Cardiopulmonary Mortality and Fine Particulate Air Pollution by Species and Source in a National U.S. Cohort

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Abstract

The purpose of this study was to estimate cardiopulmonary mortality associations for long-term exposure to $PM_{2.5}$ species and sources (i.e., components) within the U.S. National Health Interview Survey cohort. Exposures were estimated through a chemical transport model for six species (i.e., elemental carbon [EC], primary organic aerosols [POA], secondary organic aerosols [SOA], sulfate [SO_4], ammonium [NO_3], nitrate [NH_4]) and five sources of $PM_{2.5}$ (i.e., vehicles, electricity generating units [EGU], non-EGU industrial sources, biogenic sources [bio], "other" sources). In single-pollutant models, we found positive, significant ($p < 0.05$) mortality associations for all components, except POA. After adjusting for remaining $PM_{2.5}$ (total $PM_{2.5}$ minus component), we found significant mortality associations for EC (hazard ratio [HR] = 1.36; 95% CI: [1.12, 1.64]), SOA (HR = 1.11; 95% CI: [1.05, 1.17]), and vehicle sources (HR = 1.06; 95% CI: [1.03, 1.10]). HRs for EC, SOA, and vehicle sources were significantly larger than for remaining $PM_{2.5}$ (per unit $\mu g/m^3$). Our findings suggest that cardiopulmonary mortality associations vary by species and source, with evidence that EC, SOA, and vehicle sources are important contributors to the $PM_{2.5}$ mortality relationship. With further validation, these findings could facilitate targeted pollution regulations that more efficiently reduce air pollution mortality.

Keywords: air pollution, cardiopulmonary mortality, species, source, cohort study

Synopsis: This study provides evidence that cardiopulmonary mortality associations vary among $PM_{2.5}$ species and sources, suggesting that pollution regulations could be improved by targeting relatively harmful particulate air pollutants.

Introduction

Air pollution has been estimated as the fourth largest contributor to global burden of disease.[1] Specifically, cardiopulmonary mortality has consistently been associated with fine particulate air pollution ($PM_{2.5}$).[2-4] $PM_{2.5}$ is comprised of a complex mixture of chemical species, each potentially having different effects on mortality. Mortality associations have also been found to vary across $PM_{2.5}$ sources,[5, 6] which could be driven by differences in particle mass, number, size, shape, surface area, or chemical composition. Thus, targeting relatively harmful components (i.e., species or sources) may be more beneficial than simply reducing total $PM_{2.5}$. Current regulations, however, focus on total $PM_{2.5}$, in part due to uncertainty of component-specific toxicities.

Despite general interest, a limited number of cohort studies have estimated component-specific mortality associations, in part due to difficulties modelling exposures. A few early cohort studies estimated mortality relationships for sulfates,[7, 8] but only recently has a more comprehensive spectrum of species and sources been considered.[5, 9] Moreover, results of past studies have been somewhat inconsistent, establishing the need for additional analysis.

The purpose of this study was to estimate component-specific mortality associations for long-term exposure to $PM_{2.5}$ species and sources. Speciated and source-apportioned $PM_{2.5}$ exposure estimates were linked to a cohort of >160,000 adults living in metropolitan statistical areas (MSAs) across the U.S. Within this cohort, cardiopulmonary mortality associations were estimated for six chemical species (i.e., elemental carbon [EC], primary organic aerosols [POA], secondary organic aerosols [SOA], sulfates [SO_4], ammonium [NH_4], and nitrates [NO_3]) and five sources of $PM_{2.5}$ (i.e., vehicles, electricity generating units [EGU], non-EGU industrial sources, biogenic sources [bio], and "other" sources). A

secondary aim of this analysis was to determine if cardiopulmonary mortality associations differ between primary (i.e., fine particles emitted directly from sources) and secondary $PM_{2.5}$ (i.e., fine particles formed from atmospheric oxidation of gaseous precursors). As such, we separated primary (i.e., EC and POA) and secondary species (i.e., SOA, SO_4, NH_4, and NO_3) within $PM_{2.5}$ sources to estimate relative mortality associations.

Methods

Study Population Data:

For this analysis, a cohort was constructed of adults who participated in the U.S. National Health Interview Survey (NHIS). The NHIS is an annual cross-sectional survey that provides a representative sample of the civilian noninstitutionalized U.S. population. NHIS data are collected continuously throughout each survey year by the U.S. Census Bureau through in-person and telephone interviews. Public use NHIS survey data from 1986 to 2001 were linked to the National Death Index, providing mortality follow-up through December 31, 2015. A detailed description of NHIS sample design, interview procedures, and data access can be found elsewhere.[10, 11]

Several exclusion criteria limited the size and determined the composition of the analytic cohort. Merging individuals to exposure estimates required residential data, which were available only at the MSA-level and for individuals surveyed before 2002 (n = 587,100 remaining). Limited smoking and BMI data further reduced cohort size (n = 198,955 remaining), resulting in the exclusion of anyone surveyed in 1986, 1989, or 1996. Individuals missing information on any other covariate were also excluded. After

exclusions, the analytic cohort consisted of 164,291 adults living within NHIS-sampled MSAs.

Air Pollution Data:

Exposure estimates for $PM_{2.5}$ species and sources were developed via a blending of simulated and empirical data. Speciated and source-apportioned concentrations for 2001 and 2010 were derived from chemical transport model (CTM) simulations, with bias corrections to better match speciated monitor data.

A brief description of the CTM simulations follows, with details documented elsewhere.[12] We used the PMCAMx model[13-16] and the "source tagging" algorithm PSAT[17-21] to estimate species and source concentrations. PMCAMx simulates chemical reactions in the gas, aqueous, and particulate phases, with an advanced treatment of organic $PM_{2.5}$ that accounts for the semi-volatile nature of primary organic emissions and incorporates recent advances in secondary organic PM chemistry.[22-24] Simulations were performed using an internally consistent set of 2001 and 2010 emissions inventories, developed by Xing et al.[25] Emissions inventories were constructed from several activity and emission control databases, including the State Energy Data System, National Emissions Inventory trends report, and 2011 National Transportation Statistics.[25] Meteorological data used in PMCAMx were taken from simulations performed with the Weather Research Forecasting model (WRF v3.6.1).

The PMCAMx model domain covered the continental United States at a horizontal resolution of 36 kilometers. While coarse, a 36-kilometer resolution was necessary to maintain computational feasibility. Additionally, increasing simulation resolution from 36 x

36 to 1 x 1 kilometer grids in a major city (i.e., Pittsburgh) had minimal effect on predicted exposures (less than 3%).[26]

Species predicted by the model and used in the health analysis included EC, POA, SOA, SO_4, NH_4, and NO_3. These species were selected as they are major contributors to total $PM_{2.5}$ and were reliably estimated. Concentrations of sodium, chloride, and mineral dust were also estimated, but not used in the health analysis due to low concentrations or lack of speciated monitor data.

