# Relationships Between Fine Particulate Air Pollution, Cardiometabolic Disorders, and Cardiovascular Mortality

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***Rationale:*** **Growing evidence suggests that long-term exposure to fine particulate matter ($PM_{2.5}$) air pollution contributes to risk of cardiovascular disease (CVD) morbidity and mortality. There is uncertainty about who are most susceptible. Individuals with underlying cardiometabolic disorders, including hypertension, diabetes mellitus, and obesity, may be at greater risk. $PM_{2.5}$ pollution may also contribute to cardiometabolic disorders, augmenting CVD risk.**

***Objective:*** **This analysis evaluates relationships between long-term $PM_{2.5}$ exposure and cardiometabolic disease on risk of death from CVD and cardiometabolic conditions.**

***Methods and Results:*** **Data on 669 046 participants from the American Cancer Society Cancer Prevention Study II cohort were linked to modeled $PM_{2.5}$ concentrations at geocoded home addresses. Cox proportional hazards regression models were used to estimate adjusted hazards ratios for death from CVD and cardiometabolic diseases based on death-certificate information. Effect modification by pre-existing cardiometabolic risk factors on the $PM_{2.5}$–CVD mortality association was examined. $PM_{2.5}$ exposure was associated with CVD mortality, with the hazards ratios (95% confidence interval) per 10 μg/m$^3$ increase in $PM_{2.5}$ equal to 1.12 (1.10–1.15). Deaths linked to hypertension and diabetes mellitus (mentioned on death certificate as either primary or contributing cause of death) were also associated with $PM_{2.5}$. There was no consistent evidence of effect modification by cardiometabolic disease risk factors on the $PM_{2.5}$–CVD mortality association.**

***Conclusions:*** **Pollution-induced CVD mortality risk is observed for those with and without existing cardiometabolic disorders. Long-term exposure may also contribute to the development or exacerbation of cardiometabolic disorders, increasing risk of CVD, and cardiometabolic disease mortality. (*Circ Res*. 2015;116:108-115. DOI: 10.1161/CIRCRESAHA.116.305060.)**

**Key Words:** air pollution, epidemiology ■ metabolic syndrome X ■ particulate matter,

Prospective cohort studies provide robust and consistent evidence that long-term exposure to particulate matter (PM) air pollution, especially fine PM (<2.5 μm in aerodynamic diameter [$PM_{2.5}$]), is associated with increased risk of cardiovascular disease (CVD) mortality.[1–6] However, whether there are specific population subgroups that are most susceptible to the health effects of air pollution exposure remains unclear. Evidence from previous studies suggests that individuals with underlying cardiometabolic conditions, including hypertension, diabetes mellitus, and obesity, may be at greater risk of morbidity and mortality after $PM_{2.5}$ exposure when compared with those without these conditions.[4,7–11] In addition, epidemiological and mechanistic studies support the possibility that $PM_{2.5}$ exposure is involved in the development of cardiometabolic conditions.[4,12] Recent studies have shown that $PM_{2.5}$ exposures are associated with the prevalence of diabetes mellitus in the United States[13] and Canada,[14] and that long-term exposure to even modestly elevated levels of $PM_{2.5}$ may be linked to diabetes mellitus mortality.[15] Long-term exposure to $PM_{2.5}$ could also play a joint role with cardiometabolic disorders exacerbating risk of future mortality in association to these disease states.[16–18]

Key risk factors of cardiometabolic disease include insulin resistance/high blood glucose/diabetes mellitus, hypertension, obesity (especially central obesity), and dyslipidemia. These risk factors may be associated with various modifiable factors, such as physical inactivity, atherogenic diets (high saturated fat and cholesterol), and smoking, as well as with nonmodifiable risk factors, including age, race and ethnicity,

Original received August 15, 2014; revision received October 23, 2014; accepted October 27, 2014. In September, 2014, the average time from submission to first decision for all original research papers submitted to *Circulation Research* was 14.29 days.

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**The online-only Data Supplement is available with this article at http://circres.ahajournals.org/lookup/suppl/doi:10.1161/CIRCRESAHA.116.305060/-/DC1.**

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*Circulation Research* **is available at http://circres.ahajournals.org** **DOI: 10.1161/CIRCRESAHA.116.305060**

| Nonstandard Abbreviations and Acronyms | |
|---|---|
| ACS | American Cancer Society |
| BME | Bayesian Maximum Entropy |
| CPS-II | Cancer Prevention Study II |
| CVD | cardiovascular disease |
| HR | hazard ratio |
| LUR | land use regression |
| PM | particulate matter |
| $PM_{2.5}$ | fine PM <2.5 μm in aerodynamic diameter |

sex, and family history.[19,20] The present analysis is based on the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II) cohort, which collected data that included information related to multiple cardiometabolic risk factors by questionnaire at enrollment. The ACS CPS-II cohort data are linked with death certificate records and with modeled $PM_{2.5}$ exposure concentrations at residential address.

