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Systematic Reviews and Meta- and Pooled Analyses

A Meta-Analysis and Multisite Time-Series Analysis of the Differential Toxicity of Major Fine Particulate Matter Constituents

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Health risk assessments of particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) often assume that all constituents of $PM_{2.5}$ are equally toxic. While investigators in previous epidemiologic studies have evaluated health risks from various $PM_{2.5}$ constituents, few have conducted the analyses needed to directly inform risk assessments. In this study, the authors performed a literature review and conducted a multisite time-series analysis of hospital admissions and exposure to $PM_{2.5}$ constituents (elemental carbon, organic carbon matter, sulfate, and nitrate) in a population of 12 million US Medicare enrollees for the period 2000–2008. The literature review illustrated a general lack of multiconstituent models or insight about probabilities of differential impacts per unit of concentration change. Consistent with previous results, the multisite time-series analysis found statistically significant associations between short-term changes in elemental carbon and cardiovascular hospital admissions. Posterior probabilities from multiconstituent models provided evidence that some individual constituents were more toxic than others, and posterior parameter estimates coupled with correlations among these estimates provided necessary information for risk assessment. Ratios of constituent toxicities, commonly used in risk assessment to describe differential toxicity, were extremely uncertain for all comparisons. These analyses emphasize the subtlety of the statistical techniques and epidemiologic studies necessary to inform risk assessments of particle constituents.

meta-analysis; nitrates; particulate matter; risk assessment; soot; sulfates

Abbreviations: CHA, cardiovascular hospital admission; CI, confidence interval; CRF, concentration-response function; ICD-9, *International Classification of Diseases*, Ninth Revision; $PM_{2.5}$, particulate matter less than 2.5 μm in diameter; RHA, respiratory hospital admission.

Public policy assessments have demonstrated that the health benefits associated with reducing concentrations of fine particulate matter, defined as particulate matter less than 2.5 μm in diameter ($PM_{2.5}$), dominate the benefits of air pollution control (1, 2). These health risk assessments of $PM_{2.5}$ link atmospheric dispersion model outputs with concentration-response functions (CRFs; the percent change in a given health outcome per $\mu g/m^3$ change in concentration) for $PM_{2.5}$ as a whole, derived from epidemiologic evidence. However, on the basis of both toxicologic and epidemiologic evidence (3, 4), there has been growing concern that different constituents of $PM_{2.5}$ may have different levels of toxicity, which would contribute to biases in risk assessments dominated by $PM_{2.5}$.

With increasing epidemiologic evidence regarding the health effects of $PM_{2.5}$ constituents, it is timely to consider whether there is sufficient evidence to quantitatively assign different CRFs to different constituents. Advisory committees and recent regulatory analyses (4, 5) have concluded that it is not currently possible to do so. This could be true if there were few relevant studies, an issue that should be resolved over time, but the studies themselves may have fundamental limitations. Exposure data may be insufficient or flawed, or the data may be adequate but the statistical methods applied may not provide the information necessary to draw conclusions about differential toxicity. The different constituents of $PM_{2.5}$ might affect different health outcomes, and the time scales of toxicity (acute vs. chronic) might vary across constituents and health

outcomes. It may also be challenging to combine information across studies, because of underlying geographic variability, differences in statistical methods, and which constituents, health outcomes, and confounders are examined.

To frame the information needs, it is important to consider what risk assessment requires. Risk assessments often evaluate control strategies influencing numerous particle constituents, all of which would require CRFs. Estimates of the public health burden of $PM_{2.5}$ should be identical regardless of whether they are calculated from total particle mass or by combining the impacts attributed to individual constituents. Relatedly, because the primary risk assessment application of differential toxicity would be in regulatory analyses focused on $PM_{2.5}$, it is most salient to consider those constituents that could best explain the $PM_{2.5}$ epidemiology. In addition, risk assessments require reasonable quantification of uncertainty, to convey information to decision-makers and to allow for uncertainty propagation. This would be needed both for individual constituents and in the comparisons between constituents. These comparisons would need to take into account the correlations among the CRFs derived from multiconstituent models. Finally, CRFs should be derived from studies conducted in settings that could be readily generalized to the risk assessment context (i.e., similar ambient concentrations, multipollutant exposures, and population characteristics). There is evidence of geographic variability in CRFs for $PM_{2.5}$ (6, 7), which may be partly associated with particle composition but also may be related to differences in personal exposure, spatial heterogeneity of constituents, and susceptibility patterns.

