


RESEARCH

Open Access



The impact of long-term PM_{2.5} exposure on specific causes of death: exposure-response curves and effect modification among 53 million U.S. Medicare beneficiaries

Bingyu Wang^{1*} , Ki-Do Eum², Fatemeh Kazemiparkouhi², Cheng Li¹, Justin Manjourides³, Virgil Pavlu¹ and Helen Suh²

Abstract

Background: The shape of the exposure-response curve for long-term ambient fine particulate (PM_{2.5}) exposure and cause-specific mortality is poorly understood, especially for rural populations and underrepresented minorities.

Methods: We used hybrid machine learning and Cox proportional hazard models to assess the association of long-term PM_{2.5} exposures on specific causes of death for 53 million U.S. Medicare beneficiaries (aged ≥65) from 2000 to 2008. Models included strata for age, sex, race, and ZIP code and controlled for neighborhood socio-economic status (SES) in our main analyses, with approximately 4 billion person-months of follow-up, and additionally for warm season average of 1-h daily maximum ozone exposures in a sensitivity analysis. The impact of non-traffic PM_{2.5} on mortality was examined using two stage models of PM_{2.5} and nitrogen dioxide (NO₂).

Results: A 10 μg /m³ increase in 12-month average PM_{2.5} prior to death was associated with a 5% increase in all-cause mortality, as well as an 8.8, 5.6, and 2.5% increase in all cardiovascular disease (CVD)-, all respiratory-, and all cancer deaths, respectively, in age, gender, race, ZIP code, and SES-adjusted models. PM_{2.5} exposures, however, were not associated with lung cancer mortality. Results were not sensitive to control for ozone exposures. PM_{2.5}-mortality associations for CVD- and respiratory-related causes were positive and significant for beneficiaries irrespective of their sex, race, age, SES and urbanicity, with no evidence of a lower threshold for response or of lower Risk Ratios (RRs) at low PM_{2.5} levels. Associations between PM_{2.5} and CVD and respiratory mortality were linear and were higher for younger, Black and urban beneficiaries, but were largely similar by SES. Risks associated with non-traffic PM_{2.5} were lower than that for all PM_{2.5} and were null for respiratory and lung cancer-related deaths.

Conclusions: PM_{2.5} was associated with mortality from CVD, respiratory, and all cancer, but not lung cancer. PM_{2.5}-associated risks of CVD and respiratory mortality were similar across PM_{2.5} levels, with no evidence of a threshold. Blacks, urban, and younger beneficiaries were most vulnerable to the long-term impacts of PM_{2.5} on mortality.

Keywords: Air pollution, Chronic exposure, PM_{2.5}, Environmental epidemiology, Cardiovascular disease mortality, Respiratory disease mortality, Cancer mortality

* Correspondence: rainicy@ccs.neu.edu

¹Khoury College of Computer Sciences, Northeastern University, 440 Huntington Ave, Boston, MA 02115, USA

Full list of author information is available at the end of the article



Background

Studies have demonstrated associations between long-term exposure to airborne fine particles ($PM_{2.5}$, particulate matter with an aerodynamic diameter $\leq 2.5 \mu m$) and increased all-cause [1–7] and cardiovascular (CVD) and to a lesser extent respiratory and lung cancer mortality [3, 4, 8]. In our paper of almost 19 million Medicare beneficiaries [4], for example, we showed 12 month average $PM_{2.5}$ prior to death to be associated with increased all-cause, cardiovascular, respiratory, and lung cancer mortality, including from specific causes such as chronic obstructive pulmonary disease (COPD) and pneumonia mortality. While our and other studies provide key evidence of $PM_{2.5}$'s impacts on mortality from several specific causes of death, their findings were based on largely white and higher socio-economic status (SES) cohorts from specific locations [2, 9, 10] or living in urban areas close to air pollution monitoring sites [4]. More recently, studies have expanded their geographic scope through the use of spatio-temporal models to predict exposures for participants living away from air pollution monitoring sites [5, 11, 12], although most still largely focus on white, urban and higher SES populations [11, 12] or on all-cause [5] or CVD-related [13, 14] causes of death. Of note, one study of California elderly found higher risks for CVD mortality for rural as compared to urban populations [15]. While this study controlled for key demographic factors, including race, SES, and education level, the contribution of these factors to the higher mortality risks experienced by rural populations was not examined [15]. Correspondingly, a study of adult participants in the National Health Interview Survey found elevated $PM_{2.5}$ -associated CVD mortality risks, with no difference by race, possibly the result of the broad age range of their cohort, their relatively small sample size, and their time invariant $PM_{2.5}$ exposure estimates [13]. New approaches are needed to examine $PM_{2.5}$ -associated risks of mortality more comprehensively, especially with regards to differentiation of risks for specific causes of death, for potentially susceptible sub-populations, and at low $PM_{2.5}$ exposures.

The advent of machine learning methods allows us to comprehensively examine $PM_{2.5}$ impacts on mortality in “big” populations as provided by administrative data, allowing examination of the impact of low $PM_{2.5}$ exposures understudied groups, and less common causes of deaths. In this paper, we describe associations between long-term $PM_{2.5}$ and mortality from specific causes in all Medicare beneficiaries living in the conterminous US from 2000 through 2008. We examined the shape of the exposure-response curve for $PM_{2.5}$ and the impact of low $PM_{2.5}$ exposures for specific causes of death for the entire population and for specific subgroups. We further examined the impact of non-traffic $PM_{2.5}$ on mortality

and of confounding of these associations by SES and confounding and effect modification by sex, race, age, SES, and urbanicity.

Methods

Our study was approved by the Institutional Review Board of Tufts and Northeastern Universities.

Medicare mortality dataset

We compiled enrollment data from the Centers for Medicare and Medicaid Services for 53 million Medicare beneficiaries (65–120 years) living in the US between 2000 and 2008. Using the International Classification of Disease (ICD-10) codes from the National Death Index, we extracted mortality from non-accidental and accidental causes, CVD, respiratory, cancer, ischemic heart (IHD) and cerebrovascular (CBV) disease, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), pneumonia, and lung cancer.

Pollution exposure

Daily $PM_{2.5}$ estimates on a 6-km grid were obtained from validated spatio-temporal generalized additive mixed models [14]. Model inputs included $PM_{2.5}$ data from the U.S. Environmental Protection Agency (EPA), meteorological and geospatial covariates, and traffic-related PM estimated using a Gaussian line-source dispersion model. The daily $PM_{2.5}$ model performed well, with a cross-validation R^2 of 0.76, with low bias and high precision [14]. We obtained monthly NO_2 concentrations estimated on a 100 m grid from [16]. The model performed well, explaining 82 and 76% of the spatial and temporal variability, respectively, with low bias (21%) and error (2.4 parts per billion, ppb). For both pollutants, we matched beneficiaries to the grid point closest to their ZIP code centroid, accounting for residential moves, and averaged estimated values to obtain the 12-month average prior to death, hereafter referred to as “12-month average exposure”. We also estimated warm season average 1-h maximum ozone exposures for a subset of beneficiaries living in ZIP codes within 6 miles of air quality monitors from the US EPA (Environmental Protection Agency) AQS (Air Quality System) for 2000 through 2008, following methods described in [17].

Urbanicity and SES

For each ZIP code, we assessed urbanicity (urban vs. non-urban) using Categorization B from the Rural Health Research Center (RHRC) [18] and SES using the annual mean gross adjusted income from the US Internal Revenue Service (IRS) Statistics of Income Division database. [SES for the missing 2000 and 2003 years was estimated as the 2001 and 2004 values, respectively.] To examine effect modification, we classified ZIP codes

as “high”, “medium”, or “low” based on tertiles of the distribution of adjusted incomes across ZIP codes.