The objective of this analysis is to evaluate possible joint relationships between long-term $PM_{2.5}$ exposures and cardiometabolic disease on risk of death from CVD systematically. Specifically, we evaluate whether observed associations of long-term exposure to $PM_{2.5}$ air pollution on CVD mortality are greater in individuals with cardiometabolic risk factors, based on questionnaire information provided at time of cohort enrollment. Moreover, we explored the effects of long-term $PM_{2.5}$ exposure on mortality because of cardiometabolic disease (hypertension and diabetes mellitus) per se based on cause-of-death information available on death certificates.

## Methods

An expanded Methods is available in the Online Data Supplement.

### Study Population

The ACS CPS-II prospective cohort included 1 184 587 participants, enrolled by >77 000 volunteers between September 1982 and February 1983. Participants were largely friends and family members of the volunteers and were recruited from all 50 states, the District of Columbia, and Puerto Rico. Participants in the ACS CPS-II cohort had to be aged ≥30 years and have ≥1 family member aged ≥45 years. At enrollment, participants completed a 4-page, self-administered questionnaire providing their residential address and information on a range of demographic, lifestyle, medical, and other factors. The Emory University School of Medicine Human Investigations Committee provided ethics approval for the ACS CPS-II; ethics approval for the present analysis was obtained from the Ottawa Hospital Research Ethics Board.

Vital status follow-up was conducted every 2 years. For the years 1984, 1986, and 1988, vital status was obtained by the study volunteers and confirmed by obtaining death certificates. Subsequent vital status follow-ups have been conducted using computerized record linkage to the National Death Index.[21] Participants were followed up during the period 1982 to 2004 in the present analysis. During the first 6 years of follow-up, cause of death was coded using a 2-digit ACS CPS-II code that was a consolidation of *International Classification of Diseases, Ninth Revision* codes. Subsequent cause of death coding used *International Classification of Diseases, Ninth Revision* or *International Classification of Diseases, Tenth Revision* codes. Cause of death was captured for the underlying or primary cause of death, and the next 2 contributing causes of death, unless a cancer was reported later in the death certificate. In the event of a cancer reported later on a death certificate, it would be captured instead of the second contributing cause of death.

Although the total ACS CPS-II cohort included ≈1.2 million participants, we excluded ≈385 000 individuals with invalid home address information and 130 000 individuals with missing individual-level data. The final analytic cohort used in this analysis included 669 046 participants. A total of 237 201 participants, ≈35% of the initial study cohort, died during the 22-year follow-up period.

### Exposure Estimates

Exposure to $PM_{2.5}$ was estimated by linking geocoded home addresses of the study participants to ambient $PM_{2.5}$ concentrations derived using a national-level hybrid land use regression (LUR) and Bayesian Maximum Entropy (BME) interpolation model (LUR-BME) described elsewhere.[22] (Details on the geocoding of residential locations to be used in exposure assessment are presented in the Online Data Supplement.) Briefly, monthly $PM_{2.5}$ data for a total of 1464 monitoring sites from 1999 to 2008 were used to estimate the LUR-BME model in 2 stages. A training data set of 1329 monitors was used to select the variables, and 10% or 135 monitors were retained approximately for cross-validation. (Details on the model cross-validation analysis are presented in the Online Data Supplement.) In the first stage, the model was fit with a deterministic LUR with monthly pollution averages as the dependent variable and land use information as predictors. The LUR model used a deletion/substitution/addition algorithm with v-fold cross-validation to select predictor variables. This method reduces the chance of overfitting by continuously predicting on leave-out folds, meaning selected variables minimize the mean square error of predictions on data that are not used to fit the model. On the basis of this method, we selected 2 variables: traffic-weighted roads within 1000 m of a monitor (based on modeled traffic counts) and the cube of percentage of green space within a 100 m buffer around the monitor. In the second stage, a BME kriging interpolation model was used to capture the residual spatiotemporal variation in $PM_{2.5}$ concentrations not predicted in the first stage using LUR. Cross-validation resulted in an $R^2$ of 0.79. Scatter plots that illustrate the cross-validation prediction for the models, maps that illustrate the spatial variability of estimated exposures, and further documentation has been published elsewhere[22] and are summarized in the Online Data Supplement. Monthly values from 1999 to 2004 were averaged and assigned to study participants using their geocoded addresses. The estimated overall mean $PM_{2.5}$ exposure concentration was 12.6 (SD=2.9) μg/m$^3$, with a range from 1 to 28 μg/m$^3$.