In this study, we characterized the differential toxicities of $PM_{2.5}$ constituents and associated uncertainty by reviewing the literature and conducting a large multisite time-series analysis. We examined the available epidemiologic studies to determine whether they supported any quantitative inferences given the requirements of risk assessments. We then conducted an updated analysis of a national data set for which Peng et al. (8) previously provided CRFs for multiple particle constituents, incorporating additional data, evaluating results by geographic region, and conducting new analyses deemed necessary for risk assessment. Our analysis included estimation of the joint posterior distribution of the short-term effects of individual constituents on cardiovascular and respiratory hospital admissions (CHA and RHA, respectively). Posterior samples from this joint posterior distribution allowed us to calculate relevant values for risk assessment, including posterior probabilities that individual constituents had greater short-term effects on CHA or RHA than other constituents or $PM_{2.5}$ as a whole.

MATERIALS AND METHODS

Literature review

In October 2010, we searched the Science Citation Index with the keywords "(PM2.5 *or* fine particulate matter) *and* health," a broad search criterion used to ensure that relevant studies were not missed. We reviewed the abstracts of all 1,338 articles found to identify primary epidemiologic studies that evaluated at least one of the following constituents: sulfate, nitrate, elemental carbon, and organic carbon matter. While multiple metals and other constituents could influence health, we focused on constituents that dominate $PM_{2.5}$ mass and are significantly correlated with $PM_{2.5}$, since only those constituents could explain the $PM_{2.5}$ epidemiology. Using these criteria, Peng et al. (8) included the above constituents, as well as silicon, sodium, and ammonium. However, silicon and sodium contributed little mass and were statistically insignificant, and ammonium could not be included in multiconstituent models with sulfate and nitrate, given high correlations.

From the 65 remaining studies, we excluded studies that did not provide adequate information with which to quantify a CRF for at least one constituent, including a lack of information on confidence intervals or concentration units. We also eliminated studies that used factor analysis or other approaches to derive source signatures, because such studies did not provide estimates for individual constituents. We took the remaining 42 studies to comprise the core epidemiologic literature for evaluating differential $PM_{2.5}$ toxicity.

We gathered the reported relative risks or effect estimates and their associated statistical uncertainty from each study, implicitly assuming linearity of CRFs across the range of concentrations observed in the 42 studies. We also extracted information on health outcomes, statistical methods (including whether the estimate had been derived from a model that included multiple constituents), and other factors relevant to comparing or pooling estimates across studies. For health outcomes and $PM_{2.5}$ constituents for which a sufficient number of publications existed, we performed inverse-variance weighted meta-analysis, accounting for between-study heterogeneity (9), and compared the resulting CRFs across constituents.

Multisite time-series analysis

We obtained billing claims information for US Medicare enrollees in 119 counties for the years 2000–2008, corresponding to the analysis by Peng et al. (8) but with 2 more years of data. The claims data did not include individually identifiable information, so we did not obtain consent from individual study participants. This study was reviewed and exempted by the institutional review board at the Harvard School of Public Health.

The Medicare billing claims data were classified into disease categories (e.g., cardiovascular disease) according to their *International Classification of Diseases*, Ninth Revision (ICD-9), codes. While claims information also includes age and gender, data were aggregated across these variables. We considered CHA (ICD-9 codes 390.xx–459.xx) and RHA (ICD-9 codes 464.xx–466.xx and 480.xx–487.xx).

As in the literature review, we considered sulfate, nitrate, elemental carbon, and organic carbon matter. Air pollution data were obtained from the Environmental Protection Agency's $PM_{2.5}$ Chemical Speciation Trends Network. Additional data for $PM_{2.5}$ concentrations were obtained from the agency's Air Quality System. All data were summarized and processed as described by Peng et al. (8).