Analytical models

We examined the association of 12-month average $PM_{2.5}$ exposures and cause-specific mortality using Cox proportional hazards (Cox PH) models with strata for age, race, sex, and ZIP code in base models and additionally controlling for ZIP code and state SES in adjusted models. To take full advantage of the monthly resolution of our mortality data, we fit each of our models using 3.8 billion person-months of follow-up and analyzing all data simultaneously. We categorized age into 1-year intervals, with 90+ years included as 1 age interval to avoid excessive zero counts. For each cause of death, we examined effect modification using interaction terms for age, sex, race, and ZIP code-level urbanicity in SES-adjusted models and SES in base models. As a sensitivity analysis, we also fit base and SES-adjusted models additionally controlling for the warm-season average of daily 1-h maximum ozone exposures, with this analysis based on a subset of 22+ million Medicare beneficiaries who lived in ZIP codes within 6 miles of an ozone monitoring station. All results are expressed as the risk ratio (RR) per 10 $\mu g / m^3$ increase in 12-month average $PM_{2.5}$.

To characterize non-linearities in the $PM_{2.5}$ -mortality association, we fit SES-adjusted models using restricted cubic splines (RCS) with three knots [19] for all examined causes of death. RCS models with three knots were chosen as our main model, given its superior performance to models with 4 and 5 knots (Figure S4). To further examine effects of low $PM_{2.5}$ exposures, we fit SES-adjusted models restricted to beneficiaries living in ZIP codes with average $PM_{2.5}$ concentrations below 8, 10 or 12 $\mu g / m^3$. In sensitivity analyses, we fit SES- and ozone-adjusted non-linear models for a subset of 22 million Medicare beneficiaries living near EPA ozone monitors.

While we did not control for potential confounding by NO_2 due to strong correlations between $PM_{2.5}$ and NO_2 ($r = 0.59$), we used NO_2 exposures to estimate the impact of non-traffic $PM_{2.5}$ exposures on cause-specific mortality. We did so in two-stages, regressing 12-month $PM_{2.5}$ on NO_2 and using its residuals as the exposure measure in health models. Since NO_2 originates primarily from traffic-related sources [20, 21], RRs from the second stage models can be interpreted as the mortality risk from $PM_{2.5}$ that is unrelated to traffic sources. Note that our approach allows us to compare RRs associated with non-traffic $PM_{2.5}$ to those for total $PM_{2.5}$ but not to traffic-related $PM_{2.5}$. To assess the validity of our approach, we compared 1-year average residuals of $PM_{2.5}$ on NO_2 to 1-year average elemental carbon (EC), sulfate, and sulfur concentrations measured at US EPA chemical

speciation network (CSN) sites by ZIP code and year. Comparisons with EC were limited to those sites that analyzed EC using the total optical transmittance method, since these sites were located predominantly in urban and suburban areas, where the majority of our beneficiaries lived.

Since conventional statistical packages such as R and SAS are not able to analyze our large-scale data due to memory and processing limitations, we implemented both linear and non-linear Cox PH methods in Java. Our implementation overcame memory and processing limitations of conventional software packages, using data grouping and linkage methods, optimization techniques, and multi-threading, fitting our models for 53 million beneficiaries and 3.8 billion person-months of follow-up simultaneously in approximately 10 minutes. Our implementation of Cox PH is described in Appendix S1 and is hosted on GitHub (<https://github.com/Rainicy/survival>).

Results

Our study population includes approximately 53 million Medicare enrollees living in over 41,000 US ZIP codes between 2000 and 2008, with approximately 3.8 billion enrollee-months of follow-up (Table 1). During the study period, approximately 16 million deaths were reported, with 15 million deaths from non-accidental causes, 6.4 million from CVD, 1.8 million from respiratory disease, and 3.6 million from cancer. More than

Table 1 Characteristics Medicare enrollees aged 65–120 Years, United States, from 2000 to 2008

Characteristic	ICD-10	Number	%
No. of enrollees		52,954,845	
No. of ZIP Code		41,630	
No. of Person-Month		3,743,349,849	
No. of deaths			
All Causes		15,843,982	100.0 ^a
Non-accidental	A-R	15,324,059	96.7
Accidental	V-Y	381,685	2.4
All Cardiovascular (CVD)	I00-I99	6,371,713	40.2
Ischemic heart disease (IHD)	I20-I25	3,323,527	21.0
Cerebrovascular disease (CBV)	I60-I69	1,147,050	7.2
Congestive heart failure (CHF)	I50	471,127	3.0
All Respiratory	J00-J99	1,777,076	11.2
COPD	J40-J44	944,665	6.0
Pneumonia	J12-J18	462,736	2.9
All Cancer	C-D	3,576,207	22.6
Lung cancer	C34	988,643	6.2

Abbreviations: COPD Chronic Obstructive Pulmonary Disease

^a The numbers or the percentages from sub-causes of death do not sum to all causes of deaths or 100%, because additional other causes of death are not reported in this table

50% of CVD mortality was from IHD, 18% from CBV, and 7.4% from CHF. More than 50% of respiratory deaths were attributed to COPD and 26% to pneumonia; 28% of cancer deaths were from lung cancer. Seventy-four percent of beneficiaries lived in urban areas, with beneficiaries living in low income ZIP codes residing primarily in non-urban areas (Table S2). The overall mean 12-month $PM_{2.5}$ concentration was $10.32 \mu g / m^3$ (sd = 3.15), with mean concentrations higher in urban as compared to non-urban ZIP codes. Correlations between 12-month $PM_{2.5}$ and NO_2 and O_3 equaled 0.59 and 0.24, respectively. Note that correlations between $PM_{2.5}$ and ozone were stronger when analyzed by region, equaling 0.31 in the Midwest, 0.23 in the West, 0.43 in the Northeast, and 0.46 in the South.

$PM_{2.5}$ and cause-specific mortality

Table 2 shows RRs associated with 12-month $PM_{2.5}$ for mortality by cause in base and SES-adjusted models, with RRs additionally adjusting for warm-season average of daily 1-h maximum ozone presented in Table S3. In base models, RRs were positive and statistically significant for all causes of death, except for accidental mortality. RRs were attenuated after adjustment for SES, with RRs for CHF and lung cancer no longer significant. In SES-adjusted models, $PM_{2.5}$ -associated RRs were highest for CVD-related causes (1.088; 95% CI

(Confidence Interval): 1.078, 1.098), including IHD (1.126; 95% CI: 1.112, 1.140) and CBV (1.126; CI: 1.103, 1.150). Although lower, $PM_{2.5}$ -associated risks for mortality from respiratory-related and cancer (1.025; 95% CI: 1.012, 1.038) mortality were significant and positive. RRs in base and SES-adjusted models were essentially unchanged after additional adjustment for ozone (Table S3).

