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Associations between Long-Term Exposure to Chemical Constituents of Fine Particulate Matter (PM$_{2.5}$) and Mortality in Medicare Enrollees in the Eastern United States

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INTRODUCTION

Regulatory control of particulate matter (PM) could be dramatically improved with robust quantification of the evidence regarding the toxicity of various constituents of the PM mixture and of their sources [U.S. Environmental Protection Agency (EPA) 2004]. Currently, PM is regulated based on the total mass concentration without regard to its chemical composition, but scientific evidence on which types of constituents are most harmful could result in more effective regulations. However, the knowledge regarding differential toxicities of PM constituents has been identified as a crucial research gap (National Research Council 2004).

Responding to the need for such evidence, for the last decade, data have been accumulated for the constituents of fine particulate matter (≤2.5 μm in aerodynamic diameter; PM$_{2.5}$) nationwide in the United States and have provided opportunities for studying the association between morbidity/mortality risk and PM$_{2.5}$ constituents. Using these data, numerous epidemiological studies have reported evidence of health effects associated with PM$_{2.5}$ constituents, both in short-term (a few days previous) and long-term (a few years previous) exposure time frames. Studies focusing on the short-term health effects include those by Bell et al. (2014), Cao et al. (2012), Ito et al. (2011), Kim et al. (2012), Levy et al. (2012), Ostro et al. (2009), Peng et al. (2009), and Zhou et al. (2011). Fewer studies have investigated the long-term health effects of different PM$_{2.5}$ constituents, including those by Dockery et al. (1993), Ostro et al. (2010), and Pope et al. (1995, 2002). However, studies have not reported consistent findings regarding associations with specific constituents. Such discrepancies may derive from different aspects of the study design (e.g., population, confounding control, time frame, and statistical analysis), and the U.S. EPA (2009) has called for further research.

To fill this research gap, we investigated the differential toxicity of long-term PM$_{2.5}$ exposure according to its chemical composition, based on a large-scale national database including approximately 12.5 million Medicare enrollees (≥65 years of age). Combining several sources of data, we constructed a monthly multi-site time-series data set for 518 PM$_{2.5}$ monitoring locations in the eastern region of the United States during 2000–2006. We included, for each monitoring location, monthly mortality rates, monthly values of the average PM$_{2.5}$ concentration over the previous 12 months, 7-year average concentrations of PM$_{2.5}$ constituents, and community-level confounding variables/National Health Interview Survey socioeconomic status and racial composition. Using a Bayesian hierarchical (BH) regression model, we estimated spatially varying (SV) mortality rates associated with previous-year PM$_{2.5}$ and identified chemical constituents that explained the spatial variability of the mortality rates, controlling for PM$_{2.5}$ and community-level characteristics.

METHODS

Data description. PM$_{2.5}$ total mass. We obtained daily (24-hr average) concentrations of PM$_{2.5}$ at 518 monitors in the eastern United States (Figure 1) for 2000–2006 from the U.S. EPA Air Quality System (AQS) database (U.S. EPA 2014). Using the daily PM$_{2.5}$ data, we calculated monthly long-term exposure to PM$_{2.5}$ as described in detail by...

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Of the 518 PM$_{2.5}$ monitors, 241 had PM$_{2.5}$ constituent monitors within 6 miles, and we assigned 7-year averages of each PM$_{2.5}$ constituent to each PM$_{2.5}$ monitor. For the remaining 277 monitoring locations, we treated the levels of PM$_{2.5}$ chemical constituents as missing and applied a statistical approach to impute the missing data, as described in “Statistical methods.” For either measured or imputed values, we let $x_{ijl}$ denote the 7-year average concentrations of the six chemical constituents for $i$th PM$_{2.5}$ monitor location.

**PM$_{2.5}$ chemical constituents.** Although the U.S. EPA measures $>50$ PM$_{2.5}$ chemical constituents, we focused on 6 identified in previous research as contributing substantially to PM$_{2.5}$ total mass (Bell et al. 2007): elemental carbon (EC), organic carbon matter (OCM), sulfate (SO$_4^{2-}$), silicon (Si), nitrate (NO$_3^{-}$), and sodium (Na). We obtained 7-year averages of the 6 chemical constituents at 174 monitors in the eastern region for 2000–2006 (Greven et al. 2011). In brief, for the first day of every month at each of the 518 monitor locations, we calculated the previous 1-year average of daily PM$_{2.5}$ concentrations ($y_{ij}$) for $i$th monitor at $j$th month, with $i = 1, \ldots, n$ and $j = 1, \ldots, n_j$. Because not all monitors had valid measurements for the entire study period, the number of monthly PM$_{2.5}$ values at a given monitoring location ($n_j$) varied from 33 to 70.