Counties were analyzed separately, and county-level results were aggregated across large geographic regions using a Bayesian multivariate normal hierarchical model. Specifically, county-level time-series data were analyzed using log-linear Poisson regression models with overdispersion that used hospital admission counts as outcomes and particle constituents

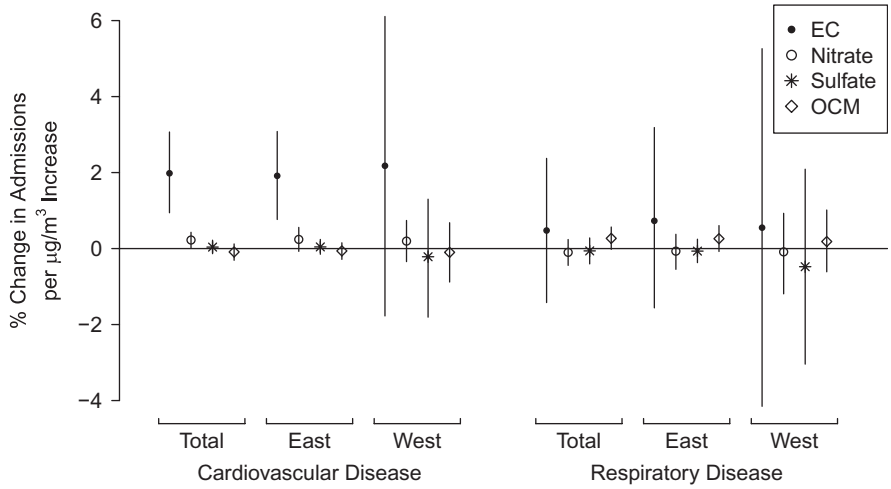

Figure 1. Percent change in hospital admissions per μg/m^3 increase in concentrations of fine particulate matter constituents, by region of the United States and disease, 2000–2008. Bars, 95% confidence interval. (EC, elemental carbon; OCM, organic carbon matter).

and potential confounders as dependent variables. More specifically, in each county-level model, we included 8 explanatory variable categories: 1) an offset of the log count of the at-risk population; 2) linear terms for sulfate, nitrate, elemental carbon, and organic carbon matter; 3) a smoothing spline for time ($t = 1$ for January 1, 2000, $t = 2$ for January 2, 2000, etc.) with 8 degrees of freedom (df) per year; 4) indicator variables for each day of the week; 5) a 6-df spline for temperature; 6) a 6-df spline for 3-day moving average of temperature; 7) a 3-df spline for average daily dew-point temperature; and 8) a 3-df spline for 3-day moving average of dew-point temperature. The splines in categories 5–8 were used to flexibly model the response function of the 4 confounding variables. Results were previously found to be insensitive to the number of degrees of freedom in these splines (8). We only considered lag 0 concentrations, in spite of prior evidence that some constituent-outcome pairs had greater effects at lag 1 or 2 (8), because of concerns about multiple comparisons and statistical challenges in including multiple lag terms given 1-in-6-day sampling and our multi-constituent modeling approach.

Table 1. Pairwise Posterior Probability that a Particular Constituent of $PM_{2.5}$ Had Greater Toxicity than Other Constituents, Expressed as Beta Coefficient per Unit Change in Concentration, United States, 2000–2008[a]

	Cardiovascular Hospital Admissions				Respiratory Hospital Admissions			
	Nitrate	Sulfate	Organic Carbon Matter	$PM_{2.5}$	Nitrate	Sulfate	Organic Carbon Matter	$PM_{2.5}$
All 119 US counties								
Elemental carbon	0.999	1.000	1.000	1.000	0.710	0.719	0.576	0.669
Nitrate		0.890	0.977	0.940		0.447	0.055	0.194
Sulfate			0.802	0.427			0.125	0.253
Organic carbon matter				0.094				0.924
Eastern counties ($n = 98$)								
Elemental carbon	0.996	0.999	0.999	0.999	0.740	0.742	0.641	0.712
Nitrate		0.827	0.924	0.870		0.496	0.124	0.280
Sulfate			0.750	0.435			0.096	0.203
Organic carbon matter				0.131				0.869
Western counties ($n = 21$)								
Elemental carbon	0.850	0.874	0.852	0.868	0.613	0.658	0.558	0.593
Nitrate		0.692	0.740	0.718		0.602	0.342	0.411
Sulfate			0.436	0.345			0.286	0.330
Organic carbon matter				0.324				0.675

Abbreviation: $PM_{2.5}$, particulate matter less than 2.5 μm in diameter.
[a] Each value represents the probability that the row constituent is more toxic than the column constituent.