The shape of the exposure-response functions for specific causes of death were examined in SES-adjusted models (Fig. 1, Figure S1, Table S5). We found RRs to increase monotonically with increased $PM_{2.5}$ for all CVD and respiratory causes of death, except for CHF and pneumonia. For both CHF and pneumonia mortality, RRs were higher for $PM_{2.5}$ exposures below as compared to above approximately $10 \mu g / m^3$. RRs were statistically significant and positive across the range of $PM_{2.5}$ exposures for pneumonia, but were no longer significant for CHF at higher $PM_{2.5}$ exposures (Figure S1). For non-accidental mortality, we found significant and positive RRs across the range of $PM_{2.5}$ exposures, with no evidence of a threshold. The shape of the exposure-response curve, however, was sub-linear, with lower RRs when $PM_{2.5}$ exposures were lower than $10 \mu g / m^3$ (Fig. 1). These findings are largely consistent with those from our analyses restricted to beneficiaries living in ZIP codes with $PM_{2.5}$ concentrations below 8,

Table 2 Mortality risk ratios (95% CI) associated with a $10 \mu g / m^3$ increase in 12-month average $PM_{2.5}$: Base and SES-Adjusted models, by cause of death, US 2000–2008

Causes of Death	$PM_{2.5}$		Non-Traffic ^a $PM_{2.5}$	
	Base Model ^b	SES-Adjusted ^c	Base Model ^d	SES-Adjusted ^e
All Causes	1.235 (1.229,1.242)	1.050 (1.044,1.056)	1.075 (1.067,1.082)	1.015 (1.008,1.022)
Non-accidental	1.244 (1.238,1.251)	1.051 (1.045,1.057)	1.070 (1.062,1.077)	1.014 (1.007,1.021)
Accidental	0.922 (0.891,0.955)	0.998 (0.960,1.037)	1.001 (0.956,1.047)	1.018 (0.972,1.066)
All Cardiovascular	1.683 (1.669,1.696)	1.088 (1.078,1.098)	1.178 (1.165,1.191)	1.016 (1.005,1.028)
IHD	1.975 (1.954,1.996)	1.126 (1.112,1.140)	1.258 (1.239,1.277)	1.027 (1.011,1.043)
CBV	1.955 (1.919,1.992)	1.126 (1.103,1.150)	1.270 (1.238,1.303)	1.057 (1.029,1.085)
CHF	1.116 (1.082,1.150)	0.986 (0.953,1.021)	1.007 (0.966,1.050)	0.970 (0.930,1.012)
All Respiratory	1.241 (1.223,1.260)	1.056 (1.038,1.074)	1.048 (1.026,1.070)	0.989 (0.968,1.010)
COPD	1.045 (1.023,1.067)	1.023 (0.999,1.047)	1.005 (0.977,1.033)	0.998 (0.969,1.027)
Pneumonia	1.769 (1.721,1.819)	1.078 (1.044,1.114)	1.184 (1.138,1.233)	0.943 (0.905,0.982)
All Cancer	1.160 (1.147,1.172)	1.025 (1.012,1.038)	1.054 (1.038,1.069)	1.016 (1.001,1.031)
Lung cancer	1.078 (1.056,1.100)	0.995 (0.972,1.018)	1.009 (0.981,1.038)	0.986 (0.958,1.014)

Abbreviations: IHD ischemic heart disease, CBV cerebrovascular disease, CHF congestive heart failure, COPD chronic obstructive pulmonary disease, SES socio-economic status, $PM_{2.5}$ fine particle, aerodynamic diameter < $2.5 \mu m$

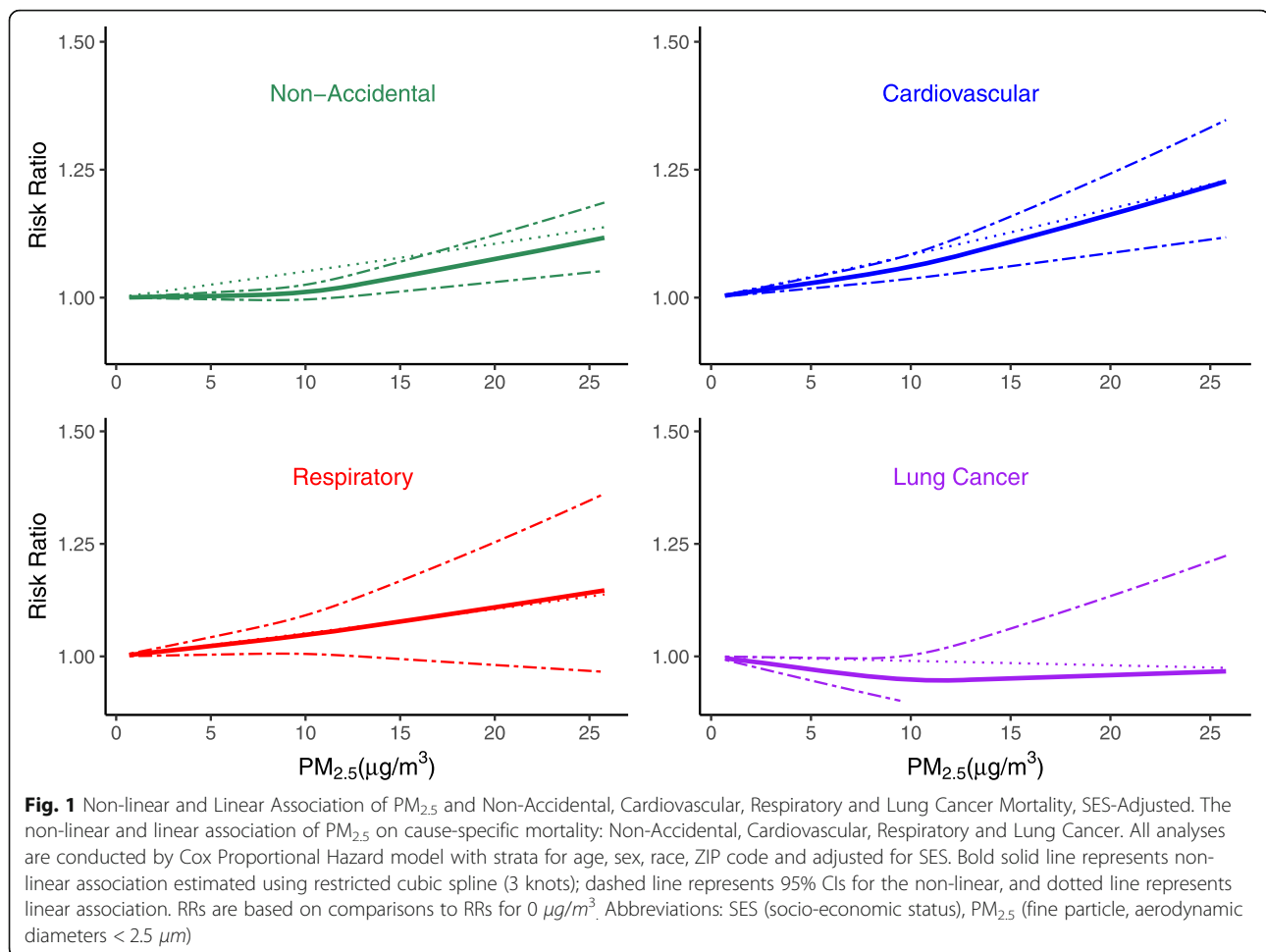
^a Non-traffic $PM_{2.5}$ estimated as the residual of $PM_{2.5}$ regressed on NO_2 concentrations for each ZIP code

^b Estimated using Cox PH models with strata for age (1 year age categories with 90+ year old as one category), race (white, non-white), sex (male, female) and ZIP Code (41,630 ZIP codes). Results are expressed as risk ratio and 95% CIs per $10 \mu g / m^3$ increase in 12-month average $PM_{2.5}$

^c Estimated using Cox PH models with strata for age, race, sex, ZIP code, SES

^d Two-stage analysis: (1) regression of 12-month $PM_{2.5}$ on NO_2 and (2) residuals of stage 1 (as non-traffic $PM_{2.5}$) as the exposure measure in Cox PH model with strata for age, race, sex, ZIP code

^e Two-stage analysis: (1) regression of 12-month $PM_{2.5}$ on NO_2 and (2) residuals of stage 1 (as non-traffic $PM_{2.5}$) as the exposure measure in Cox PH model with strata for age, race, sex, ZIP code, SES



10, or $12 \mu g/m^3$ (Table S4). Sensitivity analyses showed control for ozone had no effect on the shape of the exposure-response curves for non-accidental and CVD mortality (Figure S2). However, the exposure-response curve for respiratory mortality became supra-linear after adjustment for ozone, with higher RRs when $PM_{2.5}$ exposures were below as compared to above $10 \mu g/m^3$ for respiratory mortality (Figure S2).