Source categories were necessarily identical to those from the emissions inventories used as inputs to the CTM.[25] While $PM_{2.5}$ source categories could be defined in a variety of ways, the categories used in this study reflect sources that have traditionally been most relevant for regulatory purposes. The EGU category represents emissions from electricity-generating units included in the U.S. Environmental Protection Agency's Integrated Planning Model. Non-EGU includes all other industrial point sources. Vehicles includes emissions from on-road vehicles in the U.S. and off-road vehicles in the entire domain. Biogenic includes emissions from vegetation. The "other" source includes on-road vehicles from Canada and Mexico plus all other emissions.

As with most CTM simulations, the concentrations directly predicted by PMCAMx exhibited systematic regional biases. Therefore, speciated $PM_{2.5}$ concentrations predicted by PMCAMx were adjusted using geographically weighted regression[27] to better match speciated monitor data.[28, 29] For each species, a separate regression was used to predict the bias between CTM predictions and observed concentrations. Regression predictor variables included speciated CTM concentrations, inverse distance to nearest urban area, average monitor elevation difference, and local bias between CTM and empirically modelled $PM_{2.5}$.

158 Pollution monitor observations were weighted using a Gaussian function that decays with
159 distance. Bias predictions were made at the census-tract level to allow for finer resolution
160 corrections in areas with higher population density. The CTM fields were then corrected
161 based on predicted biases for each census tract and species. During this process, the
162 fractional source apportionment for individual species was assumed to be constant.[26]

163 In addition to component-specific exposures, multiple estimates of total $PM_{2.5}$ exposure
164 were used in this analysis. One estimate of total $PM_{2.5}$ exposure was defined as the sum of
165 speciated concentrations (i.e., $PM_{2.5}$ CTM '01, '10). An additional estimate of $PM_{2.5}$
166 exposure (i.e., $PM_{2.5}$ IEG '01, '10) was predicted using an integrated empirical geographic
167 (IEG) model, which applies pollution monitor measurements within a universal kriging
168 framework.[30] While many IEG model inputs were temporally fixed, year-to-year trends and
169 variations were accounted for through temporally variable land use data and satellite-derived
170 pollution estimates.[30]

171 Census tract level exposure estimates for $PM_{2.5}$ and components were aggregated to the
172 MSA-level as a population weighted average. Details on how MSA borders were defined in
173 the aggregation process are provided in Supporting Information Appendix A. Individual
174 exposures were assigned, based on residence at time of survey, as the simple average of
175 2001 and 2010 MSA-level concentration estimates. To assess the impacts of using only two
176 annual concentration estimates, an additional measure of total $PM_{2.5}$ was constructed as the
177 average of annual, IEG-modelled $PM_{2.5}$ from 1999-2015 (i.e., $PM_{2.5}$ IEG '99-'15).

178 *Mortality Risk Analysis:*

179 Cardiopulmonary mortality associations were quantified as adjusted hazard ratios (HRs)
180 from Cox proportional hazards models (PHREG procedure in SAS; version 9.4; SAS
181 Institute Inc.). Concentration-response curves were not estimated, as a previous analysis
182 with the NHIS cohort found that the concentration-response relationship between $PM_{2.5}$ and
183 cardiopulmonary mortality was approximately linear.[2]

184 Cardiopulmonary mortality was defined, based on the tenth revision of the International
185 Classification of Diseases (ICD-10), to include deaths from cardiovascular disease (ICD-10
186 codes: I00-I09, I11, I13, I20-I51), cerebrovascular disease (I60-I69), chronic lower
187 respiratory disease (J40-J47), and influenza or pneumonia (J09-J18). Causes of death
188 corresponding to the preceding ICD-10 codes are specified in Table S1. For
189 cardiopulmonary mortality, survival times were calculated as the difference between year of
190 death and survey year. Otherwise, survival times were censored at date of non-
191 cardiopulmonary mortality or end of follow-up (i.e., 2015).

192 Control variables were chosen *a priori* based on past research conducted with the NHIS
193 cohort.[2, 31] The following control variables were used in each model. Age, sex, and race-
194 ethnicity were controlled for by allowing each combination of age (one year), sex, and race-
195 ethnicity, to be assigned their own baseline hazard (using the STRATA statement of the
196 PHREG procedure in SAS). Models also included categorical variables for family income
197 ($0-35,000; $35,000-50,000; $50,000-75,000; > $75,000); marital status (married, divorced,
198 separated, never married, widowed); educational attainment (less than high school graduate,
199 high school graduate, some college, college graduate, more than college graduate); BMI
200 (<20, 20-25, 25-30, 30-35, >35 kg/m^2); smoking status (current, former, never); census

region (Northeast, South, Midwest, West); and survey year. For details on how control variables were harmonized across survey years, see Supporting Information Appendix B.

While control variables were consistent across models, specifications differed in how they accounted for relationships between $PM_{2.5}$ components. Single-pollutant models included all control variables along with a single component of $PM_{2.5}$. This approach provides greater statistical power as it is less affected by multi-collinearity, yet it yields inherently biased estimates due to component correlation with total $PM_{2.5}$. Mass-adjusted models addressed this issue by including remaining $PM_{2.5}$ (i.e., CTM predicted total $PM_{2.5}$ minus $PM_{2.5}$ component). Moreover, mass-adjusted models provide a formal structure for estimating the likelihood that mortality associations differ between components. That is, for each component a Wald hypothesis test was conducted, with the null hypothesis that component and remaining $PM_{2.5}$ HRs were equivalent.

Mortality associations were also estimated for primary and secondary $PM_{2.5}$, within sources. While several source categories were almost entirely primary or secondary, total $PM_{2.5}$, vehicle sources, and "other" sources had sizable portions of both primary and secondary species. Thus, only total $PM_{2.5}$, vehicle sources, and "other" sources were separated into primary and secondary species. Source-specific primary $PM_{2.5}$ was defined as the sum of EC and POA from a given source, whereas secondary $PM_{2.5}$ was defined as the sum of SOA, SO_4, NH_4, and NO_3. Single-pollutant models were estimated, along with a two-pollutant model that separately included primary and secondary $PM_{2.5}$ from a given source (e.g., primary vehicles and secondary vehicles).

