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Permalink

https://escholarship.org/uc/item/1z5470qd

Journal

Environmental Health Perspectives, 131(3)

ISSN

1542-4359

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Publication Date

2023-03-01

DOI

10.1289/ehp11095

Peer reviewed

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Using Parametric g-Computation to Estimate the Effect of Long-Term Exposure to Air Pollution on Mortality Risk and Simulate the Benefits of Hypothetical Policies: The Canadian Community Health Survey Cohort (2005 to 2015)

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Background: Numerous epidemiological studies have documented the adverse health impact of long-term exposure to fine particulate matter [particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$)] on mortality even at relatively low levels. However, methodological challenges remain to consider potential regulatory intervention's complexity and provide actionable evidence on the predicted benefits of interventions. We propose the parametric g-computation as an alternative analytical approach to such challenges.

Method: We applied the parametric g-computation to estimate the cumulative risks of nonaccidental death under different hypothetical intervention strategies targeting long-term exposure to $PM_{2.5}$ in the Canadian Community Health Survey cohort from 2005 to 2015. On both relative and absolute scales, we explored the benefits of hypothetical intervention strategies compared with the natural course that *a*) set the simulated exposure value at each follow-up year to a threshold value if exposure was above the threshold (8.8 $\mu g/m^3$, 7.04 $\mu g/m^3$, 5 $\mu g/m^3$, and 4 $\mu g/m^3$), and *b*) reduced the simulated exposure value by a percentage (5% and 10%) at each follow-up year. We used the 3-y average $PM_{2.5}$ concentration with 1-y lag at the postal code of respondents' annual mailing addresses as their long-term exposure to $PM_{2.5}$. We considered baseline and time-varying confounders, including demographics, behavior characteristics, income level, and neighborhood socioeconomic status. We also included the R syntax for reproducibility and replication.

Results: All hypothetical intervention strategies explored led to lower 11-y cumulative mortality risks than the estimated value under the natural course without intervention, with the smallest reduction of 0.20 per 1,000 participants (95% CI: 0.06, 0.34) under the threshold of 8.8 $\mu g/m^3$, and the largest reduction of 3.40 per 1,000 participants (95% CI: −0.23, 7.03) under the relative reduction of 10% per interval. The reductions in cumulative risk, or numbers of deaths that would have been prevented if the intervention was employed instead of maintaining the status quo, increased over time but flattened toward the end of the follow-up period. Estimates among those ≥65 years of age were greater with a similar pattern. Our estimates were robust to different model specifications.

Discussion: We found evidence that any intervention further reducing the long-term exposure to $PM_{2.5}$ would reduce the cumulative mortality risk, with greater benefits in the older population, even in a population already exposed to low levels of ambient $PM_{2.5}$. The parametric g-computation used in this study provides flexibilities in simulating real-world interventions, accommodates time-varying exposure and confounders, and estimates adjusted survival curves with clearer interpretation and more information than a single hazard ratio, making it a valuable analytical alternative in air pollution epidemiological research. https://doi.org/10.1289/EHP11095

Introduction

Given that collective efforts in previous decades have successfully reduced the level of fine particulate matter [particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$)] globally, quantifying the effectiveness of policies that further reduce ambient $PM_{2.5}$ is becoming particularly important in supporting evidence-based policymaking. Indeed, previous studies found consistent evidence of deleterious associations between long-term exposure to low levels of $PM_{2.5}$ (e.g., below the current health-based standards or guidelines) and risk of mortality[1–6] and morbidity,[7–9] suggesting potential reductions in health burden if the $PM_{2.5}$ level were to be further reduced. Although the evaluation of exposure–response functions in existing studies provides important information in understanding the potential effectiveness of policies, further methodological considerations are required to estimate the potential benefits of realistic interventions.

First, evidence suggested that the risk associated with the changes in acute exposure to $PM_{2.5}$ could vary with time,[10–13] potentially due to changes in chemical compositions of $PM_{2.5}$, with different toxicity and population susceptibility toward $PM_{2.5}$.[14,15] A similar disparity in toxicity across long-term exposure to $PM_{2.5}$ components was also observed,[16,17] suggesting that such temporal changes could exist in risk associated with long-term exposure to $PM_{2.5}$. In other words, it is important to use analytical methods flexible enough to incorporate such temporal changes in estimating related health burdens. However, existing studies of health impacts of long-term exposure to $PM_{2.5}$ generally considered time-fixed exposure and confounders (Table S1 provides a narrative review of recent studies on health impact of long-term exposure to $PM_{2.5}$ and their methodological considerations). Furthermore, the most widely used estimate for exposure–response function in this field is a single hazard ratio (HR) for the follow-up period estimated with a standard Cox proportional hazards model (Table S1), which is assumed to be constant over

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Supplemental Material is available online (https://doi.org/10.1289/EHP11095).

R.V.M. receives grant support currently from the Clean Air Fund and previously from the ClimateWorks Foundation. The other authors declare they have nothing to disclose.

Received 11 February 2022; Revised 5 December 2022; Accepted 14 February 2023; Published 15 March 2023.

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time and precludes consideration of temporal changes. Although extension of a Cox proportional hazards model could provide period-specific HRs that incorporate temporal changes,[18] recent developments in causal inference literature raise concern about the ambiguity in the causal interpretation of HR and period-specific HRs.[19] Specifically, period-specific HRs have a built-in selection bias because susceptible people exposed to higher $PM_{2.5}$ concentrations are more likely to die early if $PM_{2.5}$ exposure truly increases risk of mortality and they are removed from the susceptible population in later periods.[20] This differential depletion of susceptible individuals over time can lead to artificially diminished or even reversed period-specific HR later in a study even when the cumulative survival is still lower among those exposed to higher $PM_{2.5}$ concentrations, violating the proportional assumption and hindering interpretation.[21]

Second, the calculation of the health burden related to long-term exposure to $PM_{2.5}$ has commonly employed an exposure–response function previously estimated with the static intervention strategy, where a fixed change of exposure value was assigned to the entire population.[22] However, the more flexible and realistic dynamic intervention strategy—where the exposure value was assigned based on individuals' history of covariates, including exposure—is hard to apply when existing exposure–response functions are used.[22] Methods capable of incorporating a dynamic intervention strategy to imitate complexities in actual regulatory interventions are needed to provide direct evidence on effectiveness of air pollution control policies.[23] To fill this gap in knowledge translation, we propose the parametric g-computation as an analytical alternative in air pollution epidemiological research, a method that could better predict the effectiveness of hypothetical policies while being more flexible in resembling real-world interventions.

G-computation (also known as g-formula) is a generalization of nonparametric standardization developed under the potential outcome framework for causal inference,[24] and parametric g-computation is a variation that employs parametric modeling. Under the consistency (i.e., the exposure is defined unambiguously, and all exposed individuals receive the same version of treatment),[22,25] exchangeability (i.e., no unmeasured confounding or informative censoring),[25] and positivity (i.e., probability of receiving every exposure conditioning on confounders is greater than zero) assumptions,[22] and a time-to-event outcome setting, g-computation can provide marginal causal risk estimates at each follow-up time point under hypothetical intervention strategies (i.e., adjusted survival curves) while allowing other population characteristics to be altered according to the intervention.[26] Particularly, parametric g-computation excels in estimating adjusted survival curves under dynamic intervention strategies. In other words, g-computation can directly answer causal questions such as, "How many lives could we save if we promulgate a policy that further reduces air pollution to levels lower than the current standard among those whose exposure were above the current standard, compared with maintaining the status quo?" Although parametric g-computation has been widely applied in other fields of epidemiology,[27–30] its application in air pollution studies remains limited. Previous applications in this field either focused on a small cohort in occupational settings[31–33] or modeled simple air pollution changes on asthmatic outcomes among children (i.e., not considering time-varying confounding or changes in effect estimates over time).[34,35]

In this study, we aimed to demonstrate the use of parametric g-computation to evaluate the effectiveness of hypothetical intervention strategies targeting long-term exposure to $PM_{2.5}$ on reducing mortality using a Canadian cohort experiencing low $PM_{2.5}$ exposure from 2005 to 2015. This analytical alternative can account for previously unaddressed complexities, refine the effect estimates with less restrictive identification conditions, and provide estimates that are more intuitive to policy makers.

Methods

Study Population

We created a retrospective cohort with respondents to the Canadian Community Health Survey (CCHS) from three enrolling cycles in the years of 2000/2001, 2003, and 2005, respectively.[36–38] CCHS is a national cross-sectional survey collecting health status, health care utilization, and health determinants information of the Canadian population, covering the population $\geq$12 years of age in the 10 provinces and the 3 territories. The survey excluded individuals living on reserves and other Aboriginal settlements, full-time members of the Canadian Forces, the institutionalized population, and residents of certain remote regions.

Among CCHS respondents who gave permission to share and link their information with other administrative data sets, we obtained their mailing address history and death records through 31 December 2015 via Statistics Canada's Social Data Linkage Environment using probabilistic methods based on common identifiers.[2,39] We focused on nonaccidental death as outcome (*International Classification of Diseases Ninth Revision*,[40] ICD-9 codes 001–799, and *International Classification of Diseases Tenth Revision*,[41] ICD-10 codes A–R) in this study. To facilitate pooling of results across cycles, we restricted the cohort to participants who were alive on 1 January 2005 and used this date as the start of follow-up for all cycles. We also restricted our cohort to individuals >25 and <80 years of age in 2005, thus all cohort participants were adults and were followed for 11 y or until death. In addition, we dropped respondents who were missing data for covariates, including exposure in 2005. This study was approved by the Health Canada–Public Health Agency of Canada Research Ethics Board.