In SES-adjusted models, we found $PM_{2.5}$ -associated risks of death to vary by beneficiary characteristics (Fig. 2, Table S5). $PM_{2.5}$ -associated mortality risks differed most by race, with Black beneficiaries having the highest $PM_{2.5}$ -associated RRs for all causes of death, except for CBV, for which risks were similar for Blacks and Whites. For Whites, mortality risks were significant and positive for all causes of death, with lower risks than Blacks for non-accidental and CVD mortality and both Blacks and Asians for respiratory and lung cancer mortality. Risks of respiratory and lung cancer mortality for Asians were positive and second only to Blacks for respiratory and lung cancer mortality, but were null or negative for non-accidental and CVD mortality. $PM_{2.5}$ -

mortality risks for Hispanics were protective or null for all causes of death. By age, $PM_{2.5}$ -associated RRs were higher for younger (≤ 75 years) as compared to older beneficiaries for all causes of death. While lower, RRs for older beneficiaries were positive and statistically significant for CVD-related (except for CHF), all respiratory, and pneumonia mortality. Differences in $PM_{2.5}$ -associated risks of mortality by sex were small, with significant positive risks for both men and women for all causes of death, except for CHF and lung cancer, with null risks for both sexes and for women, respectively (Figure S3). The shape of the exposure-response curves when stratified by age, sex, and race largely mirrored that for the entire population, with linear RRs for CVD and respiratory mortality and lower RRs at low as compared to high $PM_{2.5}$ levels for non-accidental and cancer mortality, irrespective of age, sex, and race (Figure S3a-c).

We showed neighborhood characteristics to modify associations of $PM_{2.5}$ and mortality (Fig. 3, Table S5). Beneficiaries living in urban as compared to non-urban ZIP codes had higher $PM_{2.5}$ -associated mortality risks for non-

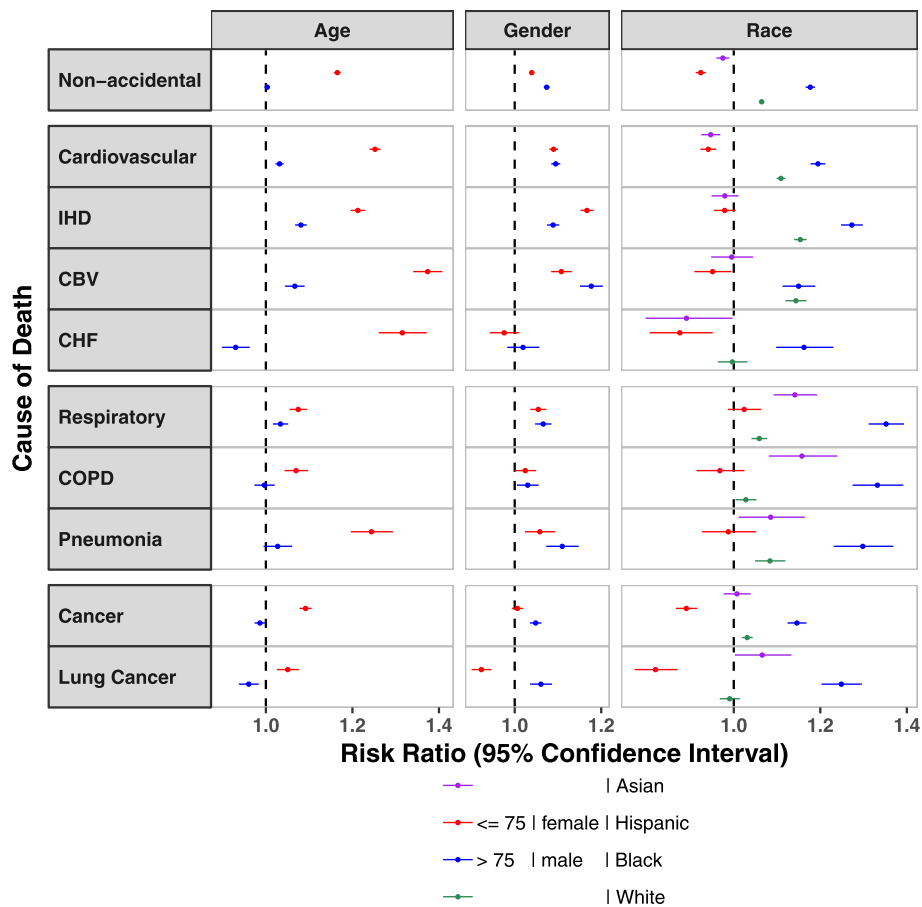


Fig. 2 Modification of the SES-adjusted Association between $PM_{2.5}$ and Cause-specific Mortality by Age, Sex, and Race. For each cause of death, we examined effect modification using interaction terms for age, sex and race respectively in the SES-adjusted models. Results are expressed as the risk ratio and 95% CIs per $10 \mu g/m^3$ increase in 12-month average $PM_{2.5}$. Abbreviations: IHD (Ischemic heart disease), CBV (Cerebrovascular disease), CHF (Congestive heart failure), COPD (Chronic Obstructive Pulmonary disease), SES (Socio-Economic Status), $PM_{2.5}$ (particles with aerodynamic diameters $< 2.5 \mu m$). Note: Each subgroup in the death-group box follows the same order defined in the figure legend

accidental, respiratory, and cancer mortality, with similar risks for CVD-related mortality. RRs for beneficiaries living in non-urban areas were positive and statistically significant for CVD-related causes of death, but were null for non-accidental, respiratory-related, cancer and lung cancer mortality. The shape of the exposure-response curves for urban areas and for beneficiaries living near monitoring sites were similar to that for all ZIP codes (Figure S3, S5). For SES, we found generally similar $PM_{2.5}$ -associated risks for all causes of death when all data were examined; however, when limited to urban areas, we found higher risks of increased CVD- and respiratory-related mortality for beneficiaries living in low as compared to high SES ZIP codes. The shapes of the exposure-response curves for ZIP codes with high and low SES mirrored that for all beneficiaries, with linear RRs across the range of $PM_{2.5}$ exposures for CVD and respiratory mortality and lower RRs for $PM_{2.5}$ exposures for low $PM_{2.5}$ exposures ($< 10 \mu g/m^3$) (Figure S3d-e).

Non-traffic $PM_{2.5}$ and cause-specific mortality

We found our method to estimate non-traffic $PM_{2.5}$ performed well, as evidenced by the lack of correlation between the residuals of $PM_{2.5}$ on NO_2 and EC, a marker of traffic-related $PM_{2.5}$ ($r = 0.02$), in the subset of data at CSN monitoring sites. As a comparison, total $PM_{2.5}$ was significantly correlated with EC ($r = 0.27$). Correlations of the residuals of $PM_{2.5}$ on NO_2 with sulfate were statistically significant ($r = 0.70$), but lower than that between total $PM_{2.5}$ and sulfate ($r = 0.87$), suggesting that the non-traffic $PM_{2.5}$ may also reflect, albeit to a lesser degree, secondary $PM_{2.5}$.