### Statistical Analysis

Adjusted mortality hazard ratios (HRs) were estimated using the Cox proportional hazards regression models. Follow-up time in days was used as the time axis since enrollment. Survival times of those still alive at the end of follow-up were censored and, in analyses of cause-specific mortality, if death occurred for another cause, survival times were censored at the time of death. The models included the estimated $PM_{2.5}$ exposure concentration as a continuous variable. The models also controlled for multiple individual-level covariates as detailed elsewhere.[3] Briefly, all models were stratified by 1-year age categories, sex, and race (white, black, and other), allowing each category to have its own baseline hazard. The individual-level covariates incorporated in the models, based on information collected from the 1982 ACS CPS-II enrollment questionnaire, included 13 variables that characterized current and former smoking habits (including smoking status of never, former, or current smoker, linear and squared terms for years smoked and cigarettes smoked per day, indicator for starting smoking at aged <18 years, and pipe/cigar smoker); 1 continuous variable that assessed exposure to second-hand cigarette smoke (hours/d exposed); 7 variables that reflected workplace $PM_{2.5}$ exposure in each subject's main lifetime occupation; a variable that indicated self-reported exposure to dust and fumes in the workplace; variables that represented marital status (separated/divorced/widowed or single versus married); variables that characterized the level of education (high school, more than high school versus less than high school); 2 body mass index variables (linear and squared terms for body mass index); variables that characterized the consumption of alcohol (beer, missing beer, wine, missing wine, liquor, and missing liquor); and variables that indicated quartile ranges of dietary fat index and quartile ranges of a dietary vegetable/fruit/fiber index.

To evaluate the sensitivity of the results to control for geographical, social, economic, and environmental settings (contextual conditions),

some models also included ecological covariates obtained from the 1990 Census of Population Long-Form for the subjects' residential zip code area. These ecological covariates are more completely documented elsewhere[23] and included median household income; percentage of people with <125% of poverty-level income; percentage of unemployed individual aged ≥16 years; percentage of adults with <12th grade education; and percentage of the population who were black or Hispanic. These ecological covariates were included in the models using both zip code level data and zip code deviations from the county means.

Baseline HRs associated with an increment of 10 μg/m$^3$ of $PM_{2.5}$ were estimated for all-cause, CVD, hypertension, and diabetes mellitus mortality. Two approaches were used to evaluate the effect modification of cardiometabolic risk factors at time of enrollment on the $PM_{2.5}$–CVD mortality association. First, adjusted HRs (and 95% confidence intervals) for CVD mortality were estimated in relation to 3 key categorical indicators of cardiometabolic risk (diabetes mellitus, doctor diagnosed high blood pressure, and heart disease at time of enrollment) and categorically high and low $PM_{2.5}$ concentrations (>75th percentile and <25th percentile). To test for additive interactions between $PM_{2.5}$ exposure and key cardiometabolic risk factors formally, the relative excess risk because of interaction, the attributable proportion because of interaction and the synergy index were calculated using the MOVER method for the analysis of 4×2 tables as documented elsewhere.[24]

The second approach to evaluate the effect modification of cardiometabolic risk factors estimated adjusted HRs associated with increases in $PM_{2.5}$ (using $PM_{2.5}$ as a continuous variable) for cardiovascular mortality, while stratifying by all cardiometabolic risk factors that were available based on information from the ACS CPS-II enrollment questionnaire. These risk factors include body mass index; doctor diagnosed high blood pressure, heart disease, and diabetes mellitus; exercise levels; vegetable/fruit/fiber and fat intake; and the use of medications including aspirin, heart medications, and diuretics. Because the likelihood of any individual in the cohort having any of the key risk factors at enrollment depends partially on age and smoking status at enrollment, indicators of cardiometabolic risk were cross-stratified with 4 age-at-enrollment and smoking status strata (never smokers, age <60 years; never smokers, age ≥60 years; ever smokers, age <60 years; ever smokers, age ≥60). To evaluate whether the associations differ for different follow-up times, we conducted the analysis, stratified across strata relating to cardiometabolic risk factors for 3 different follow-up periods: 0 to 7, 7 to 14, and 14 to 22 years.

Specific cause-of-death analyses were conducted using primary and contributing cause-of-death information provided on the death certificate focusing on hypertensive disease, diabetes mellitus, and interactions with other cardiovascular causes of death.

## Results

Estimated HRs (and 95% confidence intervals) associated with a 10 μg/m$^3$ elevation in $PM_{2.5}$ for all-cause, CVD, various subcategories of CVD, and diabetes mellitus mortality are presented in Table 1 and illustrated in Figure 1A. Estimates from these baseline Cox proportional hazards regression models indicated that all-cause and CVD mortality were significantly associated with long-term exposure to $PM_{2.5}$. The largest and most statistically robust $PM_{2.5}$–CVD mortality associations were with ischemic heart disease mortality, hypertensive disease mortality, and mortality from a cause-of-death grouping that includes heart failure, cardiac arrest, and related (*International Classification of Diseases* codes presented in Table 1). The effect estimates are similar without and with control for ecological covariates.