Exposure Assessment

To estimate respondents' long-term exposure to $PM_{2.5}$, we used the ground-level $PM_{2.5}$ concentrations from V4.NA.02.MAPLE of the Atmospheric Composition Analysis Group of Washington University,[42] which covers all of North America below the 70°N latitude. The $0.01^\circ \times 0.01^\circ$ (roughly equivalent to 1×1 km^2 at the latitudes where most Canadians live) annual estimates of $PM_{2.5}$ concentrations from 2001 to 2015 were derived using satellite retrievals of aerosol optical depth and chemical transport model simulations and calibrated with ground-based observations using geographically weighted regression.[43] The annual estimates of $PM_{2.5}$ concentrations closely agree with long-term cross-validated ground measurements at fixed-site monitors ($n = 2{,}312$) across North America ($R^2 = 0.70$).[43] Using the ground-level $PM_{2.5}$ concentration surfaces described above, we first assigned the annual $PM_{2.5}$ concentration of the grid cell into which the postal code centroid falls as the postal code–specific annual $PM_{2.5}$ concentrations. Then we calculated respondents' annual long-term exposure to $PM_{2.5}$ as 3-y average postal code–specific $PM_{2.5}$ concentrations with 1-y lag based on their mailing address history (e.g., a respondent's long-term exposure to $PM_{2.5}$ in 2013 is the average of their postal code–specific $PM_{2.5}$ concentrations in 2010, 2011, and 2012).[2] We used the 3-y average with 1-y lag to represent long-term exposure of $PM_{2.5}$ so that the exposure always preceded the outcome and that the timeframe was consistent with the regulatory review of Canadian Ambient Air Quality Standards for annual $PM_{2.5}$ exposure.[44] This metric of long-term exposure to $PM_{2.5}$ has been widely used in previous Canada-based studies of long-term health impacts of $PM_{2.5}$ exposure.[2,45,46]

Covariates Other than Exposure

In this section we summarize the data sources and meaning of covariates in this study, whereas the covariate selection to control

for in our model is discussed in the "Statistical Analysis" section. We used covariates to describe the collection of exposure, time-fixed confounders, and time-varying confounders in this study. Baseline characteristics of respondents were ascertained at the time of enrollment into CCHS via self-report and were processed using the same method as in previous studies,[2,45] including sex, age (converted to value in 2005), body mass index (BMI), marital status, immigrant status, visible minority, indigenous status, smoking status, alcohol consumption, consumption of fruits and vegetables, leisure physical activity, working status, and educational attainment (details of variable categorization are listed in Table 1). By using 2005 as the start of the follow-up period for all individuals, we assumed that all baseline characteristics other than age ascertained at the time of enrollment would remain the same through the entire follow-up period.

We also obtained characteristics of the respondents and their neighborhoods through linkage with administrative data sets using methods similar to those used in previous studies.[2,45] Specifically, we obtained the annual income quintile of respondents through linkage with tax data based on common identifiers.[45] For person-years with missing annual family income, we imputed them with the nearest prior values and the proportions of missing were 5.21%, 4.97%, and 4.69% for cycles 2000/2001, 2003, and 2005, respectively. We also obtained annual characteristics of neighborhoods through linkage with census data from the nearest census year based on respondents' mailing address postal codes, including community size at the census metropolitan area level and the Canadian Marginalization Index at the census dissemination-area level. The Canadian Marginalization Index summarizes dissemination area-level socioeconomic status into four dimensions using principal component analysis to reduce the dimensionality of census data: The immigration and visible minority index combines information on the proportion of recent immigrants and proportion of people self-identifying as a visible minority; the households and dwellings index combines information on types and density of residential accommodations and family structure characteristics; the material resources index combines information on access to and attainment of basic material needs; and the age and labor force index combines information on participation in the labor force and the proportion of seniors.[47] Last, we obtained airshed (six distinct regions of Canada that cut cross jurisdictional boundaries and show similar air quality characteristics and air movement patterns within each region) to capture large-scale spatial variation,[48] and urban form information of respondents' neighborhoods in 2005 to capture the urbanicity of participants' residences, through linkage with census data.[2]

Hypothetical Intervention Strategies

In this study, we explored three types of intervention strategies: *a*) applying the simulated value of time-varying covariates without any intervention (natural course), *b*) setting the simulated long-term exposure to the $PM_{2.5}$ value at each follow-up year to a threshold value if the $PM_{2.5}$ concentration was higher than the threshold (threshold intervention), and *c*) reducing the simulated $PM_{2.5}$ value by a fixed percentage at each interval (i.e., follow-up year; relative reduction intervention). Threshold values explored included the current Canadian Ambient Air Quality Standards for $PM_{2.5}$ of 8.8 $\mu g/m^3$, 80% of the current Canadian Ambient Air Quality Standards for $PM_{2.5}$ (or 7.04 $\mu g/m^3$), the new World Health Organization (WHO) air quality guideline of 5 $\mu g/m^3$, and a $PM_{2.5}$ level that was farther below the WHO guideline (4 $\mu g/m^3$). The interval-specific relative reduction values explored were 10% and 5% per interval. To avoid extensive model extrapolation, we restricted the relative reduction intervention so that individuals with an exposure $<1.8\ \mu g/m^3$, the background $PM_{2.5}$ level in Canada,[49] would not be further reduced. The first type of intervention strategy represents the predicted covariates based on the observed data without intervening and serves as the reference for other strategies. The second and the third are dynamic intervention strategies that incorporate the impact of intervention on covariates during earlier time points while simulating covariates in later time points.

Statistical Analysis

We applied parametric g-computation with different hypothetical intervention strategies targeting long-term exposure to $PM_{2.5}$ to understand the benefits of intervention strategies on cumulative risk of nonaccidental death. We conducted g-computation analysis for each enrollment cycle separately and pooled the results across cycles using meta-regression. Briefly, we estimated the cumulative mortality risk at each follow-up year standardized to the distribution of the confounders and long-term exposure to $PM_{2.5}$ in the study population, with all time-varying covariates (confounders and $PM_{2.5}$) conditioned on covariates history, with and without intervention on $PM_{2.5}$ (i.e., adjusted survival curves). Next, we calculated the differences in cumulative mortality risks between the natural course and other intervention strategies on both absolute and relative scales to provide estimates for the benefits of hypothetical intervention strategies compared with maintaining the status quo. We pooled results with fixed-effect meta-regression, which calculates a weighted average of cycle-specific estimates with weights equal to the inverse of the variance using the "meta" package.[50]

The proof of parametric g-computation are described extensively elsewhere,[22(chap21),29] and detailed description of how to implement such an approach in a setting similar to our study was previously published,[28] with the available R package for easy implementation.[51] However, given that the application of parametric g-computation is limited in air pollution studies, we include a diagram (Figure 1) summarizing the four steps that carry out the g-computation in a time-to-event setting with time-varying exposure and confounders and describe the steps in detail below.

Steps to Implement Parametric g-Computation

In Step 1, we fitted a pooled logistic model (i.e., discrete-time hazards model) and adjusted for baseline characteristics, time-varying characteristics, quadratic function of year, and interaction between long-term exposure to $PM_{2.5}$ and categorical year. The pooled logistic model estimated the probability of death during the year conditioning on survival until the start of the year given all covariates (including $PM_{2.5}$), which allowed the conditional probability of death and its association with $PM_{2.5}$ to vary over the year. We chose confounders to control for in the outcome model based on substantive knowledge of the relationship between long-term $PM_{2.5}$ exposure and mortality as summarized in the simplified directed acyclic graph (Figure S1). We include a full list of covariates in Table 1, with specific forms of covariates listed in Table 2. We included both individual socioeconomic status indicators (e.g., education and family income) and community socioeconomic status indicators (e.g., Canadian Marginalization Index for dissemination area) to fully capture the variation in socioeconomic status among cohort participants, which is a major source of residual confounding. We also included individual behavior indicators, such as dietary and exercise patterns, which are strong risk factors for mortality, precede the exposure, and might share common unmeasured causes with the exposure even though they might not directly cause the exposure.[52] Of note, in the setting when only time-fixed covariates were used, we could estimate marginal adjusted survival

Table 1. Descriptive statistics for participants of the Canadian Community Health Survey cohort at the start of follow-up (2005) by cycle.