**Figure 1.** Map of 518 PM$_{2.5}$ monitor locations and 174 PM$_{2.5}$ chemical constituent monitor locations in the eastern region of the United States.
random errors. We centered and scaled all explanatory variables to simplify interpretation and reduce multicollinearity. Note that $\bar{X}_i$ is included in the SV intercept in Equation 2 to control for total PM$_{2.5}$ concentration when estimating the effects of constituents on the SV mortality rate (Mostofsky et al. 2012).

To account for potential residual spatial correlation in the second level, we assumed the error terms could be spatially correlated using a standard approach (Gelfand et al. 2003) (see Supplemental Material, “Accounting for residual spatial correlation”). We fit our BH model using a Monte Carlo Markov chain (MCMC) method (see Supplemental Material, “Two-stage estimation and the Markov (MCMC) method [see Supplemental Material, model using a Monte Carlo Markov chain residual spatial correlation”). We fit our BH approach (Gelfand et al. 2003) estimating the effects of constituents on the SV intercepts and slope with the proportion of black residents. The highest positive correlations among the constituents were observed between EC and OCM (0.44), SO$_4^{2-}$ and OCM (0.41), and Si and OCM (0.43). Among the community-level confounders, strong positive correlations were observed as 0.62 between median family income and the proportion of people with high school diploma or equivalent, and 0.50 between the proportions of white residents and high school graduates, whereas the strongest negative correlation was –0.84 between the proportions of white and black residents. Between the constituents and the community-level confounders, the highest correlations were observed for OCM at 0.39 and for Si at 0.34 with the proportion of black residents.

Before the BH regression modeling, we conducted CV studies for our imputation method for the missing constituent levels. The sample correlation coefficients between the observed and predicted values for the test data are 0.64–0.94 for all constituents averaged over 5 CV data sets (see Supplemental

Table 1. Summary statistics for each variable (mean ± SD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete-case data (n = 241)</th>
<th>All-sites data (n = 518)</th>
</tr>
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<tbody>
<tr>
<td>Population size at risk (n/month)</td>
<td>16501.00 ± 17307.31</td>
<td>14538.92 ± 15453.71</td>
</tr>
<tr>
<td>Mortality count (n/month)</td>
<td>76.01 ± 74.04</td>
<td>64.93 ± 66.7</td>
</tr>
<tr>
<td>Long-term PM$_{2.5}$ exposure levels (µg/m$^3$)</td>
<td>14.56 ± 1.88</td>
<td>13.7 ± 2.13</td>
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<tr>
<td>PM$_{2.5}$ chemical constituents (µg/m$^3$)</td>
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<tr>
<td>Elemental carbon (EC)</td>
<td>0.71 ± 0.33</td>
<td>0.68 ± 0.24*</td>
</tr>
<tr>
<td>Organic carbon matter (OCM)</td>
<td>4.1 ± 1.06</td>
<td>4.05 ± 0.90*</td>
</tr>
<tr>
<td>Sulfate (SO$_4^{2-}$)</td>
<td>4.22 ± 0.81</td>
<td>4.14 ± 0.80*</td>
</tr>
<tr>
<td>Silicon (Si)</td>
<td>0.09 ± 0.03</td>
<td>0.09 ± 0.03*</td>
</tr>
<tr>
<td>Nitrate (NO$_3^-$)</td>
<td>1.86 ± 0.86</td>
<td>1.68 ± 0.85*</td>
</tr>
<tr>
<td>Sodium (Na)</td>
<td>0.16 ± 0.08</td>
<td>0.17 ± 0.07*</td>
</tr>
<tr>
<td>Community-level confounders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family income ($)</td>
<td>38247.39 ± 11149.87</td>
<td>40355.00 ± 12461.21</td>
</tr>
<tr>
<td>Percent high school graduate</td>
<td>0.78 ± 0.06</td>
<td>0.79 ± 0.08</td>
</tr>
<tr>
<td>Percent urban</td>
<td>0.93 ± 0.16</td>
<td>0.96 ± 0.23</td>
</tr>
<tr>
<td>Percent white</td>
<td>0.64 ± 0.20</td>
<td>0.70 ± 0.20</td>
</tr>
<tr>
<td>Percent black</td>
<td>0.25 ± 0.18</td>
<td>0.19 ± 0.17</td>
</tr>
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For population size at risk, mortality count and long-term (previous 1-year average) PM$_{2.5}$, location-specific monthly values are averaged across locations for the whole study period (2000–2006). For chemical constituents, location-specific 7-year averages are averaged across locations. For community-level confounders, location-specific values are averaged across locations.

