $\mu$g/m$^3$. In total, 13.3% of person-years in the cohort had outdoor PM$_{2.5}$ concentrations below 5 $\mu$g/m$^3$, which is indicated by the vertical dotted line.)

![Fig. 1. Fully adjusted restricted cubic spline relative risk predictions for non-accidental 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 during follow-up (13.3% of person-years had PM$_{2.5}$ values below 5 $\mu$g/m$^3$, which is indicated by the vertical dotted line).](https://www.science.org/)
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 µg/m$^3$) and refined the global concentration-response function over the concentration range from 2.5 to 5 µg/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 non-linear relationship (and uncertainty) between PM$_{2.5}$ and nonaccidental mortality at levels below the current WHO guideline (i.e., 5 µg/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

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**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 µg/m$^3$. (B) Global distribution of annual average outdoor PM$_{2.5}$ concentrations.

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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 $\mu$g/m$^3$) and below (≤12 $\mu$g/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 $\mu$g/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 $\mu$g/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 $\mu$g/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 $\mu$g/m$^3$ and reported stronger associations at lower PM$_{2.5}$ mass 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.
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.
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

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

for $K \geq 3$ with

$$s_l(z) = \left( \begin{array}{c} \max_0 \left( z - \lambda_1 \right) \left( (\lambda_k - \lambda_1)^{2/3} \right)^3 - \left( \lambda_k - \lambda_{l-1} \right) \\ \max_0 \left( z - \lambda_{K-1} \right) \left( (\lambda_k - \lambda_{l-1})^{2/3} \right)^3 + \left( \lambda_{K-1} - \lambda_l \right) \\ \max_0 \left( z - \lambda_K \right) \left( (\lambda_k - \lambda_{l-1})^{2/3} \right)^3 \end{array} \right)$$

and $K$ knot concentrations ($\lambda_1, \ldots, \lambda_K$). The RCS is linear below $\lambda_1$ and above $\lambda_K$ 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 ($z, s_1(z), \ldots, s_{K-2}(z)$) 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 $\ln\text{RCS}(z) = \hat{\beta} (s(z) - \bar{s}(z))$, where $\bar{s}$ is the person-year–based mean concentration, with uncertainty in the estimate given by $\hat{\sigma}(z) = (s(z) - \bar{s}(z))' \hat{V} (s(z) - \bar{s}(z))$. We summarize the information obtained from the fitted RCS model by its mean prediction at any concentration $z$, $\text{RCS}(z)$, and its $95\%$ CI: $\exp(\ln\text{RCS}(z) \pm 1.96 \times \hat{\sigma}(z))$. 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 $\text{RCS}(z)/\text{RCS}(z_{cf})$. As described below, $z_{cf}$ was set to the minimum observed concentration (2.5 mg/m$^3$).
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 sigmoidal. 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 function that is suitable for benefits analysis: SCHIF(z) = exp{θ ln((z−z0)/δ)+1/(1+exp(−(z−z0)/v))}, with parameters (θ, α, μ, and v) estimated from the cohort data. Although this function can take near linear, sub/supralinear, and sigmoidal 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{γ ln((z−z0)/δ)+1}/ 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 r_i = MVN(β, V), where MVN is the multivariate normal distribution and calculating RCS_i(z) = exp{r_i(z)} over a sequence of J concentrations (z_0, z_1, ..., z_J) with z_0 defined as the maximum concentration and i = 1, 2, ..., 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 RCS_i(z)/RCS_i(z_d). We denote our relative risk model as CanCHEC(z). It has been defined such that CanCHEC(z_d) = 1, where z_d 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 PM2.5 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 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 PM2.5 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

\[ F(z) = \exp\left[\gamma \times (\min(z, \mu) + \frac{\delta}{\rho} \left( \frac{x - \mu}{\theta - \mu} \right)^{\delta/\rho} \right] \]

\[ \rho \ln(\max(z, \theta)/(\theta)) \]

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Conceptualization: S.W., R.T.B., and M.B. Methodology and statistical analyses: R.T.B., L.P., and T.C. Data visualization: S.W. and R.T.B. Writing—review and editing: S.W., T.C., R.T.B., J.R.B., Y.C., D.L.C., A.C.E., P.H., C.L., R.V.M., J.M., A.J.P., M.T., A.v.D., C.L.W., and M.B. **Competing interests:** M.B. served on the WHO Guideline Development Group (no remuneration was provided but travel costs to meetings were covered). All other authors declare that they have no competing interests. **Data and materials availability:** Outdoor PM$_{2.5}$ data used for epidemiological analysis are available at https://zenodo.org/record/6557778. Annual average outdoor PM$_{2.5}$ data used for burden estimates are available at https://ghdx.healthdata.org/record/global-burden-disease-study-2019-gbd-2019-air-pollution-exposure-estimates-1990-2019. CanCHEC cohort data are held in secure facilities managed by Statistics Canada. These can be accessed through the microdata access portal application process (the application process and procedures are available online: www.statcan.gc.ca/en/microdata/data-centres/access). Application forms are available online: www.statcan.gc.ca/en/microdata/data-centres/forms. Briefly, users must create an account and provide the following information: (i) information on the type of project (e.g., government funded, academic, and other); (ii) a project proposal including timelines and other necessary information specified in the application procedure; and (iii) investigator profiles. Statistics Canada then reviews the application and communicates with the principal investigator to complete the remaining administrative procedures before data access is granted through Research Data Centers located across Canada. Data and code used for burden estimates are available in the Supplementary Materials.
How low can you go? Air pollution affects mortality at very low levels
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