Figure 2 illustrates the adjusted HRs for CVD mortality estimated in relation to categorical indicators of cardiometabolic risk (diabetes mellitus, high blood pressure, and heart disease at time of enrollment) and categorically high versus low $PM_{2.5}$ concentrations (>75th percentile; mean [SD], 16.21 [1.94] versus <25 percentile; mean [SD], 9.15 [1.16]). Subjects with a pre-existing condition (diabetes mellitus, high blood pressure, or heart disease) had a substantially higher risk of CVD mortality than subjects without a pre-existing condition. However, high $PM_{2.5}$ exposure was associated with higher risk of CVD mortality in subjects with or without pre-existing conditions and formal tests for interactions (including relative excess risk because of interaction, attributable proportion because of interaction, and the synergy index) between $PM_{2.5}$ exposure and key cardiometabolic risk factors provided no evidence of statistically significant interaction. Estimated HRs across strata of pre-existing disease and all other cardiometabolic factors also provide no consistent pattern of effect modification by cardiometabolic risk factors on the association between $PM_{2.5}$ and CVD (Figure 3). The lack of effect modification in the $PM_{2.5}$–CVD mortality association was not sensitive to controlling for ecological covariates or to the use of the alternative exposure model, or was it sensitive to cross-classifying the data by age and smoking status (Figure 3). These results were

**Table 1. HRs (95% CI) Per 10-μg/m$^3$ Increment in $PM_{2.5}$ for All-Cause, Cardiovascular, and Diabetes Mellitus Mortality Using the Cox Model With Individual-Level Covariates, Without and With Ecological Covariates, and With Exposure Estimated Using the LUR-BME Model, Along With Number of Deaths and Relevant ICD-9 and ICD-10 Codes**

| Primary Cause of Death | No. of Deaths | ICD-9 Codes | ICD-10 Codes | HRs (95% CIs) Per 10-μg/m$^3$ $PM_{2.5}$ | |
|---|---|---|---|---|---|
| | | | | Cox Model With Individual-Level Covariates; Exposure Based on LUR-BME | Cox Model With Individual-Level Plus Ecological Covariates; Exposure Based on LUR-BME |
| All-cause mortality | 237 201 | ... | ... | 1.07 (1.05–1.09) | 1.07 (1.06–1.09) |
| Cardiovascular disease | 100 149 | 390–459 | I00–I99 | 1.14 (1.12–1.17) | 1.12 (1.10–1.15) |
| Ischemic heart disease | 45 644 | 410–414 | I20–I25 | 1.19 (1.15–1.23) | 1.14 (1.10–1.18) |
| Heart failure, cardiac arrest, and related | 18 314 | 420–429 | I30–I51 | 1.12 (1.07–1.18) | 1.11 (1.05–1.18) |
| Cerebrovascular disease | 17 085 | 430–438 | I60–I69 | 1.04 (0.99–1.10) | 1.11 (1.05–1.17) |
| Hypertensive disease | 3129 | 401–405 | I10–I13 | 1.20 (1.06–1.35) | 1.11 (0.97–1.26) |
| Diabetes mellitus | 4890 | 250 | E10–E14 | 1.08 (0.97–1.19) | 1.13 (1.02–1.26) |

CI indicates confidence interval; HR, hazard ratio; ICD, *International Classification of Diseases*; LUR-BME, land use regression-Bayesian Maximum Entropy; and $PM_{2.5}$, fine PM <2.5 μm in aerodynamic diameter.