When RRs were estimated for non-traffic $PM_{2.5}$, we found substantially lower RRs as compared to all $PM_{2.5}$ for all causes of death in both base- and SES-adjusted models. In base models, RRs for non-traffic $PM_{2.5}$ were significant and positive for all causes of death, except for CHF, COPD, and lung cancer, for which associations remained positive but were no longer statistically

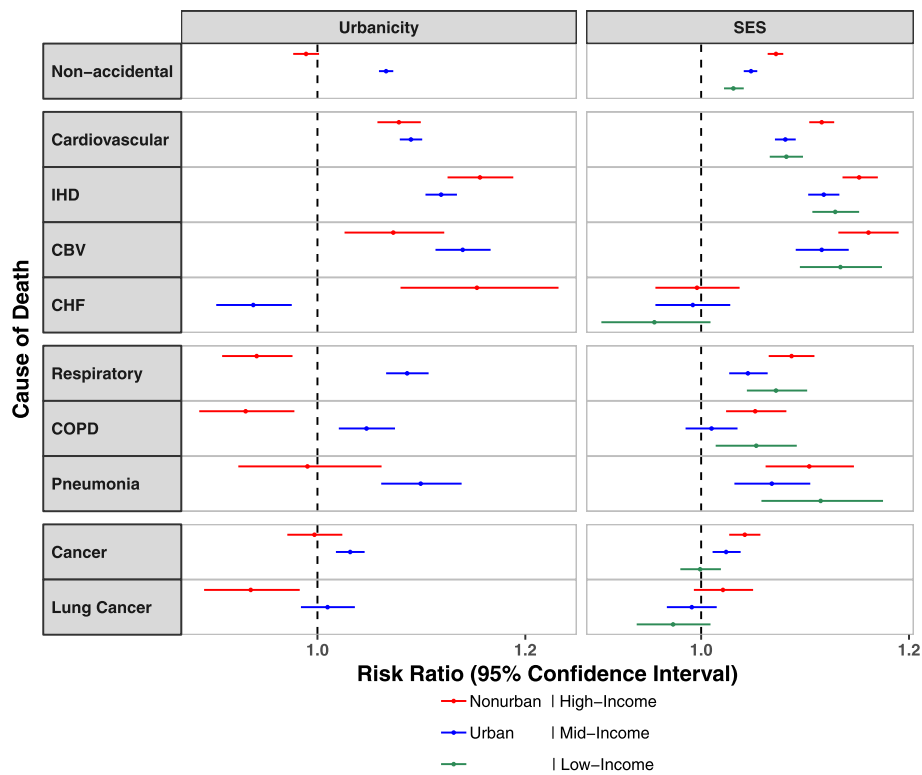


Fig. 3 Modification of the SES-adjusted Association between $PM_{2.5}$ and Cause-specific Mortality by Urbanicity and SES. For each cause of death, we examined effect modification using interaction terms for urbanicity and SES respectively in the SES-adjusted models. Results are expressed as the risk ratio and 95% CIs per $10 \mu g/m^3$ increase in 12-month average $PM_{2.5}$. Abbreviations: IHD (ischemic heart disease), CBV (cerebrovascular disease), CHF (congestive heart failure), COPD (chronic obstructive pulmonary disease), SES (socio-economic status), $PM_{2.5}$ (fine particles, aerodynamic diameters $< 2.5 \mu m$). Note: Subgroups follow the same order as in figure legend

significant (Table 2). Associations were attenuated after adjustment for SES and were no longer statistically significant for any respiratory-related cause of death. As with all $PM_{2.5}$, RRs for non-traffic $PM_{2.5}$ were highest for CVD-related causes of death, equaling 1.027 (95% CI: 1.011,1.043) for IHD and 1.057 (95% CI: 1.029,1.085) for CBV mortality, although the RR for all CVD (1.016; 95% CI: 1.005,1.028) was similar to that for non-accidental (1.014; 95% CI: 1.007,1.021) mortality.

Discussion

Our study is the first to examine the impacts of exposure to all $PM_{2.5}$ and non-traffic related $PM_{2.5}$ on specific causes of mortality for all US Medicare beneficiaries (65+ years), totaling 53 million older adults living in over 41,000 ZIP codes throughout the US, totaling 3.8 billion person-months of follow-up. By virtue of its near complete sample of US older adults, our study is also the first to show exposure-response curves for specific causes of death for non-white, low SES, and rural populations for whom the $PM_{2.5}$ -associated risks for specific causes of death are poorly understood, especially in comparison to white and urban populations. We were

able to do so by virtue of our novel computational methods, which allowed us to analyze linear and non-linear associations for the entire population and for specific subpopulations, including understudied rural and minority beneficiaries. We found a $10 \mu g / m^3$ increase in 12-month average $PM_{2.5}$ to be associated with a 5% increase in all-cause mortality, as well as an 8.8, 5.6, and 2.5% increase in all CVD-, all respiratory-, and all cancer-related deaths, respectively, in age, sex, race, ZIP code, and SES-adjusted models. $PM_{2.5}$ -associated risks were null for lung cancer. Risks were essentially unchanged after controlling for ozone. Risks associated with non-traffic $PM_{2.5}$ were lower as compared to that for all $PM_{2.5}$, with wider confidence intervals, but remained significant for all cause and CVD mortality and were null for respiratory and lung cancer-related deaths.

RRs for CVD- and respiratory-related mortality were linear, with statistically significant and positive RRs and no evidence of a threshold level below which $PM_{2.5}$ was not associated with mortality. RRs for non-accidental and all cancer mortality also showed no evidence of a threshold level. For all cancer mortality, exposure-

response curves were supra-linear, with higher RRs when $PM_{2.5}$ was below as compared to above $10 \mu g/m^3$. The opposite pattern was found for non-accidental mortality; however, for both causes of death, RRs remained statistically significant and positive across the range of $PM_{2.5}$ exposures. Importantly, our findings for non-accidental mortality (which comprise 97% of all deaths) are consistent with previous studies. Using a similar dataset but different analytical methods, Di et al. (2017) also found “almost linear” associations between $PM_{2.5}$ and all-cause mortality, with no evidence of a threshold, only small deviations from linearity, and lower associations when $PM_{2.5}$ exposures were below approximately $8 \mu g/m^3$. Notably, when our analyses were limited to urban areas, with or without control for ozone, $PM_{2.5}$ exposure-response curves for non-accidental mortality were linear, suggesting that non-linearity in exposure-response curves may reflect different mortality risks for rural beneficiaries, who experienced lower mean $PM_{2.5}$ exposures and lower RRs. Our findings for urban beneficiaries may explain the observed linear or supra-linear associations from previous US, Canadian and western European cohort studies, which were based primarily in urban areas. Note that our findings with regard to the shape of the exposure-response are not comparable to those reported in Cohen et al. [22] in their Global Burden of Disease analysis, which was intended to estimate effects of a wide range of $PM_{2.5}$ exposure levels, including those well above that observed in US, Canadian, and western European air pollution cohort studies. Thus, the range of exposures examined in Cohen et al. [22] were substantially higher than that in our study.

We found increased mortality risks from long-term $PM_{2.5}$ exposures to be strongest for CVD-related diseases, with significant and positive risks of increased mortality from all CVD, IHD, and CBV, but not CHF. While attenuated, our findings for all CVD, IHD, and CBV remained positive and significant upon adjustment for SES. In addition, CVD, IHD, and CBV mortality risks were similar across the range of $PM_{2.5}$ exposures, with no evidence of a lower threshold for response or of smaller RRs at low $PM_{2.5}$ levels. $PM_{2.5}$ -mortality associations for CVD-related causes were positive and significant for beneficiaries of different sexes, races, ages, and living in ZIP codes with different SES and urbanities. They further are within the range of previously reported findings, with comparable RRs to those reported for American Cancer Society (ACS) [23], Roman, and Netherlands (NCLS) cohorts [24], higher risks than in our earlier study of Medicare beneficiaries living near air pollution monitors [4], and lower risks than reported in several North American cohort studies [2, 25, 26], including those focused on low $PM_{2.5}$

concentrations [27, 28]. Our lower RRs may be due in part to our inclusion of understudied rural and minority beneficiaries, for whom RRs were lower, or may suggest that our models overcontrolled for SES.