In all cases, pollution exposures were measured in micrograms per cubic meter ($\mu g/m^3$) and modelled as continuous variables. Exposures were scaled such that HRs were relative to

either a unit or mean $\mu g/m^3$ increase in exposure. When scaled per unit, HRs more accurately reflect relative toxicities, especially after adjusting for remaining $PM_{2.5}$. Scaling exposures per mean incorporates a component's relative contribution to total $PM_{2.5}$ and accounts for differential scaling bias in single-pollutant models.

Results

Data Summary:

Individuals within our cohort were predominantly female (56.6%), white non-Hispanic (66%), married (50.8%), high-school graduates (30.7%), and never smokers (51.7%) (Table 1). Figure S1 maps pollution exposure estimates for $PM_{2.5}$ mass and components across NHIS surveyed MSAs, displaying the spatial distribution of exposures. Spatial variation for some components (e.g., EGU and SO_4) was mostly regional, which reduced statistical power when controlling for census region. Additionally, Figure 1 depicts the relative species composition of each source. Some sources (e.g., bio) were primarily comprised of a single species (e.g., SOA), whereas vehicle source $PM_{2.5}$ was a mixture of all species.

Additional exposure summary statistics are provided in Table 2, including means, standard deviations, and pairwise correlations between components. On average, CTM estimates for $PM_{2.5}$ exposure were about 2 $\mu g/m^3$ lower than IEG estimates, as the former did not model species such as road dust and sea salt; nevertheless, all measures of total $PM_{2.5}$ were highly correlated ($r > 0.94$). Correlations were also high between $PM_{2.5}$ components, which presented difficulties in isolating independent mortality associations. Each component was less correlated with remaining $PM_{2.5}$ than total $PM_{2.5}$, which justified including the former in mass-adjusted models.

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Table 1: Cohort Summary Statistics

Characteristic	n	%
Full Cohort	164,291	100.00
Cardiopulmonary Deaths	13,732	8.36
Age (mean, std)	44.12	17.14
Sex		
Female	93,015	56.62
Male	71,276	43.38
Race-Ethnicity		
Black Non-Hispanic	25,823	15.72
Hispanic	23,128	14.08
Other/Unknown	6,892	4.19
White Non-Hispanic	108,448	66.01
Income		
$0 - 35,000	52,713	32.09
$35,000 - 50,000	23,934	14.57
$50,000 - 75,000	32,689	19.90
$75,000 and over	54,955	33.45
Marital Status		
Married	83,435	50.78
Never married	39,431	24.00
Divorced	20,462	12.45
Widowed	14,529	8.84
Separated	6,434	3.92
Educational Attainment		
< High-school Graduate	30,891	18.80
High-school Graduate	50,491	30.73
Some College	40,837	24.86
College Graduate	25,280	15.39
Post-College Graduate	16,792	10.22
BMI		
< 20	14,955	9.10
20-25	69,175	42.11
25-30	53,810	32.75
30-35	18,212	11.09
> 35	8,139	4.95
Smoking Status		
Current	41,400	25.20
Former	37,894	23.07
Never	84,997	51.74

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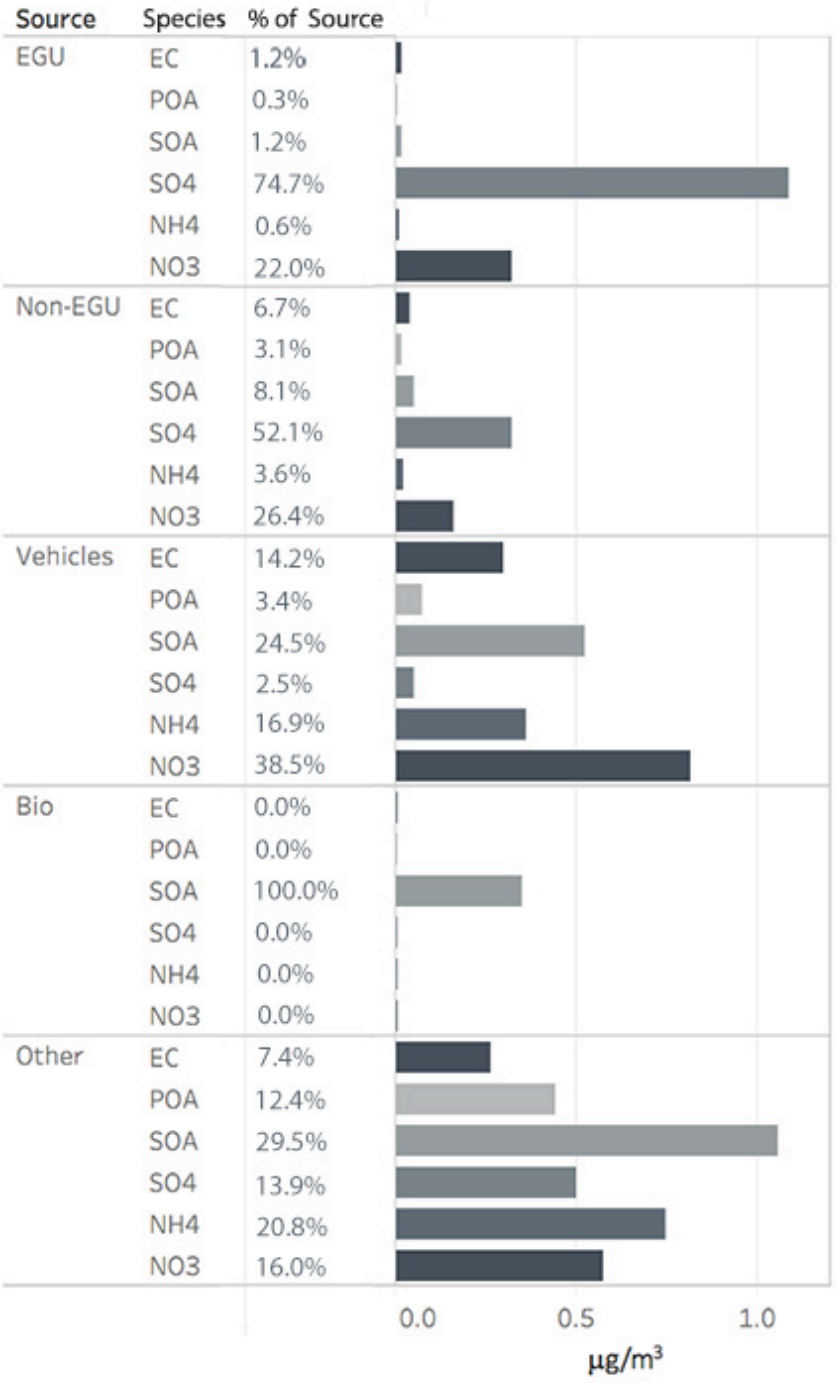


251 **Figure 1:** Average species composition within $PM_{2.5}$ sources. Averages were calculated

252 after assigning individual exposures.