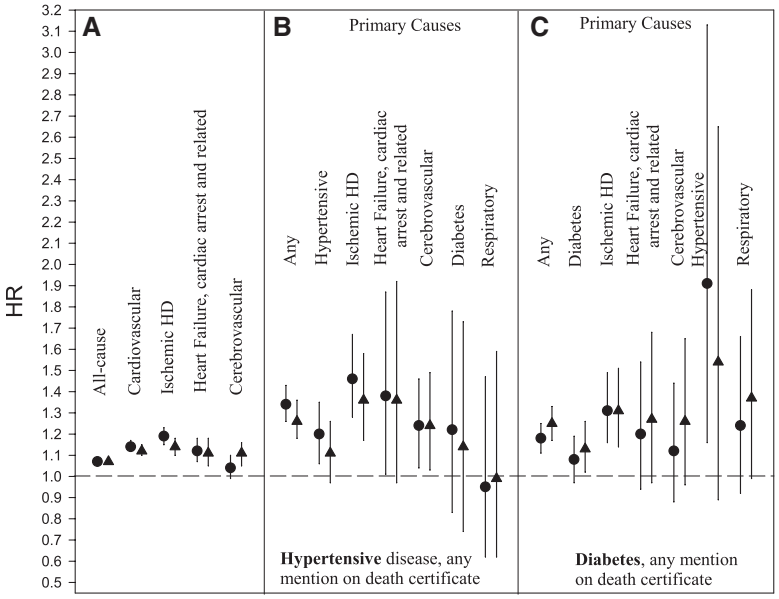


**Figure 1.** Hazard ratios (HR; 95% confidence interval) per 10-μg/m³ increase in fine particulate matter <2.5 μm in aerodynamic diameter for all-cause and cardiovascular disease deaths (**A**); for deaths with any mention of hypertensive (**B**) and diabetes mellitus (**C**) disease as primary or contributing causes of death, stratified by various primary causes of death using the Cox model with individual-level covariates, without (●) and with (▲) ecological covariates, and with exposure estimated using the land use regression-Bayesian Maximum Entropy model. HD indicates heart disease.

not substantively different when the CVD mortality HRs (95% confidence interval) per 10 μg/m³ $PM_{2.5}$ across strata relating to cardiometabolic risk factors were estimated after excluding those who reported taking blood pressure, heart, or diuretic medication or when estimated for different follow-up times.

Table 2 and Figure 1B and 1C present the HRs (95% confidence intervals) per 10 μg/m³ increase in $PM_{2.5}$ for deaths when the death certificate indicated hypertensive disease or diabetes mellitus or both as primary or contributing causes of death. Deaths with either hypertension or diabetes mellitus as a primary or contributing cause were significantly associated with long-term $PM_{2.5}$ exposure. Deaths with any indication of hypertension or diabetes mellitus on the death certificate were also stratified by primary cause of death. In general, the associations of $PM_{2.5}$ with risk of death when hypertension or diabetes mellitus were mentioned on the death certificate (as either primary or contributing causes of death) in combination with each other or with other CVD causes of mortality are relatively large and statistically significant (Figure 1B and 1C). Although these results are constrained by the number of deaths (Table 2), they are suggestive of effects of long-term exposure to $PM_{2.5}$ for CVD deaths that are linked to hypertension and diabetes mellitus.

## Discussion

The present study is based on 22 years of follow-up of the ACS CPS-II prospective cohort, coupled with enhanced exposure assessment that provided estimates of ambient residential $PM_{2.5}$ concentrations using linkage to the geocoded home addresses. As such, this analysis encompasses a large cohort, with a long follow-up time, with a large number of deaths, and with improved exposure spatial acuity. The results of this analysis corroborate previous findings of statistically robust associations of $PM_{2.5}$ with all-cause and CVD mortality observed in the ACS CPS-II cohort,[2,3,25] a finding also consistent with those from other cohorts.[1–6]

The present study evaluated potential joint relationships between long-term $PM_{2.5}$ exposures and cardiometabolic disease on risk of CVD mortality. Although showing that subjects with both high $PM_{2.5}$ exposure and a pre-existing condition are at the highest risk of CVD mortality, the increased risk of CVD death associated with $PM_{2.5}$ is similar in subjects with a

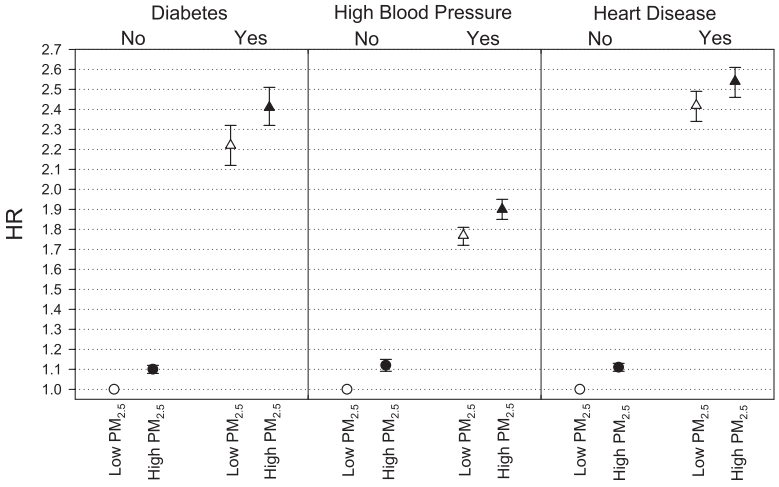


**Figure 2.** Hazard ratios (HR; 95% confidence interval) for cardiovascular disease mortality estimated in relation to categorical indicators of cardiometabolic risk (diabetes mellitus, high blood pressure, and heart disease at time of enrollment) and categorically high fine particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) concentrations (>75th percentile; mean, 16.21; SD, 1.94 μg/m³) vs low $PM_{2.5}$ concentrations (<25 percentile; mean, 9.15; SD, 1.16 μg/m³).