We saw similarly robust associations between long-term $PM_{2.5}$ and increased respiratory mortality, for which previous evidence has been mixed. As in our earlier study of Medicare beneficiaries living near air pollution monitors [4], 12-month $PM_{2.5}$ exposures were significantly associated with increased mortality from all respiratory causes, COPD and pneumonia. Although we found neighborhood SES to confound the association, RRs for respiratory mortality remained positive and significant in SES-adjusted models. Further, $PM_{2.5}$ -associated risks of increased respiratory mortality were significant for all age, sex, SES, and most racial groups, but were null for Hispanic and non-urban beneficiaries. Our null finding for respiratory mortality within rural populations raise concerns about potential confounding by smoking. Although Di et al. [5] ruled out smoking as a potential confounder in their sensitivity analysis, their analysis focused only on all-cause mortality and further did not specifically assess confounding by smoking within rural populations, who have higher smoking rates [29] and lower average $PM_{2.5}$ levels. As with CVD mortality, we found no evidence of a lower threshold for response, with linear exposure-response curves for mortality from all respiratory and COPD causes. For pneumonia mortality, higher RRs were found when $PM_{2.5}$ exposures were below as compared to above $10 \mu g/m^3$, suggesting that linear models underestimate $PM_{2.5}$ -pneumonia mortality risks at low exposure levels.

Significant and positive associations between $PM_{2.5}$ and all cancers but not lung cancer in SES adjusted models were somewhat unexpected, adding to mixed findings for lung cancer from earlier studies. While our base results are similar to those from our earlier study of Medicare beneficiaries living near air monitors [4], our non-significant SES-adjusted findings for lung cancer are consistent with null associations reported in several US and European cohort studies [30–34]. They, however, are contrary to that from a meta-analysis that showed significant $PM_{2.5}$ -associated lung cancer mortality risks [35], reflecting significant positive associations from several large-scale North American, European, and Asian cohort studies [23, 36–38].

Notably, we found mortality risks to be lower for non-traffic $PM_{2.5}$ as compared to total $PM_{2.5}$, with positive and significant associations for all cause and CVD-related mortality and null associations for respiratory and lung cancer-related deaths. While not examined explicitly, these findings suggest that traffic-related PM

is a key contributor to the risks posed by $PM_{2.5}$ for all cause and CVD mortality and the primary contributor to respiratory disease and cancer mortality. Alternatively or in addition, our findings may also indicate the importance of primary (but not secondary) $PM_{2.5}$ as a risk factor for mortality, given the high correlation of non-traffic $PM_{2.5}$ with sulfate. As a measure of non-traffic and traffic $PM_{2.5}$ -associated risks, however, our findings are consistent with previous long-term studies, including those from Netherlands Cohort Study on Diet and Cancer (NLCS) [30, 39], the Washington University–EPRI Veterans’ Cohort Mortality Study [40, 41], and the National Particle Component Toxicity Initiative (NPACT) study [42]. The NPACT study was novel in its examination of the mortality impacts of long-term $PM_{2.5}$ from traffic as well as from other sources, finding strong associations between traffic and especially coal combustion source categories and increased IHD mortality [42]. These results differ somewhat from our findings. While we found significant associations of both total and non-traffic $PM_{2.5}$ on CVD and IHD mortality, associations were comparatively stronger for total $PM_{2.5}$ as compared to non-traffic $PM_{2.5}$, which given its high correlation with sulfate, may also serve as a marker for secondary $PM_{2.5}$ and/or coal-combustion. Differences in our findings likely result from imprecision in estimates of non-traffic $PM_{2.5}$, as well as differences in our study population and control for confounders.

Across the examined causes of death, we provide compelling evidence that $PM_{2.5}$ -associated RRs differ by age, race, urbanicity, and to a lesser extent by SES. We found higher risks for older adults younger as compared to older than 75 years, likely reflecting the increasing baseline risk of death with age and the many competing risks for mortality at older ages [43]. For race, we found $PM_{2.5}$ -associated risks to be highest in Blacks for all causes of death, consistent with previous studies [11], followed by Whites for non-accidental and CVD mortality and by Asians for respiratory and cancer-related mortality. Notably, $PM_{2.5}$ -associated risks were null or protective for Asians for non-accidental and CVD-related mortality and for Hispanics for all causes of death. Protective associations for Hispanics were puzzling, possibly reflecting unmeasured confounding by social or economic factors and/or the very heterogeneous US Hispanic population, with regard to social, economic, geographic, and country of origin [44, 45]. This heterogeneity has been cited by MESA and other studies [46–48] as a possible factor explaining often null or even protective health findings for Hispanics. Clearly, additional studies are needed to examine these factors and their impact of long-term air pollution exposures on health risks in Hispanic and other minority groups.

Higher mortality risks in urban ZIP codes are consistent with findings showing combustion particles to comprise a larger fraction of $PM_{2.5}$ in urban areas [49] and to be more toxic than non-combustion components [50]. For urban beneficiaries, the risks of non-accidental and CVD-related mortality were somewhat higher for individuals living in high as compared to low SES neighborhoods, perhaps indicative of a higher portion of combustion-related pollution in low SES neighborhoods [51].

Whether the higher $PM_{2.5}$ exposures experienced by beneficiaries living in urban ZIP codes contribute to their higher RRs is not clear. For CVD- and respiratory-related mortality, the observed linear mortality risks across the range of $PM_{2.5}$ concentrations suggests that it does not, as RRs for these causes of death did not depend on the magnitude of $PM_{2.5}$ exposures. In contrast, we found lower RRs for non-accidental mortality for $PM_{2.5}$ exposures less than $10 \mu g / m^3$, consistent with our finding of lower RRs for non-urban ZIP codes. As above, our null (and even significant but protective) RRs for lung cancer and respiratory mortality within rural populations may also reflect confounding by smoking [29]; however, potential confounding of associations between $PM_{2.5}$ and lung cancer and respiratory mortality by smoking with rural populations has not yet been studied.

Our study had several limitations. First, we only had information on beneficiaries’ ZIP code of residence, contributing to exposure misclassification. We, however, accounted for beneficiaries’ residential moves and used validated spatio-temporal models to predict exposures, thus reducing error [52]. Previous studies found exposure error from imprecise spatial estimates to bias results towards the null, lending support to our findings of significant positive associations [14]. Second, we examined associations between $PM_{2.5}$ and multiple mortality causes, raising multiple comparison concerns. These concerns are balanced by the consistency of our findings across outcomes and model specifications. Third, while we did not have data on personal-level characteristics, we allowed baseline hazards to vary by age, sex, race, and ZIP code and adjusted our models for ZIP code-level SES. Confounding by other personal-level characteristics is unlikely to explain our findings, given previous findings for urban populations showing little change in mortality risks after adjustment for individual-level characteristics [53] and given the high proportion of our population living in urban areas. However, it is possible that residual confounding, such as that from smoking, may introduce bias in the $PM_{2.5}$ -mortality associations among non-urban populations, offering a possible explanation for the lower RRs observed for these populations. Finally, NO_2 serves as an imperfect proxy of traffic-related $PM_{2.5}$. As a result, the mortality risks

estimated using the residuals of NO_2 on $\text{PM}_{2.5}$ are an imperfect measure of non-traffic exposures, potentially contributing to our observed wider confidence intervals for the RRs for non-traffic $\text{PM}_{2.5}$. Nevertheless, our results provide a first direct assessment of the mortality risks resulting from long-term exposures to non-traffic $\text{PM}_{2.5}$. Importantly, our findings of lower mortality risks for non-traffic as compared to total $\text{PM}_{2.5}$ are consistent with results from studies of long-term traffic exposures and mortality. However, additional studies are needed to assess consistency of findings using this approach.