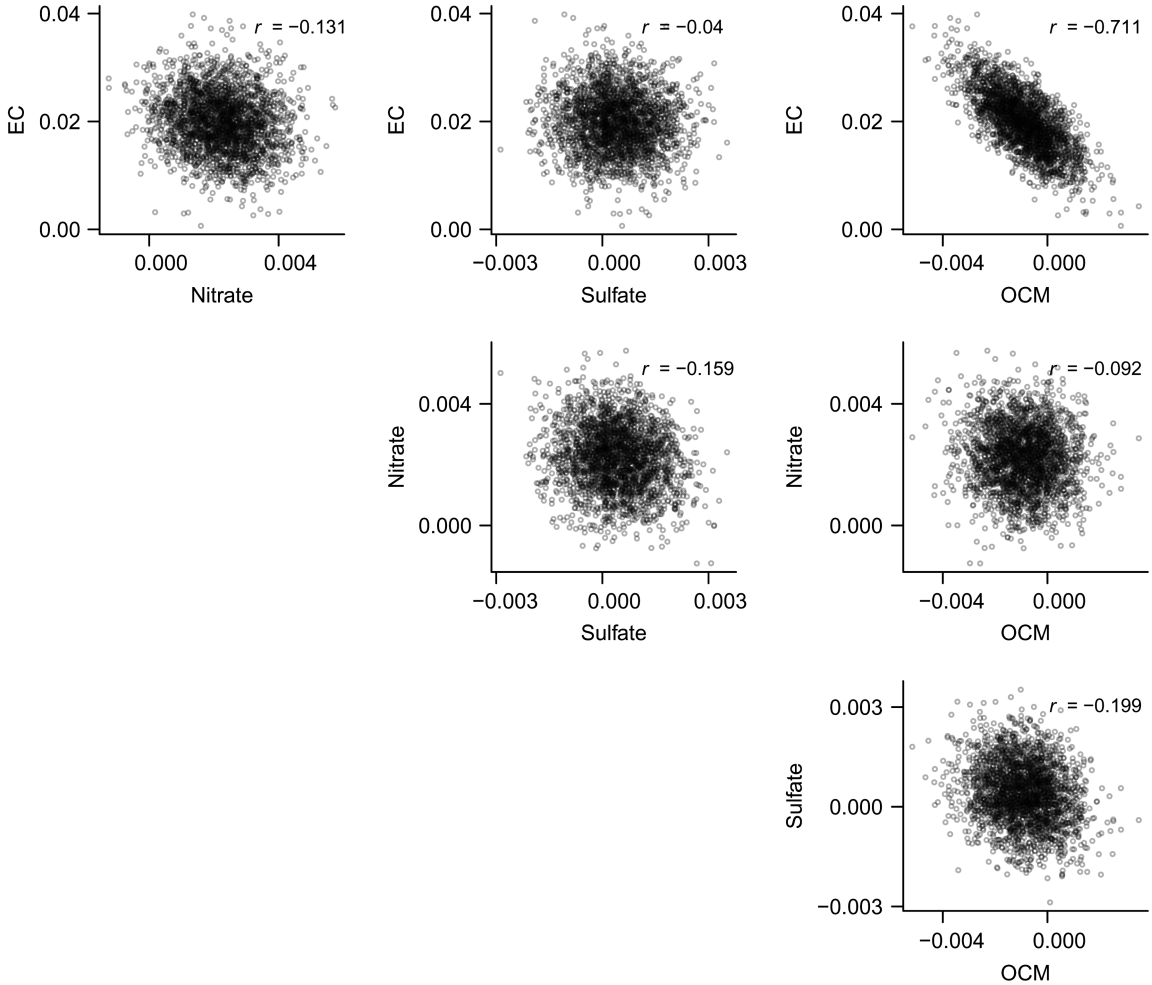

Figure 2. Scatterplots and correlations of posterior samples of beta coefficients per unit change in concentrations of fine particulate matter constituents for cardiovascular hospital admissions across the United States, 2000–2008. (EC, elemental carbon; OCM, organic carbon matter).