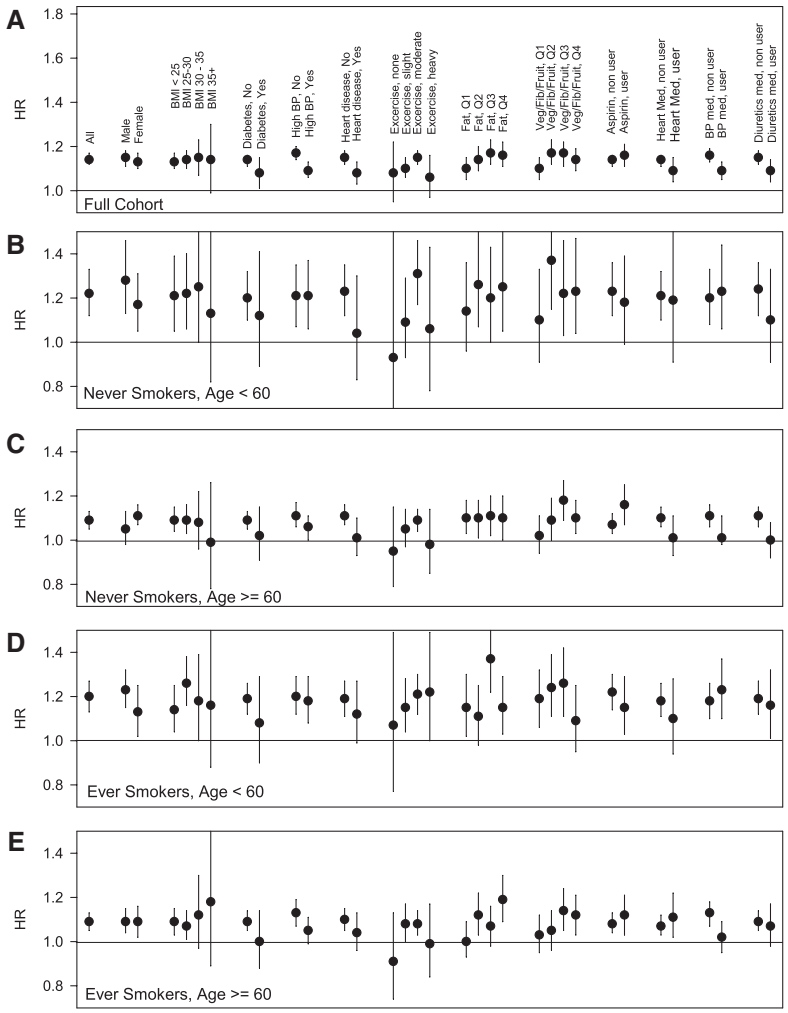


**Figure 3.** Cardiovascular disease mortality hazard ratios (HR; 95% confidence interval) per 10-μg/m$^3$ increment in fine particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) across strata relating to cardiometabolic risk factors for full cohort, stratified by smoking and age estimated using the Cox models with individual-level covariates and with exposure estimated using the land use regression-Bayesian Maximum Entropy model. BMI indicates body mass index; and BP, blood pressure.

pre-existing condition and those without. This lack of effect modification may be influenced by inevitable imperfect classification of pre-existing cardiometabolic disorders based on questionnaire data collected at enrollment when participants were younger and at much lower risk of death. However, the absence of effect modification was observed both in participants aged ≥60 years, as well as those who were aged <60 years. In addition, there may be a concern about collider-stratification bias.[26,27] For example, if $PM_{2.5}$ contributes to CVD mortality by increasing blood pressure, stratifying by hypertension removes this pathogenic pathway, and the $PM_{2.5}$–CVD mortality estimate stratified by hypertension reflects the effect of $PM_{2.5}$, independent of hypertension. Nevertheless, our results provide evidence of a $PM_{2.5}$–CVD mortality association across nearly all strata evaluated and do not substantiate previous reports, suggesting that underlying cardiometabolic diseases predispose individuals to the adverse health effects of $PM_{2.5}$, at least with respect to fatal events induced by chronic exposures.[4,11]

Alternatively, our findings suggest a less-considered mechanism where $PM_{2.5}$ influences the development of cardiometabolic disorders. Long-term $PM_{2.5}$ exposure was associated with a significant 34% increase in deaths linked to hypertension (any mention on death certificate), and with a 20% increase in deaths with hypertension as the primary cause. Previous studies have shown that short-term exposure to $PM_{2.5}$ can cause a rapid elevation in blood pressure.[4,28] Indeed, emergency department visits specifically for hypertension have been shown to increase in relation to recent air pollution levels.[29] There is also accruing evidence from epidemiological studies internationally that higher particulate pollution levels are associated with an increased incidence of hypertension.[28,30] We recently demonstrated that long-term $PM_{2.5}$ exposure is associated with chronic hypertension (13% elevation per 10 μg/m$^3$ among 35 303 adults living in Ontario, Canada).[31] These associations have some biological plausibility in that several pathways have been shown to be involved in both human and animal studies, including autonomic imbalance, systemic inflammation, and endothelial dysfunction.[28]