Numbers were calculated including the imputed PM$_{2.5}$ constituent levels for the 277 PM$_{2.5}$ monitoring locations with missing constituent levels.
Material, Table S2). The root mean square error (RMSE) for prediction for each constituent and the average RMSE over five CV data sets is about half of the sample standard deviation for all constituents (see Supplemental Material, Table S3). Scatter plots for the observed versus predicted data show that the points generally follow the reference line (meaning observed values = predicted values) (see Supplemental Material, Figure S2). Based on the CV study results, we concluded that the Bayesian spatial GP method was appropriate for imputing the missing constituents in our study.

We analyzed the complete-case data ($n = 241$) and the all-sites data ($n = 518$), separately. We fit Equations 1, 2, and 3 and Supplemental Material, Equation S1 with eight different options and chose the best fit based on the smallest DIC (see Supplemental Material, Table S4). We obtained the smallest DIC for the model including both chemical constituents and community-level confounders as explanatory variables and with spatially independent errors both for the SV intercept and slope model in complete-case data as well as in the all-sites data.

Figure 4 displays results from the first level of the BH model for complete-case data (left panels) and all-sites data (right panels), respectively. Both sets of data showed similar results. Figure 4A shows the estimated monthly mortality rate when the previous-year PM$_{2.5}$ is equal to its monitor-specific overall average ranges from 3.37 to 6.15 (deaths/month/1,000 persons) over the study region from all-sites data analysis. Also, Figure 4B shows that the estimated association of mortality rate with a 1-μg/m$^3$ increase in the previous-year PM$_{2.5}$ is from –1.0 to 4.6 (percent increase in mortality rate).

Figure 5 reports the results from the second level of the BH model for complete-case data (left-solid bars) and all-sites data (right-dashed bars), respectively. Results were similar between complete-case data and all-sites data, but the all-sites estimates were somewhat smaller and their confidence intervals are narrower. In both analyses, we observed that adjusting for the community-level confounders and PM$_{2.5}$ total mass, EC, Si, and NO$_3^-$ were positively associated with mortality rate (the SV intercept, $\beta_0$), whereas SO$_4^{2-}$ was inversely related to mortality (Figure 5A). Meanwhile, SV slope estimates ($\gamma$) indicated that the percentage increase in mortality rate with a 1-unit increase in average previous-year PM$_{2.5}$ was greater than expected when combined with a 1-SD increase in SO$_4^{2-}$ and Na (Figure 5B).

Finally, we analyzed the data stratified by two age groups (65–74 vs. ≥ 75 years). For the SV intercept model (see Supplemental Material, Figure S3), results for the younger age group were similar to those for the all-age analysis (i.e., main effect estimates for EC, Si, and NO$_3^-$ were significant), whereas for the SV slope model (see Supplemental Material, Figure S4), both age groups (65–74 and ≥ 75 years) had results similar to those for the all-age analysis (≥ 65 years).

**Discussion**

We investigated a) whether month-to-month changes in mortality rates were associated with month-to-month changes in the previous-year exposure to PM$_{2.5}$, and b) whether 7-year average levels of PM$_{2.5}$ chemical constituents modified this association.

For the SV intercept, EC, Si, and NO$_3^-$ were positively associated with mortality rates after adjusting for PM$_{2.5}$ total mass and the community-level confounders. For EC, our results are consistent with those of a previous cohort study of female public school professionals in California (Ostro et al. 2010).