Table 2: Exposure Means, Standard Deviations (SD), and Pearson Correlation Coefficients [a, b]

	$PM_{2.5}$			Species						Sources				
	IEG (99-15)	**IEG (01,10)**	**CTM (01,10)**	**EC**	**POA**	**SOA**	**SO4**	**NH4**	**NO3**	**EGU**	**Non-EGU**	**Vehicles**	**Bio**	**Other**
Mean µg/m³ (SD)	11.32 (1.93)	11.64 (2.28)	9.75 (2.25)	0.69 (0.20)	0.54 (0.17)	2.75 (0.71)	2.60 (0.92)	1.25 (0.42)	1.92 (0.96)	1.46 (0.90)	0.61 (0.23)	2.12 (0.97)	0.35 (0.16)	3.59 (0.90)
Correlations														
$PM_{2.5}$														
IEG (99-15)	1.00	--	--	--	--	--	--	--	--	--	--	--	--	--
IEG (01,10)	0.98	1.00	--	--	--	--	--	--	--	--	--	--	--	--
CTM (01,10)	0.95	0.95	1.00	--	--	--	--	--	--	--	--	--	--	--
Species														
EC	0.70	0.69	0.72	1.00	--	--	--	--	--	--	--	--	--	
POA	0.41	0.41	0.47	0.75	1.00	--	--	--	--	--	--	--	--	--
SOA	0.72	0.73	0.79	0.81	0.59	1.00	--	--	--	--	--	--	--	--
SO4	0.41	0.39	0.39	-0.05	-0.30	-0.12	1.00	--	--	--	--	--	--	--
NH4	0.80	0.80	0.84	0.35	0.11	0.37	0.75	1.00	--	--	--	--	--	--
NO3	0.71	0.74	0.77	0.65	0.56	0.78	-0.22	0.45	1.00	--	--	--	--	--
Sources														
EGU	0.30	0.29	0.31	-0.19	-0.39	-0.20	0.96	0.71	-0.24	1.00	--	--	--	--
Non-EGU	0.68	0.65	0.60	0.06	-0.11	0.14	0.73	0.80	0.25	0.70	1.00	--	--	--
Vehicles	0.73	0.74	0.77	0.86	0.69	0.89	-0.24	0.35	0.91	-0.33	0.08	1.00	--	--
Bio	0.55	0.52	0.57	0.35	0.16	0.43	0.55	0.62	0.11	0.54	0.45	0.17	1.00	--
Other	0.91	0.91	0.97	0.74	0.54	0.81	0.27	0.78	0.81	0.17	0.50	0.80	0.48	1.00
Remaining $PM_{2.5}$	--	--	--	0.68	0.41	0.61	-0.02	0.77	0.47	-0.09	0.52	0.47	0.52	0.92

Measures of temporal consistency and exposure modelling accuracy for $PM_{2.5}$ components are reported in Table 3. For each component, temporal consistency was assessed in two ways. First, by comparing the 2001 and 2010 concentration means, and second, by considering the correlation between 2001 and 2010 concentrations. Temporal consistency was relatively low for EC and POA, suggesting that these components may exhibit higher exposure measurement error. Specifically, the within component correlations between 2001 and 2010 exposures was 0.78 for both EC and POA, while all other component intertemporal correlations were 0.87 or higher. Exposure modelling accuracy was assessed through a ten-fold cross-validation (CV) R^2 comparison of CTM predictions and ground-level monitor data. In general, exposure modelling was more accurate for secondary species. For 2001 exposures, CV R^2 ranged from 0.63 for EC to 0.97 for SO_4.

a. For each component, remaining $PM_{2.5}$ was calculated as total $PM_{2.5}$ mass minus component-specific mass.
b. All statistics were cohort-weighted, as they were calculated after assigning individual-level exposures.

SO_4 also had the highest CV R^2 for 2010 exposures, whereas organic aerosols were modelled relatively imprecisely (2010 CV R^2 = 0.50).

Table 3: Temporal Consistency[a] and Accuracy[b] of Predicted Exposures

Pollutant	'01 '10 Corr.	'01 Mean	'10 Mean	'01 CV R^2	'10 CV R^2
$PM_{2.5}$					
IEG	0.70	13.62	9.67	--	--
CTM	0.93	11.56	7.94	--	--
Species					
EC	0.78	0.67	0.72	0.63	0.68
POA	0.78	0.66	0.42	0.74	0.50
SOA	0.87	3.21	2.28	0.74	0.50
SO_4	0.92	3.23	1.98	0.97	0.90
NH_4	0.90	1.50	0.99	0.93	0.82
NO_3	0.89	2.29	1.54	0.82	0.83
Sources					
EGU	0.96	1.95	0.96	--	--
Non-EGU	0.97	0.70	0.52	--	--
Vehicles	0.98	2.66	1.58	--	--
Bio	0.92	0.36	0.35	--	--
Other	0.90	4.14	3.03	--	--

Mortality Risk Analysis:

Single-pollutant HRs, per unit $\mu g/m^3$ (panel A) and per relative mean $\mu g/m^3$ (panel B), are displayed in Figure 2. Numeric equivalents of these estimates, along with HRs scaled per interquartile range, are reported in Table S2. In single-pollutant models, there were positive, significant ($p < 0.05$) mortality associations for $PM_{2.5}$ mass and each component, except POA. Relative effect sizes differed between scaling methods, as each approach answers a distinct question. When scaled per unit, HRs provide information about per mass concentration harmfulness, whereas scaling per mean reflects a component's aggregate contribution to mortality risk.

a. Measures of temporal consistency included cohort-weighted annual exposure means (e.g., '01 Mean) and Pearson correlation coefficients between 2001 and 2010 exposures (i.e., '01 '10 Corr.).

b. Exposure accuracy was measured through a ten-fold cross validation (CV) R^2 comparison of predicted concentrations and ground-level monitor observations.

Per unit $\mu g/m^3$ (panel A), single-pollutant HRs were relatively large for EC, non-EGU, and bio. These differences are difficult to interpret due to confounding from correlation with total $PM_{2.5}$. That is, in single-pollutant models components with higher correlation with total $PM_{2.5}$ likely exhibit a larger positive bias. Moreover, this bias is greater for components with lower exposure means (e.g., EC, non-EGU, bio) when estimates are scaled per unit $\mu g/m^3$.