The results of this study are also consistent with recent evidence that $PM_{2.5}$ is associated with diabetes mellitus mortality. A 10-μg/m$^3$ increase in $PM_{2.5}$ was associated with an 18% increase in diabetes mellitus–related mortality. A growing body of evidence also supports the notion that not only can exposure acutely perturb glycemic control but also living in regions with higher $PM_{2.5}$ levels is associated with increased diabetes mellitus.[12,30] For example, the incidence of diabetes mellitus increased by 8% to 11% per 10 μg/m$^3$ among 62 012 adults living in Ontario, Canada.[14] The present results corroborate previous data from a national cohort demonstrating a more robust increase (49% increase in risk per 10 μg/m$^3$) in diabetes

**Table 2. HRs (95% CI) Per 10-μg/m³ Increment in $PM_{2.5}$ for Deaths With Any Mention of Hypertensive and Diabetes Mellitus Disease as Primary and Contributing Causes of Death Stratified by Primary Cause of Death Using the Cox Model With Individual-Level Covariates, Without and With Ecological Covariates, and With Exposure Estimated Using the LUR-BME Model Along With Number of Deaths**

| Information on Cause of Death | No. of Deaths | HRs (95% CIs) Per 10-μg/m³ $PM_{2.5}$ | |
|---|---|---|---|
| | | Cox Model With Individual-Level Covariates; Exposure Based on LUR-BME | Cox Model With Individual-Level Plus Ecological Covariates; Exposure Based on LUR-BME |
| Hypertensive disease, any mention on death certificate | 10448 | 1.34 (1.26–1.43) | 1.26 (1.18–1.36) |
| Primary cause | | | |
| Hypertensive | 3129 | 1.20 (1.06–1.35) | 1.11 (0.97–1.26) |
| Ischemic heart disease | 2434 | 1.46 (1.28–1.67) | 1.36 (1.17–1.58) |
| Heart failure, cardiac arrest, and related | 482 | 1.38 (1.01–1.87) | 1.36 (0.97–1.92) |
| Cerebrovascular disease | 1584 | 1.24 (1.04–1.46) | 1.24 (1.03–1.49) |
| Diabetes mellitus | 336 | 1.22 (0.83–1.78) | 1.14 (0.74–1.73) |
| Respiratory disease | 252 | 0.95 (0.62–1.47) | 0.99 (0.62–1.59) |
| Diabetes mellitus, any mention on death certificate | 13229 | 1.18 (1.11–1.25) | 1.25 (1.17–1.33) |
| Primary cause | | | |
| Diabetes mellitus | 4890 | 1.08 (0.97–1.19) | 1.13 (1.02–1.26) |
| Ischemic heart disease | 3015 | 1.31 (1.16–1.49) | 1.31 (1.14–1.51) |
| Heart failure, cardiac arrest and related | 790 | 1.20 (0.94–1.54) | 1.27 (0.97–1.68) |
| Cerebrovascular disease. | 786 | 1.12 (0.88–1.44) | 1.26 (0.96–1.65) |
| Hypertensive | 176 | 1.91 (1.16–3.13) | 1.54 (0.89–2.65) |
| Respiratory disease | 547 | 1.24 (0.92–1.66) | 1.37 (0.99–1.88) |

CI indicates confidence interval; HR, hazard ratio; LUR-BME, land use regression-Bayesian Maximum Entropy; and $PM_{2.5}$, fine PM <2.5 μm in aerodynamic diameter.

mellitus–related mortality.[15] Several human studies and animal experiments have elucidated viable biological mechanisms, whereby $PM_{2.5}$ can be capable of impairing metabolic insulin sensitivity via autonomic and systemic proinflammatory and oxidative stress pathways.[12]

Our findings cannot explain precisely the mechanisms behind the association of $PM_{2.5}$ with increased mortality related to hypertension and diabetes mellitus. $PM_{2.5}$ may be triggering CVD deaths that are unrelated to hypertension or diabetes mellitus among individuals with previously developed hypertension and diabetes mellitus. This is suggested by the significant increase in several CVD-related causes of death listed as the primary cause among those with either hypertension or diabetes mellitus appearing anywhere on the death certificate. It is also possible that $PM_{2.5}$ might exacerbate the underlying hypertensive or diabetic disease state in a subacute manner during a period of weeks to months, thereby promoting a fatal event principally related to these disorders (hypertensive or hyperglycemic emergencies). Underlying this acute event, long-term $PM_{2.5}$ exposure might compromise chronic diabetic and blood pressure control (or contribute to their actual onset), and thereby promote the future fatal event related to these chronic disorders per se. It is likely that combinations of these 3 pathways are occurring at the population level.[12,28]

This analysis has notable strengths. It uses data from a large, nation-wide, well-characterized, and managed prospective cohort followed up for 22 years. It uses a state-of-the-art LUR-BME model to provide exposure estimates for a relatively large number of cohort members, and it provides estimates of exposure with substantially improved spatial acuity. As documented elsewhere,[22] cross-validation analysis demonstrated strong agreement between estimated exposures using the LUR-BME model and observed data ($R^2$=0.79) with no indications of bias or exceptional outliers.