These limitations are balanced by the substantial strengths of our study. With nearly 53 million Medicare beneficiaries, 16 million deaths, and complete coverage of Medicare beneficiaries living across the US, our analyses were well-powered to detect meaningful associations, allowing us to provide valuable new information on the impact of long-term $\text{PM}_{2.5}$ exposures on specific causes of CVD, respiratory, and cancer-related deaths at low $\text{PM}_{2.5}$ levels and for previously under-studied minority and rural populations. We were thus able to demonstrate linearity in exposure-response curves for CVD and respiratory mortality and disproportionate $\text{PM}_{2.5}$ -associated deaths in beneficiaries who are Black and to a lesser extent Asian, are of low SES, or live in urban neighborhoods.

Conclusions

With nearly 53 million older Medicare beneficiaries living across the U.S., we observed that $\text{PM}_{2.5}$ was associated with mortality from cardiovascular, respiratory and all cancer disease, but not lung cancer. $\text{PM}_{2.5}$ -associated risks of CVD and respiratory mortality were similar across $\text{PM}_{2.5}$ levels, with no evidence of a threshold. Blacks, urban, and younger beneficiaries were most vulnerable to the long-term impacts of $\text{PM}_{2.5}$ on mortality.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12940-020-00575-0>.

Additional file 1: Appendix S1. Cox PH for Large-scale data. **Table S1.** Validation of Java implementation of Cox PH models using public package in R. **Table S2.** Percent of deaths by cause and beneficiary characteristics. **Table S3.** Association of long-term $\text{PM}_{2.5}$ and cause-specific mortality, with and without control for ozone (O_3). **Table S4.** Association of long-term $\text{PM}_{2.5}$ and cause-specific mortality for low $\text{PM}_{2.5}$ ZIP Code. **Table S5.** Linear Effect Modification Analysis by cause of death. **Figure S1.** SES-adjusted exposure-response curves for 12-month average $\text{PM}_{2.5}$ and specific causes of death. **Figure S2.** Sensitivity analyses: (a) SES-adjusted and (b) SES- and ozone-adjusted exposure-response curves for 12-month moving average $\text{PM}_{2.5}$ and all-cause, CVD, respiratory and cancer deaths. **Figure S3.** SES-adjusted exposure-response curves for 12-month average $\text{PM}_{2.5}$ and cause-specific mortality by effect modifier.

Figure S4. SES-adjusted exposure-response curves for 12-month average $\text{PM}_{2.5}$ and all causes mortality with different number of knots. **Figure S5.** SES-adjusted exposure-response curves for 12-month average $\text{PM}_{2.5}$ and all causes mortality near monitoring sites.

Abbreviations

ACS: American Cancer Society; CBV: Cerebrovascular Disease; CHF: Congestive Heart Failure; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; Cox PH: Cox Proportional Hazards; CSN: Chemical speciation network; CVD: Cardiovascular Disease; EC: Elemental Carbon; EPA: Environmental Protection Agency; ICD: International Classification of Disease; IHD: Ischemic Heart Disease; IRS: Internal Revenue Service; NO_2 : Nitrogen Dioxide; $\text{PM}_{2.5}$: Particulate matter with aerodynamic diameter of $2.5 \mu\text{m}$ or less; ppb: Parts per Billion; RCS: Restricted Cubic Splines; RHRC: Rural Health Research Center; RRs: Risk Ratios; SES: Socio-Economic Status; U.S.: United States

Acknowledgements

Not applicable.

Authors' contributions

Wang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and Design: Suh. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Suh and Wang. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Wang. Obtained funding: Suh. Supervision: Suh, Manjourides and Pavlu. All authors read and approved the final manuscript.

Funding

This work was supported by Electric Power Research Institute grant MA10003095.

Availability of data and materials

Java implementation of Cox Proportional Hazards model is available on GitHub (<https://github.com/Rainicy/survival>) and our $\text{PM}_{2.5}$ exposure estimates for each Zip Code available upon request.

Ethics approval and consent to participate

Our study was approved by the Institutional Review Board of Tufts and Northeastern Universities.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no actual or potential competing financial interests.

Author details

¹Khoury College of Computer Sciences, Northeastern University, 440 Huntington Ave, Boston, MA 02115, USA. ²Department of Civil & Environmental Engineering, Tufts University, Medford, MA, USA. ³Bouvè College of Health Sciences, Northeastern University, Boston, MA, USA.

Received: 27 July 2019 Accepted: 7 February 2020

Published online: 17 February 2020

References

1. Kloog I, Ridgway B, Koutrakis P, Coull BA, Schwartz JD. Long- and short-term exposure to $\text{PM}_{2.5}$ and mortality: using novel exposure models. *Epidemiology*. 2013;24(4):555.
2. Puett RC, Hart JE, Yanosky JD, Paciorek C, Schwartz J, Suh H, et al. Chronic fine and coarse particulate exposure, mortality, and coronary heart disease in the nurses' health study. *Environ Health Perspect*. 2009;117(11):1697–701.
3. Pope CA III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA*. 2002;287(9):1132–41.