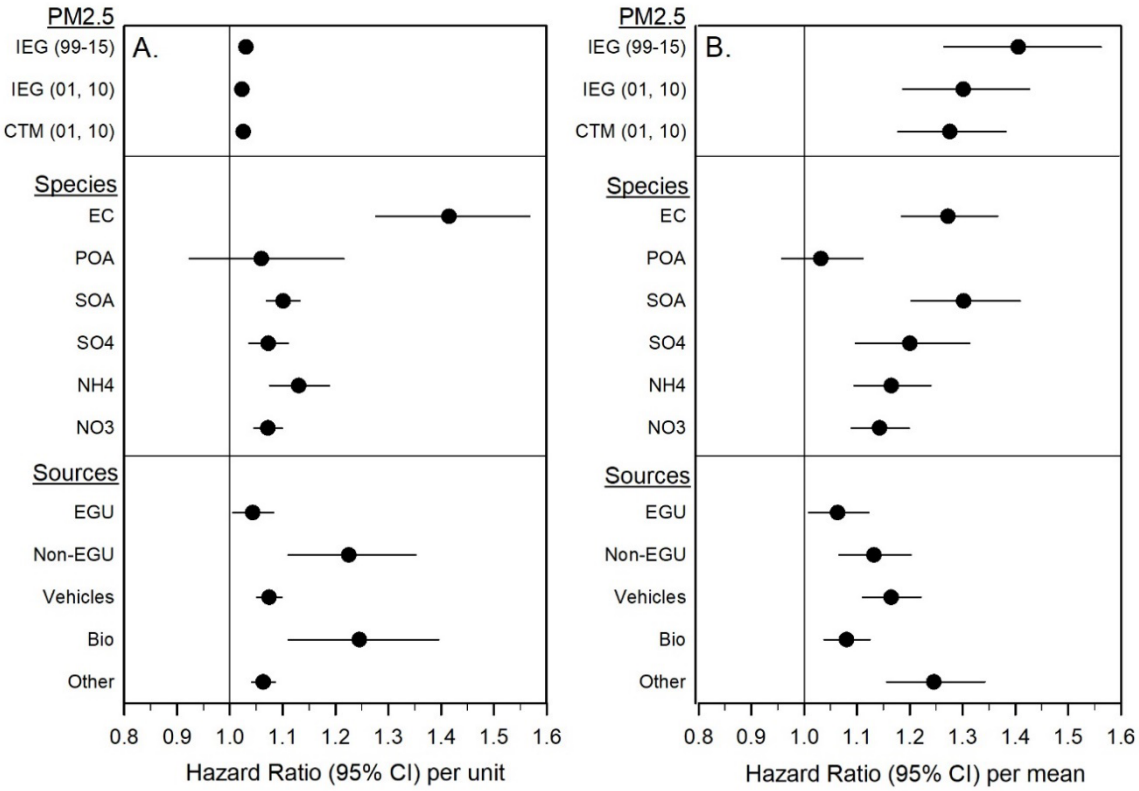


Figure 2: Single-pollutant hazards ratios and 95% confidence intervals (CI) per unit $\mu g/m^3$ (panel A) and per relative mean $\mu g/m^3$ (panel B) increase in exposure

Scaling single-pollutant HRs per mean increase in exposure (panel B) partially accounts for this problem, while allowing estimates to reflect a component's relative contribution to total $PM_{2.5}$ exposure. Of the three estimates of total $PM_{2.5}$ exposure, the seventeen-year average (i.e., 1999-2015) of IEG-modelled $PM_{2.5}$ was associated with the largest increase in

mortality risk (HR = 1.41; 95% CI [1.26, 1.56]; per 11.32 μg/m^3). Despite having a similar mean exposure, the estimated HR for the two-year average (i.e., 2001 and 2010) of IEG-modelled $PM_{2.5}$ was 26% smaller (HR = 1.30; 95% CI [1.19, 1.43]; per 11.64 μg/m^3) than its seventeen-year counterpart. This suggests that assigning component exposures as the average of two annual concentrations resulted in conservative mortality risk estimates. Among $PM_{2.5}$ components, EC (HR = 1.27; 95% CI [1.18, 1.37]; per 0.69 μg/m^3) and SOA (HR = 1.30; 95% CI [1.20, 1.41]; per 2.75 μg/m^3) had the highest HRs per relative mean increase in exposure.