This study also has limitations. Because the ACS CPS-II cohort included many friends and family members of ACS volunteers, it was not a random sample, but over-represented relatively affluent, well-educated individuals. As discussed elsewhere as part of a review and comparison of results from various cohort studies,[32] there is some evidence that air pollution has a bigger effect on the less affluent and less educated. Therefore, pooled estimates from the ACS CPS-II cohort may underestimate the effect relative to the general population. Estimates of $PM_{2.5}$ exposure are not available throughout the lives of cohort members, or even for the full cohort follow-up period. Individual-level risk-factor data, including information relating to pre-existing cardiometabolic risk factors, and residential address, are based on information from the ACS CPS-II enrollment questionnaires, with no subsequent follow-up. The lack of air pollution and risk factor follow-up data reduces the precision of control for risk factors, constrains the ability to differentiate time dependency, and introduces some exposure misclassification that may bias the results toward the null.

Another key limitation of this study pertains to the use of cause-of-death information provided on death certificates. Death certificate information is inevitably incomplete on

causes of death and comorbidities contributing to death and is clearly limited with respect to defining deaths caused by cardiometabolic disease states. With regards to cardiometabolic disease, mention of diabetes mellitus or hypertension on the death certificate is suggestive but far from definitive. Furthermore, many CVD deaths would likely include a significant number of individuals with cardiometabolic disease but did not have any mention of diabetes mellitus or hypertension on the death certificate. Similarly, because health information was collected only on the cohort enrollment questionnaire and on death certificates, subjects who developed cardiometabolic disorders during follow-up, but are still living, are not captured as events in this analysis at all. More definitive evaluations of joint contributions of air pollution and cardiometabolic disease with CVD mortality would require follow-up that also includes prospective tracking of indicators of the development and progression of cardiometabolic disease.

In conclusion, cardiometabolic disorders are common and, because of increasing obesity, sedentary lifestyles, and atherogenic diets, are growing in prevalence worldwide.[19,20,33] The prominent role of CVD, hypertension, diabetes mellitus, and air pollution in contributing to the global burden of disease has been well documented.[34,35] The potential global public health implications of joint relationships between fine PM air pollution, cardiometabolic disorders, and cardiovascular mortality are substantial.

## Sources of Funding

The American Cancer Society funded the creation, maintenance, and follow-up of the Cancer Prevention Study II cohort. C. Arden Pope III was funded, in part, by the Mary Lou Fulton Professorship, Brigham Young University. Michelle C. Turner was funded by a Government of Canada Banting Postdoctoral Fellowship. Daniel Krewski is the Natural Sciences and Engineering Research Council (NSERC) Chair in Risk Science at the University of Ottawa. Michael Jerrett was supported for the exposure assessment modeling funding from NIEHS (National Institute of Environmental Health Sciences) R01 ES019573-01, the Centers for Disease Control and Environmental Public Health Tracking and Health Canada.

## Disclosures

None.

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## Novelty and Significance

### What Is Known?

- Long-term exposure to fine particulate air pollution is associated with risk of cardiovascular mortality.
- It is unknown who is most susceptible but those with underlying cardiometabolic disorders may be at greater risk.

### What New Information Does This Article Contribute?

- Cardiovascular mortality–pollution associations were observed for those with and without existing cardiometabolic disorders ascertained at study baseline.
- Deaths with hypertension or diabetes mellitus mentioned on death certificate were more strongly associated with air pollution than deaths without these conditions mentioned, suggesting that long-term exposure may contribute to cardiometabolic disorders augmenting cardiovascular disease risk.

This analysis used data from a large, nation-wide cohort, with >20 years of follow-up, with enhanced exposure assessment, and with control for multiple key individual and geospatial contextual variables. Associations between mortality risk and elevated exposures to fine particulate air pollution were remarkably robust. Preexisting cardiometabolic risk factors (based on cohort enrollment information) did not modify the effect of pollution exposure on cardiovascular mortality. Deaths linked to hypertension or diabetes mellitus (based on information from death certificates), however, were more strongly associated with pollution, suggesting that long-term pollution exposure may contribute to the development or exacerbation of cardiometabolic disorders, increasing risk of cardiovascular and cardiometabolic disease mortality.