	Cycle		
Characteristics	2000/2001	2003	2005
Cohort size (n)	62,365[a]	62,380[a]	66,835[a]
Nonaccidental deaths [n (%)]	6,475 (10.4)	6,525 (10.5)	6,135 (9.2)
Time-fixed covariates			
Age [y (mean ± SD)]	52.1 ± 13.4	52.1 ± 14.4	50.9 ± 14.9
Sex (%)			
Female	45.2	45.9	46.2
Male	54.8	54.1	53.8
BMI [kg/m^2 (%)]			
Normal weight (18.5–24.9)	37.5	32.2	32.0
Overweight (25.0–29.9)	36.7	39.8	39.8
Obese 1 (30.0–34.9)	16.4	19.1	18.9
Obese 2 (≥35)	6.8	8.1	8.4
Underweight (<18.5)	2.6	0.8	0.9
Marital status (%)			
Married or common-law	65.9	64.3	63.0
Separated, widowed, or divorced	19.6	20.8	20.8
Single	14.5	14.9	16.2
Immigrant status (%)			
Immigrant	10.7	11.3	11.6
Time lived in Canada among immigrants [y (mean ± SD)]	37.4 ± 13.3	36.8 ± 13.9	35.7 ± 14.1
Nonimmigrant	89.3	88.7	88.4
Visible minority status (%)			
Visible minority	5.4	6.3	4.4
Not a visible minority	94.6	93.7	95.6
Indigenous status (%)			
Indigenous	1.8	2.3	0[b]
Nonindigenous	98.2	97.7	100
Smoking status (%)			
Never smoker	26.8	27.6	29.0
Occasional smoker	44.5	47.7	47.1
Smoke <10 cigarettes/d	3.8	4.3	4.2
Smoke 11–20 cigarettes/d	6.0	5.6	5.7
Smoke ≥20 cigarettes/d	10.9	9.0	8.6
Former smoker	8.0	5.8	5.4
Alcohol consumption (%)			
Never drinker	4.4	4.2	4.1
Occasional drinker	13.1	13.7	13.6
Regular drinker, binging unknown	20.3	18.7	18.2
Regular, non-binge drinker	29.4	31.0	30.4
Regular, binge drinker	26.9	26.7	27.3
Former drinker	5.9	5.7	6.4
Daily consumption of fruits and vegetables (%)			
<5 servings/d	64.7	59.6	29.9
5–10 servings/d	32.4	37.0	19.6
≥10 servings/d	2.9	3.4	1.6
Chose to not answer[c]	NA	NA	48.9
Employment status (%)			
Employed	66.6	62.3	61.8
Not employed	2.6	2.6	2.3
Not in work force	30.8	35.1	35.9
Education (%)			
No high school diploma	24.1	22.4	20.6
High school	18.9	18.0	15.4
Any postsecondary	42.0	42.5	46.1
University	15.0	17.1	17.9
Leisure time physical activity (%)			
Active	21.2	24.0	23.4
Moderately active	25.4	26.4	26.7
Inactive	53.4	49.6	49.9
Urban form (%)			
Active urban core	6.2	7.0	7.0
Transit-reliant suburb	3.9	4.3	4.6
Auto-reliant suburb or no data	26.5	29.4	29.3
Exurb	4.8	5.0	4.8
Non-CMA/CA[d]	58.6	54.3	54.3
Airshed (%)			
Western	12.0	10.7	10.4
Prairie	16.0	14.9	13.5
Western Central	9.1	8.6	7.8
Southern Atlantic	17.2	14.6	17.3

Table 1. (*Continued.*)

Characteristics	Cycle		
	2000/2001	2003	2005
East Central	44.1	49.3	48.9
Northern	1.6	1.9	2.1
Time-varying covariates			
Community size (population) [*n* (%)]			
>1,500,000	13.5	14.7	16.9
500,000–1,499,999	10.3	11.9	10.4
100,000–499,999	20.4	21.0	19.7
30,000–99,999	14.7	13.2	12.4
10,000–29,999	7.4	7.0	7.5
Non-CMA/CA[d]	33.7	32.2	33.1
Annual family income quintile (%)			
1st (lowest)	19.0	19.1	19.3
2nd	19.7	19.3	19.1
3rd	19.9	19.8	19.5
4th	20.7	20.4	20.8
5th (highest)	20.7	21.4	21.3
Canadian Marginalization Index—age and labor force [quintile (%)]			
1st (lowest marginalization)	14.4	15.3	14.8
2nd	13.5	13.6	13.7
3rd	13.7	13.9	14.1
4th	22.2	20.9	20.8
5th (highest marginalization)	36.2	36.3	36.6
Canadian Marginalization Index—material resources [quintile (%)]			
1st (lowest marginalization)	15.5	15.7	15.2
2nd	16.8	16.9	17.0
3rd	20.8	20.8	20.2
4th	18.1	17.8	17.0
5th (highest marginalization)	28.8	28.8	30.6
Canadian Marginalization Index—immigration and visible minority [quintile (%)]			
1st (lowest marginalization)	42.6	41.4	41.8
2nd	26.9	26.9	26.5
3rd	17.0	17.3	15.9
4th	8.5	9.0	9.9
5th (highest marginalization)	5.0	5.4	5.9
Canadian Marginalization Index—households and dwellings [quintile (%)]			
1st (lowest marginalization)	22.7	21.2	21.7
2nd	28.3	27.7	27.1
3rd	21.0	21.7	21.0
4th	17.3	17.8	17.6
5th (highest marginalization)	10.7	11.6	11.8
Average $PM_{2.5}$ of previous 3 y ($\mu g/m^3$) (mean ± SD)	6.4 ± 2.2	6.5 ± 2.3	6.5 ± 2.3
Average $PM_{2.5}$ of previous 3 y ($\mu g/m^3$) [median (minimum, 25th percentile, 75th percentile, maximum)]	5.9 (1.7, 15.0, 4.6, 7.8)	6.1 (1.7, 4.7, 8.1, 15.0)	6.1 (1.6, 4.6, 8.2, 15.0)

Note: BMI, body mass index; CA, census agglomeration (status); CMA, census metropolitan area; NA, not applicable; $PM_{2.5}$, particulate matter ≤2.5 μm in aerodynamic diameter.
[a]Rounded to the nearest 5 or 0 in the last digit to protect privacy.
[b]We did not include the indigenous status indicator in models of cycle 2005.
[c]Consumption of fruit and vegetable was listed with an additional option in cycle 2005 but not in the other two cycles.
[d]Not categorized as CMA or CA status and likely in rural area.

curves directly using outputs from this pooled logistic model by predicting the probability of death standardized to the distributions of covariates under the intervention of interest (e.g., setting the baseline level of exposure to a specific value while keeping all baseline covariates the same as observed for all participants).[19,53] However, in our study setting of time-varying covariates and time-to-event outcome, we also needed to model time-varying covariates (including $PM_{2.5}$) concentration so that we could simulate time-varying covariates at all follow-up years for all cohort participants, especially for periods after participants' death.[28,29]

In Step 2, we modeled the time-varying covariates (including $PM_{2.5}$ concentration) using linear regressions while including variables such as the previous-year value of the covariate of interest, baseline characteristics, same-year values of time-varying covariates set to occur before the covariate of interest, and quadratic function of time. The choice of independent variables in covariate models was based on substantive knowledge as summarized in the simplified directed acyclic graph (Figure S1). We summarize the list of all covariates in Table 1 and the specific forms of covariates included in the covariate models in Table 2. We set the sequence of time-varying covariates as community size, income, immigration and visible minority, material resources, households and dwellings, age and labor force, and long-term exposure to $PM_{2.5}$. Given that previous studies using different cycles of CCHS found a supralinear $PM_{2.5}$–mortality association,[2,45,54,55] we used natural logarithm-transformed long-term exposure to $PM_{2.5}$ as the independent variable in both the outcome and covariate model in the main analysis.

In Step 3, we simulated new data sets based on the intervention strategies. For each intervention, we randomly sampled 10,000 participants from the cohort with replacement (i.e., Monte Carlo sampling) and created an empty data set of all sampled participants for all follow-up years until the end of the period of interest (normally the end of the follow-up period, as in this study, but extrapolation is possible with extra assumptions). We simulated new data sets for only 10,000 individuals instead of the number of participants in the study cohorts (~ 60,000 participants in each cohort) to save computation time, and a similar practice was conducted

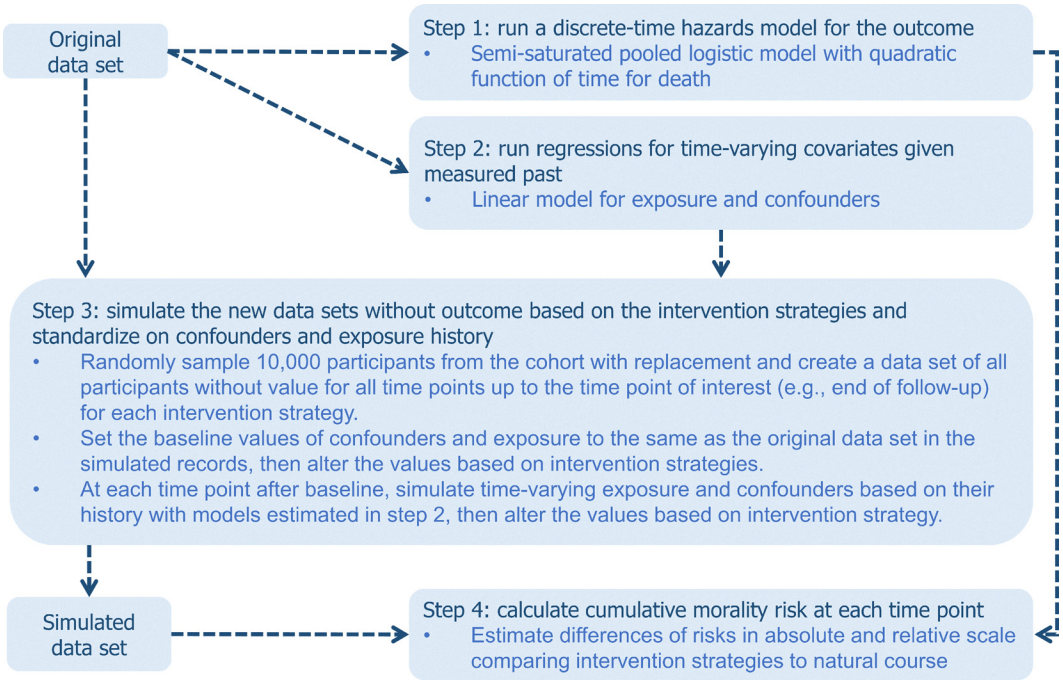

Figure 1. Diagram of g-computation with time-to-event outcome and time-varying covariates. Arrows indicate source of information for the indicated step.

before with the smaller cohort.[29] Next, we assigned the baseline values of all covariates (values of baseline covariates and values of time-varying covariates at the start of the follow-up period) in each simulated data set to the same as its original data set, we then altered the relevant covariate values based on the intervention strategy (e.g., setting the baseline long-term exposure to $PM_{2.5}$ to 5 $\mu g/m^3$ if it was higher than 5 $\mu g/m^3$ in the threshold intervention of 5 $\mu g/m^3$, but we could include other covariates if needed). Last, we simulated time-varying covariates at each year after baseline based on their history with covariate models estimated in the second step and altered the covariates based on the intervention strategy.