Within each county-level analysis, we obtained the point estimates of the short-term effects of the 4 constituents, $\widehat{\beta}^c = (\widehat{\beta}^c_A, \widehat{\beta}^c_B, \widehat{\beta}^c_C, \widehat{\beta}^c_D)$, and the associated covariance matrix V^c. These results were aggregated across counties using the following Bayesian multivariate hierarchical modeling:

$$\widehat{\beta}^c \,|\, \beta^c, V^c \sim N(\beta^c, V^c)$$

$$\beta^c \,|\, \beta, \textstyle\sum \sim N(\beta, \textstyle\sum),$$

where $\beta^c = (\beta^c_A, \beta^c_B, \beta^c_C, \beta^c_D)$ is the vector of the true county-specific health effects, $\beta = (\beta_A, \beta_B, \beta_C, \beta_D)$ is the vector of the true overall health effects, and Σ is the covariance matrix of the β^c across counties. The hierarchical model defined above was fitted using TLNise 2-level normal independence sampling estimation software (10). We pooled the county-specific results separately for the West and the East (as defined by 100°W longitude) and nationally. TLNise provided 1) samples from the joint posterior distribution of the health effects of the 4 constituents, denoted by $p(\beta_A, \beta_B, \beta_C, \beta_D|\text{data})$, and 2) samples from the posterior distribution of the 4×4 covariance matrix, denoted by $p(\Sigma|\text{data})$. Posterior samples from $p(\beta_A, \beta_B, \beta_C, \beta_D|\text{data})$ allowed us to calculate 1) the posterior probability that $\beta_i \geq \beta_j$; 2) posterior correlations between each pair of health effects $\text{Cor}(\beta_i, \beta_j)$; and 3) the posterior distribution of toxicity ratios $\beta_i|\beta_j$. Posterior samples $p(\Sigma|\text{data})$ allowed us to calculate 1) the posterior distribution of the variance across counties of each parameter $(\text{Var}(\beta^c_i))$ and 2) the posterior distribution of the correlation across counties of each pair of health effects $\text{Cor}(\beta^c_i, \beta^c_j)$. Separate county-level models were also fitted with a linear term for $PM_{2.5}$ concentration replacing the terms representing the constituents. The posterior probability that constituent A is more toxic than or equally as toxic as $PM_{2.5}$ was computed as the fraction of posterior samples from the 2 separate models, where $\beta_A \geq \beta_{PM2.5}$. Statistical analyses were performed using R, version 2.11.1 (R Development Core Team, 2010; R Foundation for Statistical Computing, Vienna, Austria).