Evidence for the toxicity of Si was also found in other studies. Ostro et al. (2010) reported that long-term exposure to Si was positively associated with pulmonary mortality. Si may serve as a surrogate for toxic constituents found in mineral dust associated with traffic (Reff et al. 2009). A previous study reported that long-term exposure to traffic or traffic-related pollutants is associated with cardiopulmonary mortality (Jerrett et al. 2005). Few studies examined associations for NO$_3^-$ with mortality in a long-term framework. Ostro et al. (2010) reported that long-term exposure to NO$_3^-$ was significant for mortality in a single-pollutant model but not in a multipollutant model. Additionally, SO$_4^{2-}$ was found to be inversely associated with mortality rates, which is inconsistent with previous studies where positive associations were found (Dockery et al. 1993; Ostro et al. 2010; Pope et al. 1995, 2002).

Although the observed positive associations were from single-pollutant approaches, our study used a multipollutant analysis that also included adjustment for the PM$_{2.5}$ total mass and community-level confounders. Therefore, the inverse associations that we observed should be interpreted with caution, because they may be an artifact of multicollinearity resulting from correlations between SO$_4^{2-}$ and other constituents, PM$_{2.5}$ total mass, and community-level confounders.

SO$_4^{2-}$ and Na were significant modifiers of monitor-specific associations between previous-year average PM$_{2.5}$ and mortality rates. Previous long-term exposure studies for PM$_{2.5}$ constituents have reported significant positive associations of SO$_4^{2-}$ with all-cause mortality (Dockery et al. 1993; Pope et al. 2002) or with cardiopulmonary mortality (Ostro et al. 2010; Pope et al. 2002). Na was also a significant modifier that strengthened the association between
Exposure to PM$_{2.5}$ constituents and mortality. Few studies have estimated associations between Na and health outcomes, with some showing evidence of associations with mortality (Krall et al. 2013) or hospital admission (Zanobetti et al. 2009). Several possible mechanisms have been proposed in human subject studies linking constituents to biomarkers: systemic inflammation and oxidative stress associated with EC (Neophytou et al. 2013), altered DNA methylation related to Si (Hou et al. 2014),

![Figure 3. Maps of 7-year (2000–2006) averages of each of the six PM$_{2.5}$ chemical constituents (µg/m$^3$) for 241 monitor locations with available data.](image)
and inflammation related to NO$_3^-$ and SO$_4^{2-}$ (Wu et al. 2012). However, because of limited evidences from experimental/toxicological studies, the biological pathway through which short-term exposure to PM$_{2.5}$ and its components affects health is still an area of active investigation, and the mechanisms for long-term exposure are less understood.

The U.S. EPA measures > 50 different chemical constituents. Analyzing all available constituents would present problems of multiple comparisons. We selected the six constituents that were previously shown to be the largest contributors to PM$_{2.5}$ total mass and/or co-vari with PM$_{2.5}$ total mass (Bell et al. 2007). Also, the reliability of a community-level average of PM$_{2.5}$ constituent exposure varies by constituent. For the six constituents investigated in the present study, the average correlation of monitors in close proximity (< 5 km) ranges from 0.60 to 0.93 and for larger distances (20–50 km) ranges from 0.46 to 0.88 (Bell et al. 2011). The spatial heterogeneity of many other constituents may be larger, limiting the interpretation of community-level exposures. However, we recognize that other constituents have also been found to be associated with human health. In particular, associations of health outcomes with PM$_{2.5}$ metal constituents that were not included in our analysis, such as aluminum, calcium, chromium, lead, manganese, nickel, titanium, vanadium, and zinc, have been reported in previous studies (Bell et al. 2014; Cavallari et al. 2008; Hsu et al. 2011; Lippmann et al. 2006; Wu et al. 2012).

One limitation of the available air pollution data is that monitors that measure PM$_{2.5}$ total mass and monitors that measure the PM$_{2.5}$ chemical constituents are misaligned (Figure 1). We addressed this limitation by assuming that ambient levels of PM$_{2.5}$ constituents were homogeneous within a 6-mile radius. This spatial homogeneity assumption for air pollutants builds on previous research (Bell et al. 2011) where 6 miles (about 10 km) in radius is a reasonable buffer size for the homogeneity assumption. In Bell et al. (2011), the estimated spatial correlations between pairs of monitors with distances of 5–10 km are 0.67, 0.85, 0.95, 0.62, 0.95, and 0.59 for EC, OCM, SO$_4^{2-}$, Si, NO$_3^-$, and Na, respectively. However, spatial variability varies by constituent—for example, with more heterogeneity for Si or Na than for SO$_4^{2-}$ or NO$_3^-$—and different buffer sizes may be applied for different constituents when aligning various sources of data.