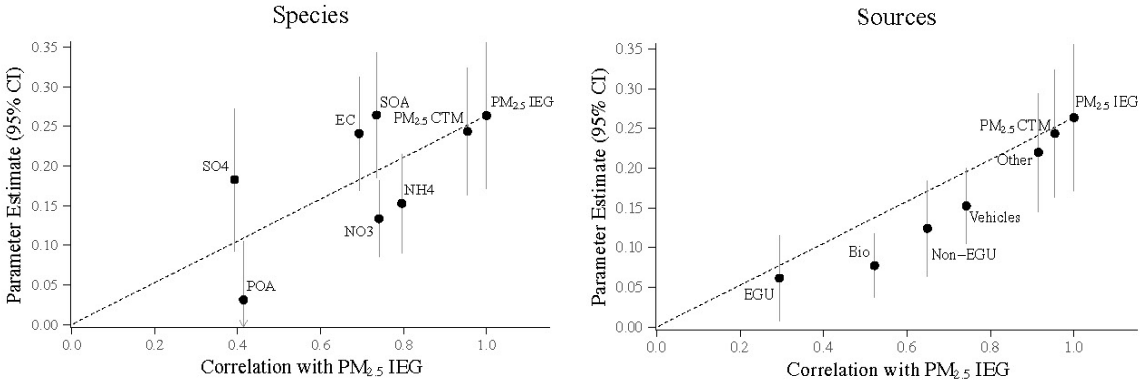


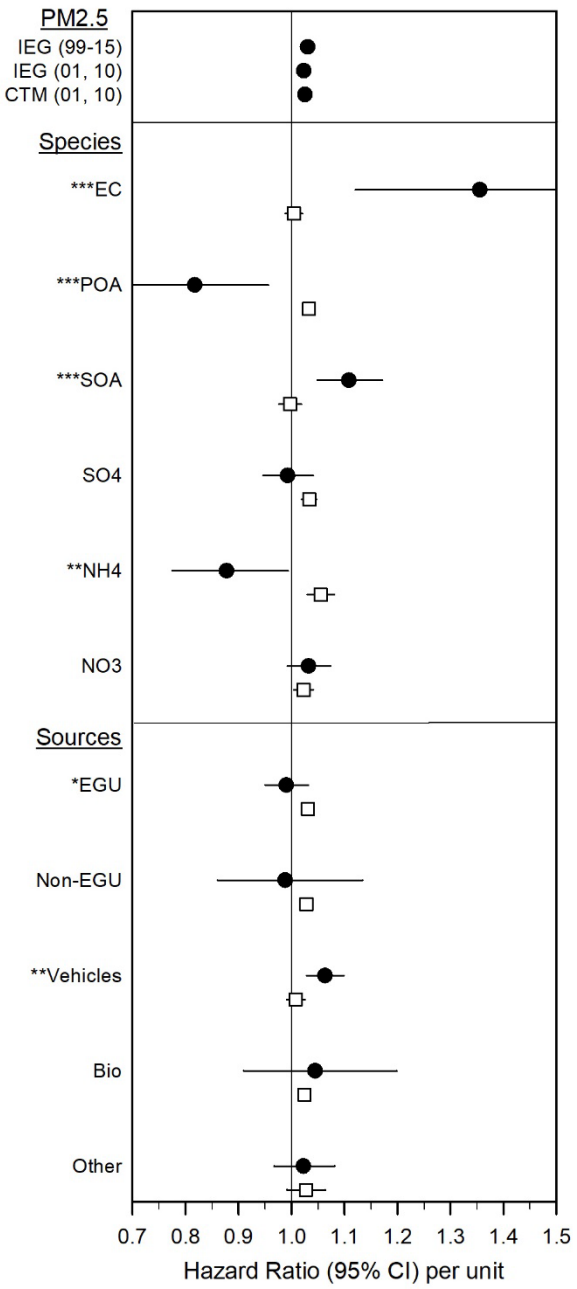
Figure 3: parameter estimates (i.e., natural log of hazard ratio) and 95% confidence intervals (CI) from single-pollutant models plotted according to component correlation with $PM_{2.5}$ mass. Estimates are relative to a component mean increase in exposure.

To account for bias from correlation between component and total $PM_{2.5}$ exposure, Figure 3 plots single-pollutant parameter estimates (i.e., natural log of HR) according to component correlation with $PM_{2.5}$ mass. The plotted diagonal provides a baseline comparison by indicating the effect size one would expect to see solely from component correlation with $PM_{2.5}$ exposure. Thus, distance from the plotted diagonal serves as a basic

metric for whether single-pollutant mortality associations are relatively high or low. As such, Figure 3 provides some indication that EC, SOA, and SO_4 have relatively high single-pollutant associations with cardiopulmonary mortality.

While Figure 3 is useful for interpreting single-pollutant estimates, a more thorough attempt at estimating component-specific mortality associations is to explicitly control for remaining mass. Figure 4 plots HRs from mass-adjusted models, which included a given $PM_{2.5}$ component (black circle point estimates) and remaining $PM_{2.5}$ mass (white square point estimates). Estimates are reported per unit $\mu g/m^3$ to reflect relative toxicities. Numeric equivalents of these estimates are provided in Table S3.

For several components, controlling for remaining $PM_{2.5}$ reduced the magnitude of single-pollutant HRs. Specifically, for POA, SO_4, NH_4, EGU, and non-EGU, positive single-pollutant risk estimates became either null or negative after controlling for remaining $PM_{2.5}$. In contrast, EC maintained an elevated HR when controlling for remaining mass (HR = 1.36; 95% CI [1.12, 1.64]; per unit $\mu g/m^3$), with risk estimates ten times greater than total $PM_{2.5}$ (per unit $\mu g/m^3$). Similarly, SOA mortality risk estimates remained large after controlling for remaining mass (HR = 1.11; 95% CI [1.05, 1.17]; per unit $\mu g/m^3$). For $PM_{2.5}$ sources, controlling for remaining mass generally reduced the magnitude of single-pollutant HRs, except for vehicle sources. That is, vehicle source HRs were nearly identical in single-pollutant (HR = 1.07; 95% CI [1.05, 1.10]; per unit $\mu g/m^3$) and mass-adjusted models (HR = 1.06; 95% CI [1.03, 1.10]; per unit $\mu g/m^3$).



330 **Figure 4:** Remaining $PM_{2.5}$ mass adjusted hazard ratios (HRs) and 95% confidence intervals
331 (CI) per unit $\mu g/m^3$. For each component, a separate model was specified to include two
332 pollutants: the component (black circle point estimates) and remaining $PM_{2.5}$ mass (i.e., total
333 $PM_{2.5}$ minus component) (white square point estimates). Stars reflect p-values from a
334 hypothesis test with the null hypothesis that component and remaining $PM_{2.5}$ HRs were
335 equivalent (* $p < 0.10$; ** $p < 0.05$; *** $p < 0.01$).

In Figure 4, component HRs are plotted adjacent to remaining $PM_{2.5}$ mass HRs to facilitate a comparison of relative toxicities. For species, both EC and SOA had higher HRs than their remaining $PM_{2.5}$ mass. A formal hypothesis test revealed that these differences were statistically significant, with p-values of 0.004 and 0.005 for EC and SOA respectively. Source-specific HRs were generally lower than HRs for remaining mass. However, the HR for vehicle source pollution was significantly larger ($p = 0.03$) than its respective remaining mass term.

In addition to component-specific HRs, an aim of this analysis was to estimate mortality associations for primary and secondary $PM_{2.5}$. Figure 5 plots single-pollutant (black point estimates) and two-pollutant HRs (red point estimates) for primary (circle point estimates) and secondary species (diamond point estimates) from total $PM_{2.5}$, vehicles, and "other" sources. Estimates are reported per unit (panel A) and per mean $\mu g/m^3$ (panel B) increase in exposure. Numeric equivalents of these estimates are provided in Table S4.

Per unit $\mu g/m^3$, single-pollutant HRs were consistently larger for primary species. This was likely due to confounding from correlated components, as the same did not hold in two-pollutant specifications. In two-pollutant models, HRs were similar for total primary and total secondary $PM_{2.5}$, as well as for primary and secondary $PM_{2.5}$ from vehicle sources. For "other" sources, the primary $PM_{2.5}$ HR was significantly smaller, as "other" source primary $PM_{2.5}$ was predominantly POA (see Figure 1).