In Step 4, with the simulated data sets and outcome model from the first step, we calculated for each individual the probability of dying during each year, conditioning on surviving to the beginning of this year, standardized to the distribution of the confounders and long-term exposure to $PM_{2.5}$ under the intervention strategies, regardless of their observed outcomes. Next, we calculated for each individual the cumulative mortality risk at each year as the cumulative sum of the abovementioned conditional probability of mortality times the probability of surviving until the beginning of the time interval. The estimated cumulative mortality risk at each year equals the average of estimates from all individuals for all hypothetical interventions. We also calculated the absolute difference in cumulative mortality risk and the percentage change in cumulative mortality risk with estimated cumulative mortality risk from the natural course as the reference.

In addition, we calculated the 95% confidence intervals (CIs) for all estimates using standard errors from 200 bootstrap iterations.[56] In each iteration, we randomly sampled the same number of participants as in the original cohort with replacement and ran the four steps described above to calculate cumulative mortality risks under the intervention strategies. We chose this number of iterations because we were constrained by available computational resources (>1 h of computational time for each bootstrap iteration), and the original application of parametric g-computation in time-varying covariates and time-to-event setting used the same number.[29] Future studies with more computational resources might consider a larger number of bootstrap iterations.

Sensitivity Analyses

To test the robustness of our results to model misspecification, we considered a number of different model specifications for both outcome and covariate models, including *a*) reordering the sequence of time-varying covariates in covariate models by moving "age and labor force" to before other dimensions of the Canadian Marginalization Index, moving income to after all dimensions of the Canadian Marginalization Index, and moving $PM_{2.5}$ to the first place among all covariates; *b*) extending the extent of history modeled by including the previous 1- and 2-y values of all the time-varying covariates in the covariate models other than just the previous-year value of the covariate of interest; and *c*) including time-varying covariates other than long-term $PM_{2.5}$ as categorical in the outcome model and using the multinomial logistic model for them in the covariate model instead of modeling them as continuous with bounds using the linear model (Table 2 presents the details of the model specifications for each time-varying covariate in the main analysis). We also visually evaluated the simulated and observed adjusted survival curves and histories of covariates under no intervention in the main analysis as a heuristic check of model misspecification.[27]

Next, to facilitate comparison with previous studies, we used long-term $PM_{2.5}$ concentrations in the original scale in all models as a sensitivity analysis, which assumed the same log-linear $PM_{2.5}$–mortality association used in other cohorts[4,7] instead of the supralinear one supported by previous studies of different cycles of the CCHS cohort.[2,45,54,55] In addition, we also ran a Cox proportional hazards model with the same specification as the outcome model in our main analysis except that we included no time variable and used long-term $PM_{2.5}$ concentrations in the original scale, which assumed a log-linear $PM_{2.5}$–mortality association.

Last, given that most deaths occurred among older individuals and that age could modify the health impact of long-term exposure to $PM_{2.5}$, we conducted a subset analysis restricted to cohort participants ≥65 years of age at the time of enrollment. Because it took up to 24 h to run one round of the sensitivity analysis without bootstrapping, we were unable to perform bootstrapping

Table 2. Details for covariate formats and model types for both outcome and covariate models in main analysis.

Variable name	Type	
	Independent variable	Dependent variable and corresponding model used
Time-fixed covariates		
Age in 2005 (y)[a]	Restricted cubic spline function with 5 knots	Not predicted
Sex	Binary	Not predicted
BMI	5 categories	Not predicted
Marital status	3 categories	Not predicted
Immigrant	An indicator for immigrant and an interaction term between the indicator and a continuous variable for years in Canada among immigrants	Not predicted
Visible minority	Binary	Not predicted
Indigenous status	Binary	Not predicted
Smoking status	6 categories	Not predicted
Alcohol consumption	6 categories	Not predicted
Daily consumption of fruit and vegetables	4 categories	Not predicted
Leisure time physical activity	3 categories	Not predicted
Employment status	3 categories	Not predicted
Education attainment	4 categories	Not predicted
Urban form	5 categories	Not predicted
Airshed	6 categories	Not predicted
Time-varying covariates		
Time	Year and quadratic term of year[b]	Not predicted
Community size	Continuous	Bounded normal[c] (1 to 6) and linear regression
Annual family income quintile	Continuous	Bounded normal (1 to 5) and linear regression
Canadian Marginalization Index		
Immigration and visible minority	Continuous	Bounded normal (1 to 5) and linear regression
Material resources	Continuous	Bounded normal (1 to 5) and linear regression
Households and dwellings	Continuous	Bounded normal (1 to 5) and linear regression
Age and labor force	Continuous	Bounded normal (1 to 5) and linear regression
3-y average $PM_{2.5}$ concentration with 1-y lag	Natural logarithm-transformed	Normal with linear regression

Note: BMI, body mass index; $PM_{2.5}$, particulate matter $\leq$2.5 μm in aerodynamic diameter.
[a]In subset analysis restricted to cohort participants ≥65 years of age, we used restricted cubic spline function with 3 knots for age.
[b]Categorical year was used in the interaction terms between time and the exposure.
[c]Variables with bounded normal category were modeled and simulated by using the standardized value (subtracting the minimum value and dividing by the range) in linear regression. Simulated values that fell outside the observed range were set to the minimum or maximum of the observed range.

to calculate CIs for sensitivity analyses owing to computational constraints and, therefore, do not present variances for our estimates. We pooled cycle-specific estimates from sensitivity analyses by averaging the estimates in each cycle. All analyses were done in R (version 4.0.5; R Development Core Team) with the "gfoRmula" package.[51] The R code to replicate these analyses and a simulated data set are available at the following link: https://github.com/suthlam/cchs_g_computation.git.

Results

We observed 6,475 (10.4%), 6,525 (10.5%), and 6,135 (9.2%) nonaccidental deaths in the 11 y follow-up period starting from 2005 among the three cycles of CCHS cohorts of 62,365, 62,380, and 66,385 participants, respectively (Table 1). The three cycle cohorts were comparable in all descriptive statistics (Table 1). Without any hypothetical intervention, the observed average long-term exposure to $PM_{2.5}$ in three cycles of our cohort decreased slightly from $6.4 \pm 2.2\,\mu g/m^3$, $6.5 \pm 2.3\,\mu g/m^3$, $6.5 \pm 2.3\,\mu g/m^3$ in 2005 to $5.8 \pm 2.0\,\mu g/m^3$, $6.0 \pm 2.0\,\mu g/m^3$, and $6.0 \pm 2.0\,\mu g/m^3$ in 2015, respectively (Table 1).

All hypothetical intervention strategies explored in this study led to lower 11-y cumulative mortality risks than the estimated value under a natural course without intervention, 102.5 per 1,000 participants (95% CI: 100.3, 104.8). The reductions in 11-y cumulative mortality risks from the natural course were 0.20 per 1,000 participants (95% CI: 0.06, 0.34) under the threshold of $8.8\,\mu g/m^3$, 0.63 per 1,000 participants (95% CI: 0.18, 1.07) under the threshold of $7.04\,\mu g/m^3$, 1.87 per 1,000 participants (95% CI: 0.53, 3.21) under the threshold of $5\,\mu g/m^3$, 3.08 per 1,000 participants (95% CI: 0.85, 5.31) under the threshold of $4\,\mu g/m^3$, 1.68 per 1,000 participants (95% CI: −0.15, 3.51) under the relative reduction of 5% per interval, and 3.40 per 1,000 participants (95% CI: −0.23, 7.03) under the relative reduction of 10% per interval. Of note, the reduction in 11-y cumulative mortality risks could also be interpreted as the number of deaths that would have been prevented if the intervention was employed instead of maintaining the status quo. Changes in relative scale showed a similar pattern (Table 3). To fulfill the four threshold intervention strategies, averages of 18.7%, 38.3%, 72.0%, and 91.4% of participants experienced change in their natural course exposure every year, respectively, whereas 100% had their exposure changed under the two relative reduction intervention strategies (Table 3). The corresponding reductions in average simulated $PM_{2.5}$ from the start of follow-up to the end of year 11 ranged from 0.13 to $1.87\,\mu g/m^3$ for threshold intervention strategies, and from 1.25 to $2.18\,\mu g/m^3$ for relative reduction intervention strategies (Table 3). Across all strategies, we observed steady expansions in differences of yearly cumulative mortality risks between the natural course and other strategies until the seventh year of follow-up, after which the differences remain constant and shrank during the last year of follow-up (Figure 2, numeric results in Table S2). In the main analysis, we pooled estimates of yearly cumulative mortality risks across cycles using random-effect meta-regression and pooled estimates of differences (absolute and relative scale) in cumulative mortality risks using fixed-effect meta-regression. Cycle-specific results with corresponding I^2 values are summarized in Figure S2, with numeric results in Table S3.