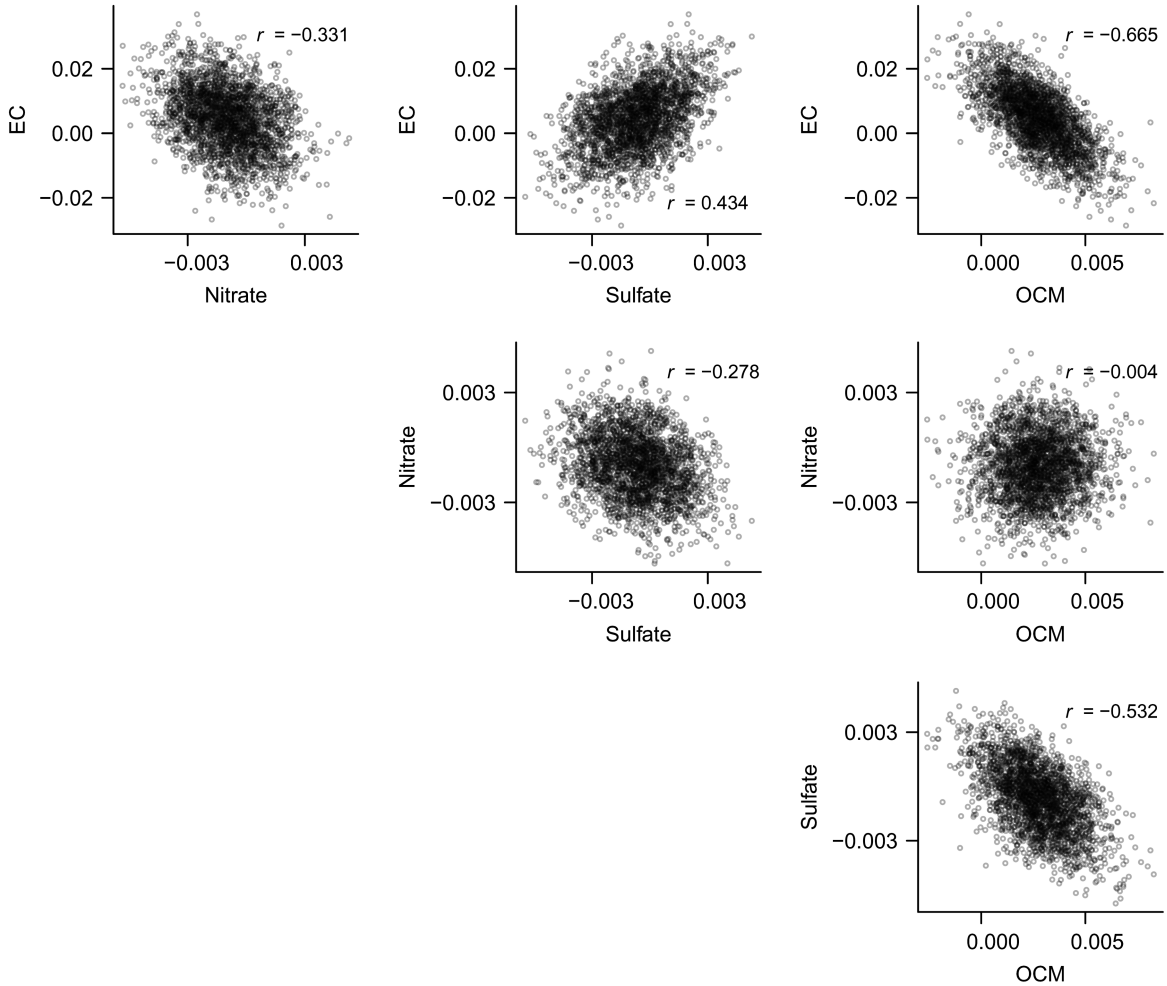

Figure 3. Scatterplots and correlations of posterior samples of beta coefficients per unit change in concentrations of fine particulate matter constituents for respiratory hospital admissions across the United States, 2000–2008. (EC, elemental carbon; OCM, organic carbon matter).

RESULTS

For the 42 studies identified within the literature review (8, 11–51), there was substantial heterogeneity in health outcomes, constituents included, geographic locations, and statistical methods (see Web Appendix and Web Tables 1–8, which appear on the *Journal*'s website (http://aje.oxfordjournals.org/)). While the majority of studies addressed elemental carbon or sulfate, fewer than half considered organic carbon matter or nitrate. For those studies evaluating elemental carbon, some used coefficient of haze as the exposure metric, while others used black smoke, black carbon, or elemental carbon, complicating joint interpretation of estimates. Only 8 studies provided quantitative estimates for all 4 constituents, including the previous national-scale Medicare assessment and studies in Atlanta and California (8, 21, 27, 29, 38–41). The reported effect estimates were almost all from single-constituent models (which may have adjusted for gaseous pollutants and other confounders but only included 1 particle constituent at a time). A few investigators did construct multiconstituent models, but quantitative results were generally not reported or were presented for a subset of constituents.

The largest numbers of CRFs were available for all-cause mortality from time-series studies, although only one of these studies reported multiconstituent CRFs. In spite of the limitations of these estimates (including the possibility that some CRFs could be overestimated), we quantitatively pooled the single-constituent model estimates to illustrate some of the challenges in determining differential CRFs from the current literature.

Pooling the 11 all-cause time-series mortality estimates (Web Table 1) yielded an estimated 1.2% increase in mortality per 10-$\mu g/m^3$ increase in $PM_{2.5}$ concentrations (95% confidence interval (CI): 0.5, 1.9). Only 4 of these studies provided estimates for elemental carbon with concentration measured in $\mu g/m^3$ (rather than coefficient of haze units). There were 2 estimates for organic carbon matter, 11 for sulfate, and 4 for nitrate. Pooled analyses for the individual constituents yielded estimates of 0.4% (95% CI: −0.4, 1.2), 1.4%