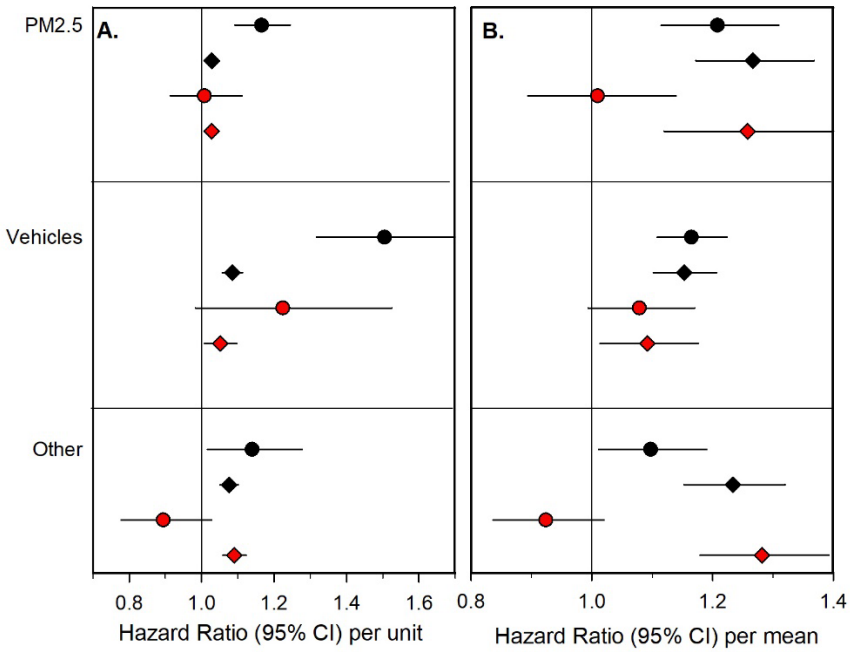


Figure 5: Hazard ratios and 95% confidence intervals (CI) for primary (circle point estimates) and secondary species (diamond point estimates) within $PM_{2.5}$ sources. Single-pollutant models (black point estimates) included one pollutant (e.g., primary vehicles), whereas two-pollutant models (red point estimates) included both primary and secondary species from a given source (e.g., primary vehicles and secondary vehicles). Estimates are reported per unit $\mu g/m^3$ (panel A) and per mean $\mu g/m^3$ (panel B) increase in exposure.

When scaled per mean, HRs for primary and secondary $PM_{2.5}$ from vehicle sources were nearly identical, in both single-pollutant and two-pollutant specifications. In contrast, for total $PM_{2.5}$ and "other" sources, HRs were larger for secondary species. Specifically, in a two-pollutant model, the HR for secondary total $PM_{2.5}$ (HR = 1.26; 95% CI [1.12, 1.41]; per 8.52 $\mu g/m^3$) was significantly larger ($p = 0.05$) than for primary total $PM_{2.5}$ (HR = 1.01; 95% CI [0.89, 1.14]; per 1.23 $\mu g/m^3$). While this can be attributed to higher exposure levels for

secondary species, it does suggest that secondary $PM_{2.5}$ contributes more than primary $PM_{2.5}$ to actualized risk of cardiopulmonary mortality.

Measures of model fit from single-pollutant models, along with two additional specifications that included all species (six pollutants) or all sources (five pollutants) simultaneously, are provided in Table S5. IEG estimates fit mortality outcomes better than CTM estimates of total $PM_{2.5}$ exposure. Single-pollutant models for EC, SOA, and vehicles fit mortality better than both (i.e., IEG and CTM) two-year averages of $PM_{2.5}$, but not the seventeen-year average of IEG-modelled $PM_{2.5}$. Including all species or all sources separately did not improve model fit over aggregate $PM_{2.5}$ specifications.

Discussion

In this analysis, there were positive, significant ($p < 0.05$) single-pollutant mortality associations for $PM_{2.5}$ and all components, except POA. While most associations became insignificant after controlling for remaining $PM_{2.5}$, we found evidence that EC, SOA, and vehicle sources are important contributors to risk of cardiopulmonary mortality.

Species:

Of the considered components, we found that EC was associated with the largest increase in cardiopulmonary mortality risk (per unit $\mu g/m^3$), with and without controlling for remaining $PM_{2.5}$. Moreover, in a mass-adjusted model the HR for EC was significantly larger ($p = 0.004$) than for remaining $PM_{2.5}$ mass.

In past studies, EC has shown elevated single-pollutant mortality associations that lose significance after adjusting for other pollutants.[9, 32, 33] A previous analysis of the American

392 Cancer Society (ACS) cohort estimated eight times greater cardiopulmonary mortality risk
393 for EC than $PM_{2.5}$ in single-pollutant models (per unit $\mu g/m^3$), with EC HRs substantially
394 reduced and insignificant in multi-pollutant models.[32] Similarly, in the California Teacher's
395 Study (CTS) cohort, Ostro et al.[9] found that significant ($p < 0.05$), single-pollutant EC
396 mortality associations became insignificant after adjusting for NO_3.
397 Instability in the EC mortality association has been attributed to EC's complex,
398 heterogenous nature.[9, 34] Specifically, high spatial variation presents difficulties in accurately
399 modeling EC exposures. While EC was modelled relatively imprecisely (see Table 3), we
400 observed significant EC HRs when controlling for remaining $PM_{2.5}$, providing some
401 evidence that EC has a direct relationship with cardiopulmonary mortality.
402 In addition to EC, our results suggest that SOA may be a key contributor to the $PM_{2.5}$
403 mortality relationship. That is, in a mass-adjusted model the HR for SOA was significantly
404 larger ($p = 0.005$) than for remaining $PM_{2.5}$ (per unit $\mu g/m^3$). Similarly, in the CTS cohort
405 anthropogenic SOA was significantly ($p < 0.05$) associated with ischemic heart disease
406 (IHD) mortality in single-pollutant models.[9] Moreover, they found that mortality
407 associations for anthropogenic SOA in the ultrafine range remained significant in all
408 combinations of two-pollutant models.[9] Short-term analyses have found similar results, with
409 a study in Xi'an, China reporting significant cardiovascular and respiratory mortality
410 associations for organic carbon, with and without adjusting for $PM_{2.5}$ mass.[35]
411 While EC and SOA maintained relatively high HRs, single-pollutant mortality
412 associations for SO_4 vanished after controlling for remaining $PM_{2.5}$, suggesting that SO_4 is,
413 at least in part, a tracer of other harmful pollutants. SO_4, along with its precursor SO_2, has
414 been significantly associated with mortality in several observational cohort studies, [32, 36]

including some of the earliest to consider speciated $PM_{2.5}$.[7, 37] However, the plausibility of a causal link between SO_4 and mortality is not supported by toxicology studies, which collectively report minimal biological potency in humans or animals at environmentally relevant levels.[38] Thus, observational associations could represent the mortality relationship of particulate species and co-pollutants correlated with SO_4, not SO_4 alone.[32]

Similarly, mortality associations were relatively low for POA and NH_4, as exposures were inversely associated with cardiopulmonary mortality risk in mass-adjusted models. With high correlations between remaining and total $PM_{2.5}$, mass-adjusted HRs could reflect changes in the $PM_{2.5}$ composition, not an aggregate decrease in $PM_{2.5}$ exposure. Specifically, inverse NH_4 and POA mortality associations could represent a decrease in average $PM_{2.5}$ toxicity when the fractional $PM_{2.5}$ composition has larger proportions of these species. Alternatively, inverse NH_4 and POA mortality associations could be the result of statistical noise or some unobserved confounder. In any case, it remains unlikely that exposure to NH_4 or POA decreases risk of cardiopulmonary mortality.