Heuristic checks of model fitting in the main analysis support the robustness of our estimates: *a*) The cumulative mortality risk estimated by parametric g-computation under the natural course closely tracked the value observed (Figure S3), and *b*) the observed

Table 3. Summaries of estimated 11-y cumulative mortality risk under different intervention strategies pooled across cycles and differences in estimated risk compared with natural course in relative and absolute scale, and corresponding average simulated $PM_{2.5}$ and proportion of cohort participants with exposure changed for all intervention strategies.

Intervention strategy	11-y CMR (per 1,000 participants) (95% CI)	Difference in 11-y CMR (per 1,000 participants) (95% CI)	Percentage change in 11-y CMR (95% CI)	Average percentage of participants with exposure changed[a]	Average simulated $PM_{2.5}$ concentration ($\mu g/m^3$)[a]
Natural course	102.5 (100.3, 104.8)	Ref	Ref	0	5.62
Threshold ($\mu g/m^3$)					
8.8	102.3 (100.1, 104.6)	−0.20 (−0.34, −0.06)	−0.19 (−0.33, −0.05)	18.7	5.49
7.04	102.0 (99.7, 104.2)	−0.63 (−1.07, −0.18)	−0.60 (−1.03, −0.17)	38.3	5.21
5	100.9 (98.4, 103.5)	−1.87 (−3.21, −0.53)	−1.79 (−3.11, −0.48)	72.0	4.42
4	99.8 (96.7, 102.9)	−3.08 (−5.31, −0.85)	−2.95 (−5.14, −0.77)	91.4	3.75
Percentage reduction per interval (%)					
5	101.4 (98.6, 104.2)	−1.68 (−3.51, 0.15)	−1.61 (−3.40, 0.17)	100	4.37
10	99.8 (95.6, 103.9)	−3.40 (−7.03, 0.23)	−3.27 (−6.81, 0.28)	100	3.44

Note: CI, confidence interval; CMR, cumulative mortality risk; $PM_{2.5}$, particulate matter ≤2.5 μm in aerodynamic diameter; Ref, reference.
[a]This is the three-cycle average of the mean value across all years.

mean values of all time-varying covariates were similar to those simulated under the natural course over time (Figure S3). Of note, given that cohort participants had no time-varying covariates recorded after their death, whereas we simulated participants' time-varying covariates for all years, differences between observed and simulated covariates were to be expected, especially later in the study period. Furthermore, sensitivity analyses with different model specifications (i.e., different sequence of time-varying covariate, extent of history modeled, and parametrization of time-varying confounders) resulted in estimates similar to those for the main analysis (Figure 3, numeric results in Table S4).

When assuming a log-linear $PM_{2.5}$–mortality association in the sensitivity analysis (compared with the supralinear association assumed in main analysis by log-transforming the exposure), reductions in 11-y cumulative mortality risks comparing other intervention strategies to the natural course ranged from 0.01 per 1,000 participants to 1.65 per 1,000 participants, slightly smaller than in the main analysis assuming a supralinear $PM_{2.5}$–mortality association (log-transformed $PM_{2.5}$ was used as exposure in modeling) (Table S4). The Cox model assuming a log-linear $PM_{2.5}$–mortality association found a 15.6% (95% CI: 4.0%, 28.5%) increase in hazard of death per 10-$\mu g/m^3$ increase in $PM_{2.5}$. When focusing on cohort participants ≥65 years of age at the start of follow-up, reductions in 11-y cumulative mortality risks comparing other intervention strategies to the natural course ranged from 0.49 per 1,000 participants to 7.07 per 1,000 participants (Table S4), which is larger than was found for the main analysis using the general population at ≥25 years of age.

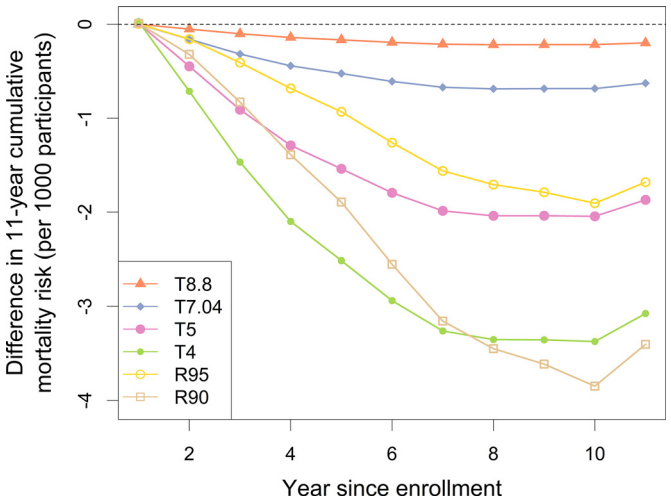

Figure 2. Differences in yearly cumulative mortality risks pooled across cycles comparing different intervention strategies to natural course, with weights equal to the inverse of variance. Numeric results are presented in Table S2. Note: $PM_{2.5}$, particulate matter ≤2.5 μm in aerodynamic diameter; R90, yearly relative reduction values set at 10% per interval; R95: yearly relative reduction values set at 5% per interval; T4, threshold value set at a $PM_{2.5}$ level that was further below the WHO guideline (4 $\mu g/m^3$); T5, threshold value set at the new WHO guideline of 5 $\mu g/m^3$; T7.04, threshold value set at 80% of the current Canadian Ambient Air Quality Standards for $PM_{2.5}$ (or 7.04 $\mu g/m^3$); T8.8, threshold value (reduced to threshold value if above) set at the current Canadian Ambient Air Quality Standards for $PM_{2.5}$ of 8.8 $\mu g/m^3$; WHO, World Health Organization.

Discussion

In the present study, we applied the parametric g-computation as an analytical alternative that is particularly valuable for air pollution epidemiological research, especially for evaluating specific intervention strategies. With application in a large Canadian cohort, we demonstrated how to incorporate consideration of complex time structure in the data and how to calculate causally interpretable cumulative risk estimates over the follow-up period (i.e., adjusted survival curves) with parametric g-computation. We described that any intervention further reducing the long-term exposure to $PM_{2.5}$ would reduce the cumulative mortality risk, even in a region with relatively low levels of ambient $PM_{2.5}$. Such a reduction in cumulative risk increased over time and flattened toward the end of the follow-up period on both the relative and the absolute scales. The older population also experienced greater benefits from the explored hypothetical intervention strategies than the general population.

Numerous observational studies have found positive associations between long-term exposure to $PM_{2.5}$ and nonaccidental mortality. A meta-analysis reported a pooled effect estimate of 6% (95% CI: 4%, 8%) increase in hazard of death per 10-$\mu g/m^3$ increase in $PM_{2.5}$ (HR-1).[5] A recent study from 2000 to 2012 in a similar Canadian cohort found an 11% (95% CI: 4%, 18%) increase in hazard of nonaccidental death per 10-$\mu g/m^3$ increase in chronic exposure to $PM_{2.5}$ with a Cox proportional hazards model.[2] Our sensitivity analysis using the Cox model without time-varying coefficients found similar numeric results [15.6% (95% CI: 4.0%, 28.5%)]. Although we cannot directly compare our estimates from the main analysis to previous results given the difference in interventions explored, the consistent reductions in cumulative mortality risk over the follow-up period across intervention strategies when compared with the natural course in this study lend further support to previous findings that $PM_{2.5}$ is detrimental to health, even at levels below current standards. For example, we identified a 0.19% (95% CI: 0.05%, 0.33%) decrease in 11-y cumulative mortality risk comparing the hypothetical intervention strategy with the threshold of 8.8 $\mu g/m^3$ to natural

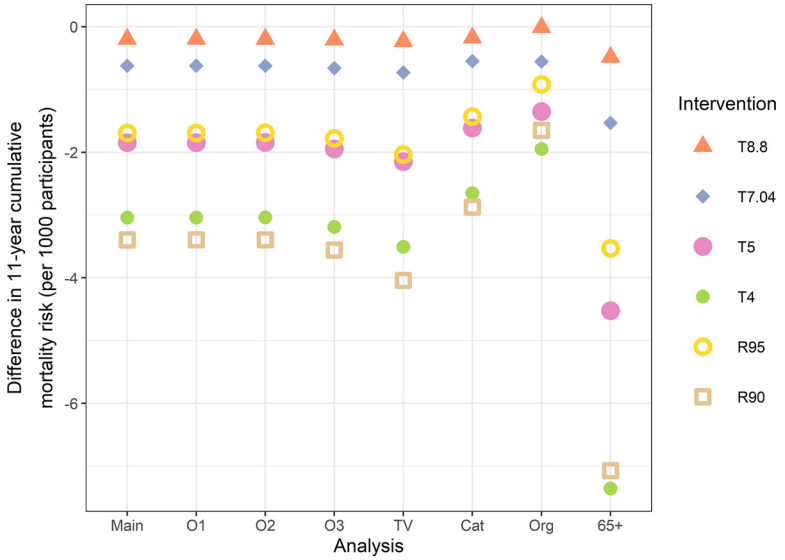

Figure 3. Differences in 11-y cumulative mortality risks comparing different intervention strategies to natural course for main analysis and sensitivity analyses. Numeric results are presented in Tables 3 and S4. Note: 65+, subset analysis restricted to cohort participants ≥65 years of age; Cat, including time-varying covariates other than long-term $PM_{2.5}$ as categorical in outcome model and using multinomial logistic model for them in the covariate model; O1, placing Canadian Marginalization Index-age and labor force before the other Canadian Marginalization Index in occurring sequence of time-varying covariate; O2, moving income to after Canadian Marginalization Index in occurring sequence of time-varying covariate; O3, moving $PM_{2.5}$ to the first in occurring sequence of time-varying covariate; Org, using long-term $PM_{2.5}$ in original scale in all models; $PM_{2.5}$, particulate matter ≤2.5 μm in aerodynamic diameter; R90, yearly relative reduction values set at 10% per interval; R95, yearly relative reduction values set at 5% per interval; T4, threshold value set at a $PM_{2.5}$ level that was further below the WHO guideline (4 $\mu g/m^3$); T5, threshold value set at the new WHO guideline of 5 $\mu g/m^3$; T7.04, threshold value set at 80% of the current Canadian Ambient Air Quality Standards for $PM_{2.5}$ (or 7.04 $\mu g/m^3$); T8.8, threshold value (reduced to threshold value if above) set at the current Canadian Ambient Air Quality Standards for $PM_{2.5}$ of 8.8 $\mu g/m^3$; TV, adding all time-varying covariates of the previous 1 and 2 y to the covariate model; WHO, World Health Organization.