Another limitation for air pollution data is that monitors that measure PM$_{2.5}$ total mass are much denser than monitors

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**Figure 4.** (A) Maps of the estimates (posterior means) of the SV intercept from the complete-case data analysis (n = 241, left) and the all-sites data analysis (n = 518, right). The values represent the monthly mortality rate (deaths/month/1,000 persons) when previous-year PM$_{2.5}$ is at location-specific average. (B) Maps of the estimates (posterior means) of the SV slope from the complete-case data analysis (n = 241, left) and the all-sites data analysis (n = 518, right). The values represent the percent increase in the monthly mortality rate associated with a 1-$\mu$g/m$^3$ increase in previous-year PM$_{2.5}$. 

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that measure PM$_{2.5}$ chemical constituents (Figure 1). When we aligned the two kinds of monitors, missing data occurred for almost half of the PM$_{2.5}$ monitors. To avoid simply removing the observations with missing values and reducing the sample size to half, we adopted a Bayesian spatial GP modeling and conducted a single value imputation for the missing data separately for each constituent. We compared the results between the complete-case data analysis and the all-sites data analysis with the imputed values. Although imputation did not change our primary conclusions, results based on the imputed data should be interpreted with caution. Specifically, using a single-value imputation does not incorporate uncertainty for prediction, and measurement error can occur for the explanatory variables in regression modeling (Gryparis et al. 2009).

In our study, the PM data are the ambient levels, which we use to approximate the actual human exposure. The ambient level of a given pollutant is not a perfect surrogate of personal exposure to that pollutant, which can induce exposure measurement error into the analysis with variations in error by constituent. In a multipollutant analysis such as the present study, this type of error may induce upward bias in regression coefficient estimates, resulting in anticonservative inference on health effects. However, several authors have shown that this type of bias barely occurs in situations in which the amount of error or the correlations among pollutants in analysis are extremely large (Schwartz and Coull 2003). Therefore, it is unlikely that differences between ambient levels and personal exposures explain the observed associations in our study.

Our analysis is based on multi-site time-series data where long-term exposure was estimated by calculating previous 1-year average of daily exposure values at each temporal point (i.e., first day of each month). However, results may be sensitive to different choices of time frames. Kim et al. (2012) reported that different lag values should be selected for the short-term effects of PM$_{2.5}$ constituents depending on health outcomes. Shorter or longer time frames than a year could be considered for examining long-term health effects of PM$_{2.5}$.

Our study focused on the eastern region of the United States, and our findings may not be generalizable to other areas because the characteristics of PM mixtures and populations are quite different across the United States (Bell et al. 2007), and effect modification by the chemical composition of PM$_{2.5}$ may vary among regions. Also, we focused on the elderly population, which may be more susceptible to effects of exposure than other age groups. In our study, slight differences in results were found between two age groups (65–74 and ≥75 years).

To our knowledge, this is the first large-scale study (covering the eastern United States) to investigate the association between long-term exposure to PM$_{2.5}$ and mortality and effect modification by the chemical constituents of PM$_{2.5}$. Unlike previous studies of PM$_{2.5}$ constituents, we used a BH regression approach, where PM$_{2.5}$ constituents were modeled as potential modifiers of the main effect of PM$_{2.5}$ on health outcomes. Despite limitations, our findings add new evidence regarding the differential toxicity of PM$_{2.5}$ constituents and their potential influence on the long-term health effects of PM$_{2.5}$.

**Figure 5.** (A) Posterior estimates with 95% posterior intervals for the $\beta_k$ regression coefficients in the second-level SV intercept model. Solid error bars are for the complete-case data (n = 241) and dashed error bars are for the all-sites data (n = 518). Values correspond to the estimated percentage increase in monthly mortality rate associated with a 1-SD increase in each constituent, adjusted for previous-year average of PM$_{2.5}$ total mass and for community-level covariates. (B) Posterior estimates with 95% posterior intervals for the $\gamma_k$ regression coefficients in the second-level SV slope model. Solid error bars are for the complete-case data (n = 241) and dashed error bars are for the all-sites data (n = 518). Values correspond to the estimated percentage increase in the association between previous-year average of PM$_{2.5}$ and mortality when combined with a 1-SD increase in each constituent, adjusted for community level covariates.

### References


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