Sources:

While each considered source was significantly ($p < 0.05$) associated with mortality in single-pollutant models, only vehicle sources remained significant after adjusting for remaining $PM_{2.5}$ mass. In mass-adjusted models, the estimated increase in cardiopulmonary mortality risk from exposure to vehicle source $PM_{2.5}$ was eight times greater (per unit $\mu g/m^3$) than from remaining $PM_{2.5}$ mass. This difference was statistically significant ($p = 0.03$) when formally testing for equality of vehicle source and remaining $PM_{2.5}$ HRs.

Past analyses have supported a relationship between mortality and long-term exposure to vehicle source $PM_{2.5}$, although uncertainty remains due to a limited number of studies.[39] In the CTS cohort, there were statistically significant ($p < 0.05$) single-pollutant associations between IHD mortality and four subgroups of vehicle source $PM_{2.5}$.[9] Short-term analyses have also reported significant associations between adverse health effects and vehicle source $PM_{2.5}$. An analysis in Barcelona, Spain found that traffic related $PM_{2.5}$ was associated with a more than 8% increase in daily cardiovascular mortality (per 9.7 $\mu g/m^3$ with 2-day lag), in single and multi-source models.[40] Similarly, a U.S. study found that 10 $\mu g/m^3$ of mobile source $PM_{2.5}$ increased daily mortality by 3.4%.[41] In addition to daily mortality, a series of short-term studies in New York State found that vehicle source $PM_{2.5}$ was significantly associated with hospitalizations and emergency department visits for influenza, cardiac arrythmia, ischemic stroke, and congestive heart failure.[42, 43] These studies, combined with the present analysis, provide suggestive evidence that vehicle sources are an important contributor to the $PM_{2.5}$ morbidity and mortality relationship.

Primary vs. Secondary:

Estimating the relative mortality associations of primary and secondary $PM_{2.5}$ yielded little insight beyond what can be explained by component-specific mortality associations and differences in exposure means. That is, differences in source-specific primary and secondary mortality associations were driven either by the species composition within source (see Figure 3) or relative exposure means. Ultimately, our results suggest that mortality associations differ more within primary and secondary designations (e.g., EC vs. POA) than between primary and secondary designations (e.g., primary vehicles vs.

secondary vehicles). Nevertheless, with a significantly larger HR per mean exposure, total secondary $PM_{2.5}$ likely contributes more than total primary $PM_{2.5}$ to actualized risk of cardiopulmonary mortality.

Limitations:

An inherent limitation of observational air pollution analyses is imperfect assignment of pollution exposures. In our analysis, individuals were assigned an MSA-level average of 2001 and 2010 concentration estimates, as a proxy for lifetime exposure. Assigning lifetime exposure as the average of two annual estimates fails to account for the temporal complexity of component levels and composition. However, we found that intertemporal correlations for $PM_{2.5}$ components were consistently high ($r > 0.78$), which suggests that incorporating additional years of CTM exposure estimates would provide only marginal improvements in exposure accuracy. If anything, using the average of 2001 and 2010 concentrations resulted in conservative mortality risk estimates. For a thorough analysis on the influence of temporal exposure windows in the NHIS cohort, see Lefler et al.[31]

Additionally, NHIS public-use residential data included only MSA of residence, which required assigning exposures at the MSA level. For this reason, along with the 36-kilometer resolution in the CTM, we were unable to account for local variations in $PM_{2.5}$ components. This is particularly problematic for components with high spatial variability, such as EC.

Another limitation is that differences in component mortality associations could have been driven by statistical factors aside from toxicity. As previously mentioned, exposure modelling accuracy, observed variation, and component intercorrelation all affect the precision and magnitude of mortality risk estimates. While these factors vary between

components, they are likely independent of relative toxicity. Thus, differences in effect size and statistical significance could simply reflect varying statistical advantages, not differential mortality associations.

A final limitation is potential confounding from unobserved or inadequately controlled for risk factors. If correlated with pollution and cardiopulmonary mortality, unobserved characteristics such as dietary habits, physical activity, and climate could have resulted in spurious findings. Additionally, dynamic risk factors such as smoking status, BMI, income, and residence were reported only at time of survey, providing an imperfect measure of the lifetime pathway of these variables.

Notwithstanding these limitations, our findings suggest that there are differences in mortality associations across $PM_{2.5}$ species and sources. These differences appear to be driven by factors other than whether $PM_{2.5}$ is primary or secondary. After controlling for remaining $PM_{2.5}$, the mortality association for EC was ten times greater (per unit $\mu g/m^3$) than for total $PM_{2.5}$. Similarly, SOA and vehicle sources had significantly larger HRs than remaining $PM_{2.5}$ mass (per unit $\mu g/m^3$). These findings suggest that targeted abatement strategies could be more beneficial to public health than simply reducing total $PM_{2.5}$. If corroborated in other studies, this analysis could help inform a targeted, efficient approach to reducing air pollution mortality.

Supporting Information Figure and Table Descriptions

Table S1: Breakdown of Cardiopulmonary Mortality by ICD 10 Codes

Figure S1: Illustration of Pollution Exposures across NHIS Surveyed MSAs

Table S2: Numeric Single-Pollutant Hazard Ratios (95% Confidence Intervals)

Table S3: Numeric Mass-Adjusted Hazard Ratios (95% Confidence Intervals)

Table S4: Numeric Hazard Ratios (95% Confidence Intervals) for Primary and Secondary Species within $PM_{2.5}$ Source

Table S5: Measures of Model Fit

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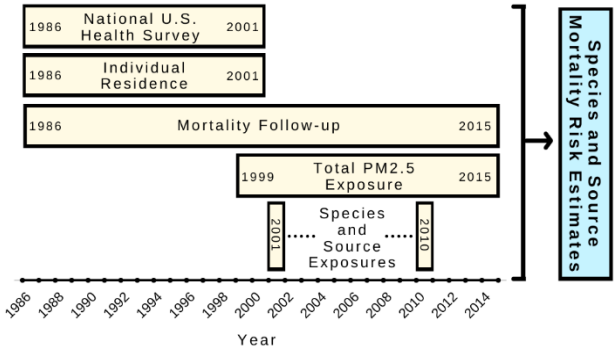

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