course, providing evidence of health benefits from policies that further reduce the air pollution level to below the current Canadian standard of 8.8 $\mu g/m^3$, which is already lower than the 12-$\mu g/m^3$ standard of the United States explored by previous studies.[4,9] To facilitate comparison with previous studies assuming a log-linear $PM_{2.5}$–mortality association, we included sensitivity analysis using $PM_{2.5}$ on the normal scale and found reduced cumulative mortality risks in all hypothetical interventions compared with maintaining the status quo, but the numeric values are smaller than those in the main analysis. The observed difference in the numeric values of analysis assuming log-linear association and analysis assuming supralinear association is a combination of difference in how the exposure–response relationship is modeled and how the exposure model performs. However, given the existing evidence from Canadian cohorts and the similarity between the observed survival curve and the estimated survival curve using parametric g-computation under no intervention in the main analysis,[2,45,54,55] we have confidence in the validity of results assuming a supralinear association.

More importantly, in this study we demonstrated how to incorporate more flexibilities in simulating real-world interventions with g-computation and provide intuitive estimates for the benefits of such interventions. Taking the hypothetical intervention strategy with the threshold of the current Canadian Ambient Air Quality Standards as an example, the average long-term exposure to $PM_{2.5}$ in 2005 was $\sim$6.5 $\mu g/m^3$, below the standard of 8.8 $\mu g/m^3$. However, some cohort participants were exposed to $PM_{2.5}$ levels >8.8 $\mu g/m^3$ during some years of follow-up, and our hypothetical intervention affected only these subject-years by reducing their exposure to 8.8 $\mu g/m^3$, representing a three-cycle average of 18.7% of participants across all years. Because the observed $PM_{2.5}$ levels decreased without any intervention in our study, fewer participants were directly intervened on in later years under threshold intervention strategies, explaining the flattened differences observed in the cumulative risks between intervention strategies in later years. However, all time-varying covariates after the intervention on $PM_{2.5}$ would change accordingly owing to the intervention on $PM_{2.5}$, thus influencing future outcomes as well. Such a dynamic intervention strategy incorporated the consideration of people who could be intervened on and is more realistic than the static intervention strategy commonly employed in health burden estimation with traditional exposure–response function, which sets change in exposure at a fixed value for all individuals throughout the period of interest. In addition, although we provided differences only in cumulative risk as compared with the natural course, it is easy to estimate differences between any two hypothetical intervention strategies.

Furthermore, the estimated cumulative risks over the follow-up period by g-computation (i.e., adjusted survival curves) and corresponding comparisons of values between different hypothetical interventions provided clearer causal interpretation and more information than a single HR or period-specific HRs, as generally used in air pollution studies (Table S1). In the context of health impacts from chronic exposure to $PM_{2.5}$, HR can change over time because the toxicity of $PM_{2.5}$ (e.g., chemical composition of $PM_{2.5}$) and the susceptibility of the population to $PM_{2.5}$ could change over time, whereas the standard Cox model assumed a constant HR and period-specific HR from extensions of the Cox model had a built-in bias that led to ambiguity in causal interpretation.[57] On the other hand, the cumulative mortality risks estimated in the present study avoided such ambiguity in interpretation while also demonstrating the change of intervention effect over time.[19] In addition, obtaining the casually interpretable absolute differences in cumulative risks between hypothetical intervention strategies over time could be particularly helpful for comparing different scenarios regarding public health benefits.[58] Moreover, if policies affecting air pollutants such as $PM_{2.5}$ could further affect prognostic covariates influencing both future $PM_{2.5}$ levels and health

outcomes (commonly referred to as exposure–confounder feedback), traditional regression methods based on adjustment in a multivariable model would fail and lead to biased estimates for the effect, whereas g-computation is designed particularly to solve this problem.[24,26,59] An example of such exposure-confounder feedback is that people might move due to high level of $PM_{2.5}$ in their current community and subsequently change the characteristics of their community of residence, while the characteristics of their new community also affect the level of $PM_{2.5}$ and probability of death. Controlling for such community characteristics is necessary for confounding control, but doing so with traditional methods will remove the indirect effect mediated through community characteristics and introduce collider-stratification bias[60] if any unmeasured confounder of the community characteristics and death exists.[59] However, making the decision to move based on the community level of $PM_{2.5}$ is unlikely in countries with relatively low $PM_{2.5}$ levels, such as Canada. Therefore, exposure–confounder feedback is expected to be negligible in our study, but it is possible to be meaningful in countries with higher $PM_{2.5}$ levels.

This study has a few limitations that need to be acknowledged. First, parametric g-computation can only account for measured confounders and a lack of conditional exchangeability (i.e., residual confounding) might exist due to unmeasured confounders or measurement errors of existing confounders, regardless of our extensive list of confounders considered based on substantive knowledge on risk factors of $PM_{2.5}$ exposure and death (Figure S1). For example, we assumed many individual behavior, demographic, and socioeconomic variables to be time-invariant (e.g., employment status, BMI) owing to data availability (these variables were only reported once at the time of enrollment), whereas they likely actually changed over the study period. However, we also included time-varying individual income and community demographic and socioeconomic variables in our models, mitigating the concern of residual confounding from these baseline variables. In addition, like other cohort studies of air pollution, we used postal code–level $PM_{2.5}$ levels as surrogates for individual exposure to $PM_{2.5}$, which might introduce exposure misclassification.[61] Recent studies, however, have shown that such bias may either not bias effect estimates[62] or bias these estimates toward the null,[63] making our estimates more conservative.

Second, although we explored different model specifications and found similar results in the sensitivity analyses, we cannot rule out the possibility of model misspecification, especially given the fact that parametric g-computation requires correct model specification of both the outcome and covariate models to achieve unbiased results. Notably, McGrath et al. demonstrated that the g-null paradox, a form of model misspecification that was traditionally believed to cause false rejection of null hypothesis under a sharp null effect,[64] is unavoidable in parametric g-computation even when the sharp null hypothesis does not hold, and they recommended using more flexible models in analysis.[65] However, the magnitude of bias depends on the extent of exposure–confounder feedback and time-varying confounding. In the context of this study, we would expect relatively small exposure–confounder feedback and, thus, less concern over the g-null paradox. In addition, consistent results from sensitivity analysis using more flexible models supported the robustness of our results.

Third, this being an active research field, the existing R package for parametric g-computation does not support features like incorporation of spline functions of time-varying covariates into the model, direct estimation of randomized interventional strategy,[66] model fit checking with significance tests, or bias analysis. However, the current package provided enough flexibility for our study to employ flexible models that mitigated the possibility of violating the positivity assumption via model extrapolation. For example, we were able to *a*) incorporate flexible supralinear $PM_{2.5}$–mortality association and temporal changes into the conditional probability of mortality in the estimation as supported by previous studies,[2,54,55] *b*) incorporate restricted cubic spline function of baseline age in all models, and *c*) conduct sensitivity analysis with categorical time-varying confounders. In addition, although not relevant to our cohort given that we had the all-cause mortality as the outcome and no loss to follow-up, right censoring and informative loss to follow-up could be handled by parametric g-computation and the existing R package by simulating data on participants as though they had not been censored.[67] It is worth mentioning that other methods could also handle the methodological considerations that g-computation addresses—consideration of complex time structure and reporting of adjusted survival curves—and have been applied in air pollution epidemiological research, including Inverse Probability of Treatment Weighting.[6] Furthermore, some recent approaches, such as the targeted maximum likelihood estimation, can also be used to directly evaluate individualized dynamic intervention strategies of continuous exposures and provide doubly robust estimates that are less vulnerable to model misspecification with valid statistical inference when data-adaptive/machine-learning methods are incorporated.[68,69]

Finally, $PM_{2.5}$ is a mixture of varying chemical components and toxicity and is generated from different sources of emissions (e.g., traffic, industries, wildfires). In this paper, we focused on $PM_{2.5}$ without distinguishing the $PM_{2.5}$ composition or the sources of emissions. This potentially violated the consistency assumption (i.e., no-multiple-versions-of-treatment and all exposed individuals received the same version of treatment). If there is any unmeasured confounder of the "version of treatment" and outcome relationship, the effect estimates could be biased according to a recent simulation study, with magnitude and direction of such bias depending on the strength of confounding.[70] In future studies, it would be important to consider the possible differential toxicity of $PM_{2.5}$ components and define hypothetical interventions targeting different sources of $PM_{2.5}$ emissions separately.