4. Pun VC, Kazemiparkouhi F, Manjourides J, Suh HH. Long-term PM_{2.5} exposure and respiratory, cancer, and cardiovascular mortality in older US adults. *Am J Epidemiol*. 2017;186(8):961–9.
5. Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, et al. Air pollution and mortality in the Medicare population. *N Engl J Med*. 2017;376(26):2513–22.
6. Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, et al. An association between air pollution and mortality in six US cities. *N Engl J Med*. 1993;329(24):1753–9.
7. Pope CA, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, et al. Particulate air pollution as a predictor of mortality in a prospective study of US adults. *Am J Respir Crit Care Med*. 1995;151(3):669–74.
8. Atkinson RW, Kang S, Anderson HR, Mills IC, Walton HA. Epidemiological time series studies of PM_{2.5} and daily mortality and hospital admissions: a systematic review and meta-analysis. *Thorax*. 2014;69(7):660–5.
9. Woodruff TJ, Parker JD, Schoendorf KC. Fine particulate matter (PM_{2.5}) air pollution and selected causes of postneonatal infant mortality in California. *Environ Health Perspect*. 2006;114(5):786–90.
10. Laden F, Neas LM, Dockery DW, Schwartz J. Association of fine particulate matter from different sources with daily mortality in six US cities. *Environ Health Perspect*. 2000;108(10):941–7.
11. Wang Y, Shi L, Lee M, Liu P, Di Q, Zanobetti A, et al. Long-term exposure to PM_{2.5} and mortality among older adults in the southeastern US. *Epidemiology*. 2017;28(2):207.
12. Cakmak S, Hebbern C, Pinault L, Lavigne E, Vanos J, Crouse DL, et al. Associations between long-term PM_{2.5} and ozone exposure and mortality in the Canadian census health and environment cohort (CANCHEC), by spatial synoptic classification zone. *Environ Int*. 2018;111:200–11.
13. Parker JD, Kravets N, Vaidyanathan A. Particulate matter air pollution exposure and heart disease mortality risks by race and ethnicity in the United States: 1997 to 2009 National Health Interview Survey with mortality follow-up through 2011. *Circulation*. 2018;137(16):1688–97.
14. Yanosky JD, Paciorek CJ, Laden F, Hart JE, Puett RC, Liao D, et al. Spatio-temporal modeling of particulate air pollution in the conterminous United States using geographic and meteorological predictors. *Environ Health*. 2014;13(1):63.
15. Garcia CA, Yap P-S, Park H-Y, Weller BL. Association of long-term PM_{2.5} exposure with mortality using different air pollution exposure models: impacts in rural and urban California. *Int J Environ Health Res*. 2016;26(2):145–57.
16. Bechle MJ, Millet DB, Marshall JD. National spatiotemporal exposure surface for NO₂: monthly scaling of a satellite-derived land-use regression, 2000–2010. *Environ Sci Technol*. 2015;49(20):12297–305.
17. Kazemiparkouhi F, Eum KD, Wang B, Manjourides J, Suh HH. Long-term ozone exposures and cause-specific mortality in a US Medicare cohort. *J Expo Sci Environ Epidemiol*. 2019. p. 1. <https://www.nature.com/articles/s41370-019-0135-4>.
18. Rural-Urban Commuting Area Codes. WWAMI Rural Health Research Center. 2014. Available from: <http://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes.aspx>
19. Croxford R. Restricted cubic spline regression : a brief introduction. Toronto: Institute for Clinical Evaluative Sciences; 2016. p. 1–5.
20. Schauer JJ, Lough GC, Shafer MM, Christensen WF, Arndt MF, DeMinter JT, et al. Characterization of metals emitted from motor vehicles. *Res Rep Health Eff Inst*. 2006;133:1–76.
21. Hamra GB, Laden F, Cohen AJ, Raaschou-Nielsen O, Brauer M, Loomis D. Lung cancer and exposure to nitrogen dioxide and traffic: a systematic review and meta-analysis. *Environ Health Perspect*. 2015;123(11):1107–12.
22. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the global burden of diseases study 2015. *Lancet*. 2017;389(10082):1907–18.
23. Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y, et al. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. Boston: Health Effects Institute; 2009.
24. Brunekreef B, Beelen RMJ, Hoek G, Schouten LJ, Bausch-Goldbohm S, Fischer P, et al. Effects of long-term exposure to traffic-related AIR pollution on respiratory and cardiovascular mortality in the Netherlands: the NLCS-AIR study. *Res Rep Health Eff Inst*. 2009;139:5–71.
25. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard six cities study. *Am J Respir Crit Care Med*. 2006;173(6):667–72.
26. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med*. 2007;356(5):447–58.
27. Pinault L, Tjepkema M, Crouse DL, Weichenthal S, van Donkelaar A, Martin RV, et al. Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian community health survey cohort. *Environ Health*. 2016;15(1):18.
28. Crouse DL, Peters PA, van Donkelaar A, Goldberg MS, Villeneuve PJ, Brion O, et al. 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*. 2012;120(5):708–14.
29. Association AL. Cutting tobacco's rural roots: tobacco use in rural communities. Chicago: American Lung Association; 2012.
30. Beelen R, Hoek G, van Den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, et al. Long-term effects of traffic-related AIR pollution on mortality in a Dutch cohort (NLCS-AIR study). *Environ Health Perspect*. 2007;116(2):196–202.
31. McDonnell WF, Nishino-Ishikawa N, Petersen FF, Chen LH, Abbey DE. Relationships of mortality with the fine and coarse fractions of long-term ambient PM₁₀ concentrations in nonsmokers. *J Expo Sci Environ Epidemiol*. 2000;10(5):427.
32. Hart JE, Garshick E, Dockery DW, Smith TJ, Ryan L, Laden F. Long-term ambient multipollutant exposures and mortality. *Am J Respir Crit Care Med*. 2011;183(1):73–8.
33. Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, et al. Spatial analysis of air pollution and mortality in California. *Am J Respir Crit Care Med*. 2013;188(5):593–9.
34. Carey IM, Atkinson RW, Kent AJ, Van Staa T, Cook DG, Anderson HR. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. *Am J Respir Crit Care Med*. 2013;187(11):1226–33.
35. Kim H-B, Shim J-Y, Park B, Lee Y-J. Long-term exposure to air pollutants and Cancer mortality: a meta-analysis of cohort studies. *Int J Environ Res Public Health*. 2018;15(11):2608.
36. Cao J, Yang C, Li J, Chen R, Chen B, Gu D, et al. Association between long-term exposure to outdoor air pollution and mortality in China: a cohort study. *J Hazard Mater*. 2011;186(2–3):1594–600.
37. Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M, et al. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect*. 2013;121(3):324–31.
38. Katanoda K, Sobue T, Satoh H, Tajima K, Suzuki T, Nakatsuka H, et al. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. *J Epidemiol*. 2011;21:132–43 1102090211.
39. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet*. 2002;360(9341):1203–9.
40. Lipfert FW, Baty JD, Miller JP, Wyzga RE. PM_{2.5} constituents and related air quality variables as predictors of survival in a cohort of US military veterans. *Inhal Toxicol*. 2006;18(9):645–57.
41. Lipfert FW, Wyzga RE, Baty JD, Miller JP. Traffic density as a surrogate measure of environmental exposures in studies of air pollution health effects: long-term mortality in a cohort of US veterans. *Atmos Environ*. 2006;40(1):154–69.
42. Lippmann M, Chen LC, Gordon T, Ito K, Thurston GD. National Particle Component Toxicity (NPACT) initiative: integrated epidemiologic and toxicologic studies of the health effects of particulate matter components. *Res Rep Health Eff Inst*. 2013;177:5–13.
43. Koller MT, Raatz H, Steyerberg EW, Wolbers M. Competing risks and the clinical community: irrelevance or ignorance? *Stat Med*. 2012;31(11–12):1089–97.
44. Eschbach K, Ostir GV, Patel KV, Markides KS, Goodwin JS. Neighborhood context and mortality among older Mexican Americans: is there a barrier advantage? *Am J Public Health*. 2004;94(10):1807–12.
45. Wilson KL, Portes A. Immigrant enclaves: an analysis of the labor market experiences of Cubans in Miami. *Am J Sociol*. 1980;86(2):295–319.
46. Do DP, Moore K, Barber S, Roux AD. Neighborhood racial/ethnic segregation and BMI: a longitudinal analysis of the multi-ethnic study of atherosclerosis. *Int J Obes*. 2019;43:1601–10.
47. Kershaw KN, Osypuk TL, Do DP, De Chavez PJ, Diez Roux AV. Neighborhood-level racial/ethnic residential segregation and incident cardiovascular disease: the multi-ethnic study of atherosclerosis. *Circulation*. 2015;131(2):141–8.

48. Lee M-A, Ferraro KF. Neighborhood residential segregation and physical health among Hispanic Americans: good, bad, or benign? *J Health Soc Behav.* 2007;48(2):131–48.
49. Agency USEP. Integrated science assessment for particulate matter. EPA/600/R-08/139F. Research Triangle Park: US EPA; 2009.
50. Park M, Joo HS, Lee K, Jang M, Kim SD, Kim I, et al. Differential toxicities of fine particulate matters from various sources. *Sci Rep.* 2018;8(1):17007.
51. Pratt G, Vadali M, Kvale D, Ellickson K. Traffic, air pollution, minority and socio-economic status: addressing inequities in exposure and risk. *Int J Environ Res Public Health.* 2015;12(5):5355–72.
52. Paciorek CJ, Yanosky JD, Puett RC, Laden F, Suh HH. Practical large-scale spatio-temporal modeling of particulate matter concentrations. *Ann Appl Stat.* 2009;3(1):370–97.
53. Krewski D, Burnett RT, Goldberg M, Hoover K, Siemiatycki J, Jerrett M, et al. Reanalysis of the Harvard six-cities study and the American Cancer Society study of air pollution and mortality, phase II: sensitivity analysis, vol. 295. Cambridge: Health Effects Institute; 2000.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