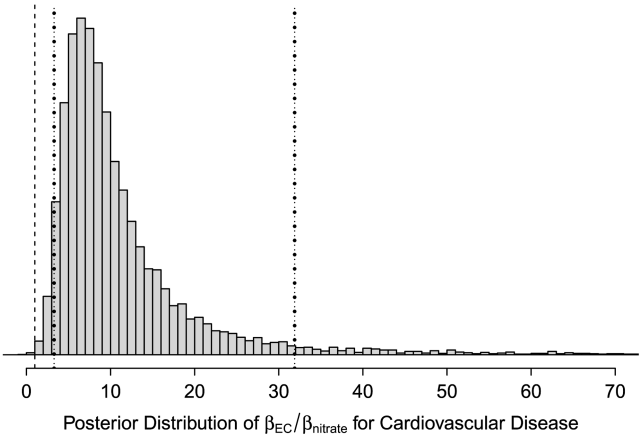

Figure 4. An example (elemental carbon (EC) vs. nitrate) of a posterior distribution of toxicity ratios for cardiovascular hospital admissions across the United States, 2000–2008. Also shown are the second percentile ($x = 1$; dashed line), the fifth percentile ($x = 3.3$; left dotted line), and the 95th percentile ($x = 31.9$; right dotted line) of the posterior distribution.

(95% CI: −0.9, 3.7), 2.8% (95% CI: 0.9, 4.6), and 2.7% (95% CI: −0.7, 6.1) per 10-μg/m^3 increase in elemental carbon, organic carbon matter, sulfate, and nitrate concentrations, respectively. Based on the central estimates only, these data would seem to imply that organic carbon matter, sulfate, and nitrate are more toxic per unit of concentration than $PM_{2.5}$ as a whole.

However, focusing solely on the central estimates does not appropriately represent the evidence. Information is not available in the literature for quantifying the probabilities that individual constituents had greater CRFs than other constituents. Even if we restrict the analysis to pairwise comparisons (i.e., looking at the 4 studies with estimates for both elemental carbon and $PM_{2.5}$ to determine whether the pooled estimates differ), without knowing the correlations among CRFs, we can do little other than examine central estimates. For these pairwise comparisons, elemental carbon, sulfate, and nitrate all have central estimates greater than that for $PM_{2.5}$, with a slightly lower central estimate for organic carbon matter than for $PM_{2.5}$. Given that these 4 constituents contribute approximately two-thirds of $PM_{2.5}$ mass nationally (52), and close to 80% if ammonium is included, it is unlikely that all 4 have comparable or greater toxicity than $PM_{2.5}$.

The earlier analysis of the Medicare database (8) was the only study to provide any probabilistic insight about differential toxicity, but Peng et al. only reported the posterior probability that elemental carbon had a larger coefficient than the average of the other constituents for CHA. Therefore, the published literature does not provide the necessary information for incorporating differential toxicity into risk assessment, necessitating new analyses.

In our multisite time-series analysis, we estimated the percent change in CHA and RHA associated with a 1-μg/m^3 increase in each of the 4 constituents, aggregated to national and regional levels (Figure 1). Elemental carbon concentrations are strongly associated with changes in CHA. Elemental carbon also has the largest central estimate per unit change in concentration for RHA, although organic carbon matter has a greater impact per interquartile-range change in concentrations and greater statistical significance.

Table 1 shows the pairwise probabilities that each constituent has greater toxicity than another per unit of concentration change. There is a high posterior probability that elemental carbon is more toxic than other constituents (>0.99) for CHA nationally and in the East, with lower probabilities in the West. Comparisons among other constituents are more equivocal. For RHA, the probabilities are closer to 0.5, with the highest probabilities being seen for organic carbon matter in comparison with nitrate and sulfate. Table 1 also provides the posterior probabilities that each constituent is more toxic than $PM_{2.5}$ as a whole. For example, for CHA nationally, there are high probabilities that elemental carbon and nitrate have greater toxicity than $PM_{2.5}$ (1 and 0.940, respectively), a low probability (0.094) that organic carbon matter has greater toxicity than $PM_{2.5}$, and approximately equal probabilities that sulfate has greater or lesser toxicity than $PM_{2.5}$.

Our analyses also provide posterior correlations between CRFs for CHA (Figure 2) and RHA (Figure 3). Coupled with the posterior distributions from multiconstituent models in Figure 1, this would allow for the CRFs to be incorporated into risk assessments. The posterior samples also allow us to characterize the ratios of CRFs for different constituents, which have often been used to incorporate differential toxicity in risk assessments. Figure 4 provides the posterior distribution of the ratio of CRFs for elemental carbon versus nitrate for CHA. The nonnormality, skew, and long tails are immediately apparent. All distributions of toxicity ratios were quite uncertain, even when posterior probabilities of differential toxicity were close to 1.