Conclusion

This study demonstrated the benefits of using parametric g-computation as an analytical alternative for air pollution epidemiological research, especially for evaluating the potential effects of realistic dynamic intervention strategies in the time-to-event setting with time-varying exposure and confounders. With a large Canadian cohort, we calculated causally interpretable cumulative risk estimates over the follow-up period and corresponding benefits compared with maintaining the status quo. We also found that any intervention further reducing the long-term exposure to $PM_{2.5}$ would reduce the cumulative mortality risk from maintaining the status quo, even in a population already exposed to relatively low levels of ambient $PM_{2.5}$.

Acknowledgments

This study was funded by Health Canada (810630). The funder supported the study design, data collection, and analysis in this study.

References

1. Beelen R, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, Hoffmann B, et al. 2014. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet 383(9919):785–795, PMID: 24332274, https://doi.org/10.1016/S0140-6736(13)62158-3.
2. Christidis T, Erickson AC, Pappin AJ, Crouse DL, Pinault LL, Weichenthal SA, et al. 2019. Low concentrations of fine particle air pollution and mortality in the

Canadian Community Health Survey cohort. Environ Health 18(1):84, PMID: 31601202, https://doi.org/10.1186/s12940-019-0518-y.
3. Crouse DL, Peters PA, van Donkelaar A, Goldberg MS, Villeneuve PJ, Brion O, et al. 2012. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. Environ Health Perspect 120(5):708–714, PMID: 22313724, https://doi.org/10.1289/ehp.1104049.
4. Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, et al. 2017. Air pollution and mortality in the Medicare population. N Engl J Med 376(26):2513–2522, PMID: 28657878, https://doi.org/10.1056/NEJMoa1702747.
5. Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, et al. 2013. Long-term air pollution exposure and cardio-respiratory mortality: a review. Environ Health 12(1):43, PMID: 23714370, https://doi.org/10.1186/1476-069X-12-43.
6. Wu X, Braun D, Schwartz J, Kioumourtzoglou MA, Dominici F. 2020. Evaluating the impact of long-term exposure to fine particulate matter on mortality among the elderly. Sci Adv 6(29):eaba5692, PMID: 32832626, https://doi.org/10.1126/sciadv.aba5692.
7. Cesaroni G, Forastiere F, Stafoggia M, Andersen ZJ, Badaloni C, Beelen R, et al. 2014. Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE project. BMJ 348:f7412, PMID: 24452269, https://doi.org/10.1136/bmj.f7412.
8. Danesh Yazdi M, Wang Y, Di Q, Wei Y, Requia WJ, Shi L, et al. 2021. Long-term association of air pollution and hospital admissions among Medicare participants using a doubly robust additive model. Circulation 143(16):1584–1596, PMID: 33611922, https://doi.org/10.1161/CIRCULATIONAHA.120.050252.
9. Makar M, Antonelli J, Di Q, Cutler D, Schwartz J, Dominici F. 2017. Estimating the causal effect of low levels of fine particulate matter on hospitalization. Epidemiology 28(5):627–634, PMID: 28768298, https://doi.org/10.1097/EDE.0000000000000690.
10. Bi J, D'Souza RR, Rich DQ, Hopke PK, Russell AG, Liu Y, et al. 2020. Temporal changes in short-term associations between cardiorespiratory emergency department visits and $PM_{2.5}$ in Los Angeles, 2005 to 2016. Environ Res 190:109967, PMID: 32810677, https://doi.org/10.1016/j.envres.2020.109967.
11. Breitner S, Stölzel M, Cyrys J, Pitz M, Wölke G, Kreyling W, et al. 2009. Short-term mortality rates during a decade of improved air quality in Erfurt, Germany. Environ Health Perspect 117(3):448–454, PMID: 19337521, https://doi.org/10.1289/ehp.11711.
12. Chen C, Warrington JA, Dominici F, Peng RD, Esty DC, Bobb JF, et al. 2021. Temporal variation in association between short-term exposure to fine particulate matter and hospitalisations in older adults in the USA: a long-term time-series analysis of the US Medicare dataset. Lancet Planet Health 5(8):e534–e541, PMID: 34390671, https://doi.org/10.1016/S2542-5196(21)00168-6.
13. Dominici F, Peng RD, Zeger SL, White RH, Samet JM. 2007. Particulate air pollution and mortality in the United States: did the risks change from 1987 to 2000? Am J Epidemiol 166(8):880–888, PMID: 17728271, https://doi.org/10.1093/aje/kwm222.
14. Atkinson RW, Mills IC, Walton HA, Anderson HR. 2015. Fine particle components and health—a systematic review and meta-analysis of epidemiological time series studies of daily mortality and hospital admissions. J Expo Sci Environ Epidemiol 25(2):208–214, PMID: 25227730, https://doi.org/10.1038/jes.2014.63.
15. Rohr AC, Wyzga RE. 2012. Attributing health effects to individual particulate matter constituents. Atmos Environ 62:130–152, https://doi.org/10.1016/j.atmosenv.2012.07.036.
16. Wyzga RE, Rohr AC. 2015. Long-term particulate matter exposure: attributing health effects to individual PM components. J Air Waste Manag Assoc 65(5):523–543, PMID: 25947312, https://doi.org/10.1080/10962247.2015.1020396.
17. Yang Y, Ruan Z, Wang X, Yang Y, Mason TG, Lin H, et al. 2019. Short-term and long-term exposures to fine particulate matter constituents and health: a systematic review and meta-analysis. Environ Pollut 247:874–882, PMID: 30731313, https://doi.org/10.1016/j.envpol.2018.12.060.
18. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. 2018. Time-varying covariates and coefficients in Cox regression models. Ann Transl Med 6(7):121, PMID: 29955581, https://doi.org/10.21037/atm.2018.02.12.
19. Hernán MA. 2010. The hazards of hazard ratios. Epidemiology 21(1):13–15, PMID: 20010207, https://doi.org/10.1097/EDE.0b013e3181c1ea43.
20. Flanders WD, Klein M. 2007. Properties of 2 counterfactual effect definitions of a point exposure. Epidemiology 18(4):453–460, PMID: 17473709, https://doi.org/10.1097/01.ede.0000261472.07150.4f.
21. Stovitz SD, Banack HR, Kaufman JS. 2018. 'Depletion of the susceptibles' taught through a story, a table and basic arithmetic. BMJ Evid Based Med 23(5):199, PMID: 29982175, https://doi.org/10.1136/bmjebm-2018-110972.
22. Hernán MA, Robins JM. 2020. *Causal Inference: What If*. Boca Raton, FL: CRC Press.
23. Zigler CM, Dominici F. 2014. Point: clarifying policy evidence with potential–outcomes thinking—beyond exposure–response estimation in air pollution epidemiology. Am J Epidemiol 180(12):1133–1140, PMID: 25399414, https://doi.org/10.1093/aje/kwu263.
24. Robins J. 1986. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. Math Model 7(9–12):1393–1512, https://doi.org/10.1016/0270-0255(86)90088-6.
25. Cole SR, Frangakis CE. 2009. The consistency statement in causal inference: a definition or an assumption? Epidemiology 20(1):3–5, PMID: 19234395, https://doi.org/10.1097/EDE.0b013e31818ef366.
26. Naimi AI, Cole SR, Kennedy EH. 2016. An introduction to g methods. Int J Epidemiol 46(2):756–762, PMID: 28039382, https://doi.org/10.1093/ije/dyw323.
27. Chiu YH, Chavarro JE, Dickerman BA, Manson JE, Mukamal KJ, Rexrode KM, et al. 2021. Estimating the effect of nutritional interventions using observational data: the American Heart Association's 2020 dietary goals and mortality. Am J Clin Nutr 114(2):690–703, PMID: 34041538, https://doi.org/10.1093/ajcn/nqab100.
28. Keil AP, Edwards JK, Richardson DR, Naimi AI, Cole SR. 2014. The parametric g-formula for time-to-event data: intuition with a worked example. Epidemiology 25(6):889–897, PMID: 25140837, https://doi.org/10.1097/EDE.0000000000000160.
29. Taubman SL, Robins JM, Mittleman MA, Hernán MA. 2009. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. Int J Epidemiol 38(6):1599–1611, PMID: 19389875, https://doi.org/10.1093/ije/dyp192.
30. Westreich D, Cole SR, Young JG, Palella F, Tien PC, Kingsley L, et al. 2012. The parametric g-formula to estimate the effect of highly active antiretroviral therapy on incident AIDS or death. Stat Med 31(18):2000–2009, PMID: 22495733, https://doi.org/10.1002/sim.5316.
31. Keil AP, Buckley JP, Kalkbrenner AE. 2021. Bayesian g-computation for estimating impacts of interventions on exposure mixtures: demonstration with metals from coal-fired power plants and birth weight. Am J Epidemiol 190(12):2647–2657, PMID: 33751055, https://doi.org/10.1093/aje/kwab053.
32. Neophytou AM, Costello S, Picciotto S, Brown DM, Attfield MD, Blair A, et al. 2019. Diesel exhaust, respirable dust, and ischemic heart disease: an application of the parametric g-formula. Epidemiology 30(2):177–185, PMID: 30489348, https://doi.org/10.1097/EDE.0000000000000954.
33. Neophytou AM, Costello S, Picciotto S, Noth EM, Liu S, Lutzker L, et al. 2019. Accelerated lung function decline in an aluminum manufacturing industry cohort exposed to $PM_{2.5}$: an application of the parametric g-formula. Occup Environ Med 76(12):888–894, PMID: 31615860, https://doi.org/10.1136/oemed-2019-105908.
34. Garcia E, Urman R, Berhane K, McConnell R, Gilliland F. 2019. Effects of policy-driven hypothetical air pollutant interventions on childhood asthma incidence in southern California. Proc Natl Acad Sci USA 116(32):15883–15888, PMID: 31332016, https://doi.org/10.1073/pnas.1815678116.
35. Urman R, Garcia E, Berhane K, McConnell R, Gauderman WJ, Gilliland F. 2020. The potential effects of policy-driven air pollution interventions on childhood lung development. Am J Respir Crit Care Med 201(4):438–444, PMID: 31644884, https://doi.org/10.1164/rccm.201903-0670OC.
36. Statistics Canada. 2007. Canadian Community Health Survey (CCHS) Cycle 1.1. Last modified 24 October 2007. https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=3359 [accessed 26 September 2021].
37. Statistics Canada. 2007. Canadian Community Health Survey (CCHS) Cycle 2.1. Last modified 24 October 2007. https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=4995 [accessed 26 September 2021].
38. Statistics Canada. 2007. Canadian Community Health Survey (CCHS) Cycle 3.1. Last modified 24 October 2007. https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=22642 [accessed 26 September 2021].
39. Sanmartin C, Decady Y, Trudeau R, Dasylva A, Tjepkema M, Finès P, et al. 2016. Linking the Canadian Community Health Survey and the Canadian Mortality Database: an enhanced data source for the study of mortality. Health Rep 27(12):10–18, PMID: 28002578.
40. WHO (World Health Organization). 1978. *International Statistical Classification of Diseases, Ninth Revision, Basic Tabulation List with Alphabetic Index*. http://apps.who.int/classifications/icd10/browse/2016/en [accessed 8 March 2023].
41. WHO. 2016. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*. https://apps.who.int/iris/handle/10665/39473 [accessed 8 March 2023].
42. van Donkelaar A, Martin RV, Li C, Burnett RT. 2019. Regional estimates of chemical composition of fine particulate matter using a combined geoscience-statistical method with information from satellites, models, and monitors: v 4. NA.02.MAPLE. Nenodo. Published online 30 January 2019. https://doi.org/10.5281/zenodo.6557778.
43. van Donkelaar A, Martin RV, Li C, Burnett RT. 2019. 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(5):2595–2611, PMID: 30698001, https://doi.org/10.1021/acs.est.8b06392.
44. Canadian Council of Ministers of the Environment. n.d. Canadian Ambient Air Quality Standards. https://ccme.ca/en/air-quality-report#slide-7 [accessed 11 June 2022].
45. Pinault L, Tjepkema M, Crouse DL, Weichenthal S, van Donkelaar A, Martin RV, et al. 2016. Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian Community Health Survey cohort. Environ Health 15:18, PMID: 26864652, https://doi.org/10.1186/s12940-016-0111-6.
46. Pinault LL, Weichenthal S, Crouse DL, Brauer M, Erickson A, van Donkelaar A, et al. 2017. Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment cohort. Environ Res 159:406–415, PMID: 28850858, https://doi.org/10.1016/j.envres.2017.08.037.
47. Ontario Community Health Profiles Partnership. 2020. Canadian Marginalization Index (CAN-Marg). http://www.ontariohealthprofiles.ca/canmargCAN.php [accessed 14 October 2020].
48. Crouse DL, Philip S, van Donkelaar A, Martin RV, Jessiman B, Peters PA, et al. 2016. A new method to jointly estimate the mortality risk of long-term exposure to fine particulate matter and its components. Sci Rep 6(1):18916, PMID: 26732864, https://doi.org/10.1038/srep18916.
49. Health Canada. 2021. *Health Impacts of Air Pollution in Canada: Estimates of Morbidity and Premature Mortality Outcomes—2021 Report*. https://www.canada.ca/en/health-canada/services/publications/healthy-living/2021-health-effects-indoor-air-pollution.html [accessed 17 June 2021].
50. Balduzzi S, Rücker G, Schwarzer G. 2019. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 22(4):153–160, PMID: 31563865, https://doi.org/10.1136/ebmental-2019-300117.
51. McGrath S, Lin V, Zhang Z, Petito LC, Logan RW, Hernán MA, et al. 2020. gfoRmula: an R package for estimating the effects of sustained treatment strategies via the parametric g-formula. Patterns (NY) 1(3):100008, PMID: 32656541, https://doi.org/10.1016/j.patter.2020.100008.
52. VanderWeele TJ, Shpitser I. 2011. A new criterion for confounder selection. Biometrics 67(4):1406–1413, PMID: 21627630, https://doi.org/10.1111/j.1541-0420.2011.01619.x.
53. Snowden JM, Rose S, Mortimer KM. 2011. Implementation of G-computation on a simulated data set: demonstration of a causal inference technique. Am J Epidemiol 173(7):731–738, PMID: 21415029, https://doi.org/10.1093/aje/kwq472.
54. Nasari MM, Szyszkowicz M, Chen H, Crouse D, Turner MC, Jerrett M, et al. 2016. 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(8):961–972, PMID: 27867428, https://doi.org/10.1007/s11869-016-0398-z.
55. Pappin AJ, Christidis T, Pinault LL, Crouse DL, Brook JR, Erickson A, et al. 2019. Examining the shape of the association between low levels of fine particulate matter and mortality across three cycles of the Canadian Census Health and Environment cohort. Environ Health Perspect 127(10):107008, PMID: 31638837, https://doi.org/10.1289/EHP5204.
56. Efron B, Tibshirani RJ. 1993. *An Introduction to the Bootstrap*. New York, NY: Chapman & Hall/CRC.
57. Stensrud MJ, Hernán MA. 2020. Why test for proportional hazards? JAMA 323(14):1401–1402, PMID: 32167523, https://doi.org/10.1001/jama.2020.1267.
58. Schwartz LM, Woloshin S, Dvorin EL, Welch HG. 2006. Ratio measures in leading medical journals: structured review of accessibility of underlying absolute risks. BMJ 333(7581):1248, PMID: 17060338, https://doi.org/10.1136/bmj.38985.564317.7C.
59. Daniel RM, Cousens SN, De Stavola BL, Kenward MG, Sterne JAC. 2013. Methods for dealing with time-dependent confounding. Stat Med 32(9):1584–1618, PMID: 23208861, https://doi.org/10.1002/sim.5686.
60. Hernán MA, Hernández-Díaz S, Robins JM. 2004. A structural approach to selection bias. Epidemiology 15(5):615–625, PMID: 15308962, https://doi.org/10.1097/01.ede.0000135174.63482.43.
61. Sheppard L, Burnett RT, Szpiro AA, Kim SY, Jerrett M, Pope CA III, et al. 2012. Confounding and exposure measurement error in air pollution epidemiology. Air Qual Atmos Health 5(2):203–216, PMID: 22662023, https://doi.org/10.1007/s11869-011-0140-9.
62. Richmond-Bryant J, Long TC. 2020. Influence of exposure measurement errors on results from epidemiologic studies of different designs. J Expo Sci Environ Epidemiol 30(3):420–429, PMID: 31477780, https://doi.org/10.1038/s41370-019-0164-z.
63. Samoli E, Butland BK, Rodopoulou S, Atkinson RW, Barratt B, Beevers SD, et al. 2020. The impact of measurement error in modeled ambient particles exposures on health effect estimates in multilevel analysis: a simulation study. Environ Epidemiol 4(3):e094, PMID: 32656489, https://doi.org/10.1097/EE9.0000000000000094.
64. Robins JM, Wasserman LA. 1997. Estimation of effects of sequential treatments by reparameterizing directed acyclic graphs. Proceedings of the thirteenth conference on uncertainty in artificial intelligence.
65. McGrath S, Young JG, Hernán MA. 2022. Revisiting the g-null paradox. Epidemiology 33(1):114–120, PMID: 34711734, https://doi.org/10.1097/EDE.0000000000001431.
66. VanderWeele TJ, Vansteelandt S, Robins JM. 2014. Effect decomposition in the presence of an exposure-induced mediator-outcome confounder. Epidemiology 25(2):300–306, PMID: 24487213, https://doi.org/10.1097/EDE.0000000000000034.
67. Keil AP, Edwards JK. 2018. A review of time scale fundamentals in the g-formula and insidious selection bias. Curr Epidemiol Rep 5(3):205–213, PMID: 30555772, https://doi.org/10.1007/s40471-018-0153-0.
68. Muñoz ID, van der Laan M. 2012. Population intervention causal effects based on stochastic interventions. Biometrics 68(2):541–549, PMID: 21977966, https://doi.org/10.1111/j.1541-0420.2011.01685.x.
69. van der Laan MJ, Petersen ML. 2007. Causal effect models for realistic individualized treatment and intention to treat rules. Int J Biostat 3(1):article 3, PMID: 19122793, https://doi.org/10.2202/1557-4679.1022.
70. Weichenthal S, Ripley S, Korsiak J. 2023. Fine particulate air pollution and the "no-multiple-versions-of-treatment" assumption: does particle composition matter for causal inference? Am J Epidemiol 192(2):147–153, PMID: 36331277, https://doi.org/10.1093/aje/kwac191.