DISCUSSION

Our 2-pronged approach toward evaluating the differential toxicity of particle constituents provided some helpful insights and illustrated some barriers. First, our review showed that the present literature generally lacks multiconstituent models and other information necessary to determine the probability of differential toxicity. This may be due to statistical power issues and the fact that the goal of many investigations was to determine which constituents are more strongly associated with health outcomes, rather than to quantify their relative toxicity. In the absence of changes in how particle constituent epidemiology is generally conducted, even the expansion of this literature over time would not resolve the question of differential toxicity within risk assessment.

To our knowledge, our extended analysis of the national Medicare database is the largest multisite time-series analysis of $PM_{2.5}$ constituents to have been conducted to date. We followed a multiconstituent modeling approach and applied the statistical methods necessary to determine correlations among CRFs and posterior probabilities of toxicity differences, providing the core information for risk assessment. We found some evidence of toxicity differences that vary by health outcome, with more limited evidence supporting geographic variability,

partly because of statistical power issues in the West. In contrast, the primary approach for including differential toxicity in risk assessment to date has been assumptions that one constituent is *X* times more toxic than another (53, 54), applied as point estimates without formal consideration of the appreciable uncertainties that would exist. The ratios of 2 uncertain distributions will have even greater uncertainties—a well-described phenomenon in statistics and comparative risk assessment (55, 56)—but this has not been discussed in the context of $PM_{2.5}$.

Although there are significant uncertainties in the probabilistic comparisons, epidemiology needs to provide the foundation for any differential toxicity analysis used in $PM_{2.5}$ health risk assessments, given the need to quantify and potentially monetize specific health outcomes (e.g., emergency room visits). That having been said, creative approaches for incorporating insight from toxicology should be considered, including using toxicologic evidence as informative priors in a Bayesian analysis.

A few limitations within our extended Medicare analysis should be acknowledged. First, as described previously (8), we were limited by 1-in-6-day sampling and by the nonuniform distribution of speciation monitors. Second, our results could be affected by exposure measurement error due to the spatial variability of the ambient concentrations of each constituent within each county. Lastly, there may have been some error due to spatial misalignment and aggregation of the data, given that most counties have just 1 or 2 monitors (57).

In addition, the specific probabilities ascertained in our analysis should not be directly extrapolated to other health outcomes. The relative influence of different constituents may differ for acute responses versus chronic responses, and there could be differences across diseases and at-risk populations. Lack of statistical significance for specific constituents and endpoints should also be interpreted in the context of the broader literature, especially for RHA, for which rates are lower and statistical power is reduced in comparison with CHA. Interpretation of the effects of sulfate and nitrate is complicated by the strong association with ammonium. In the prior analysis of the Medicare data set, ammonium was associated with CHA, which likely reflects effects of correlated constituents like sulfate and nitrate (8). We excluded ammonium given our multiconstituent focus, which may have reduced our ability to characterize secondary inorganic aerosols. Our focus on lag 0 effects may have underestimated impacts, given prior evidence that organic carbon matter influences CHA at lag 1 and sulfate influences RHA at lags 1 and 2 (8). Finally, our analysis defined differential toxicity by the CRF for each constituent, "adjusted" for exposure to other constituents and time-varying confounders. While this matches most risk assessments, burden-of-disease studies may be more concerned with the effects per interquartile range, which would yield different conclusions and avoid complications related to variable contributions to mass.

In spite of these challenges, our methods are generalizable and could be applied within other data sets, and our findings provide helpful insights for future $PM_{2.5}$ risk assessments and epidemiologic investigations. The methods we applied to estimate posterior probabilities of differential toxicity and correlations among CRFs could have been used in many previous studies. Posterior samples from the joint posterior distribution of the short-term effects of each constituent from a multiconstituent model can provide the necessary information to conduct risk assessments and appropriately account for significant correlations among constituents that exist in some settings. The lack of such applications may have reflected a lack of recognition among epidemiologists of the value of these calculations and among risk assessors that such information could be generated. Most risk assessments involve post hoc interpretation of the literature, often making assumptions necessitated by the limited information provided. More direct communication between risk assessors and epidemiologists could enhance the utility of epidemiologic evidence in risk assessment, especially for criteria air pollutants, where epidemiology is paramount.

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