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Original Contribution

Individual-Level Concentrations of Fine Particulate Matter Chemical Components and Subclinical Atherosclerosis: A Cross-Sectional Analysis Based on 2 Advanced Exposure Prediction Models in the Multi-Ethnic Study of Atherosclerosis

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Long-term exposure to outdoor particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) has been associated with cardiovascular morbidity and mortality. The chemical composition of $PM_{2.5}$ that may be most responsible for producing these associations has not been identified. We assessed cross-sectional associations between long-term concentrations of $PM_{2.5}$ and 4 of its chemical components (sulfur, silicon, elemental carbon, and organic carbon (OC)) and subclinical atherosclerosis, measured as carotid intima-media thickness (CIMT) and coronary artery calcium, between 2000 and 2002 among 5,488 Multi-Ethnic Study of Atherosclerosis participants residing in 6 US metropolitan areas. Long-term concentrations of $PM_{2.5}$ components at participants' homes were predicted using both city-specific spatiotemporal models and a national spatial model. The estimated differences in CIMT associated with interquartile-range increases in sulfur, silicon, and OC predictions from the spatiotemporal model were 0.022 mm (95% confidence interval (CI): 0.014, 0.031), 0.006 mm (95% CI: 0.000, 0.012), and 0.026 mm (95% CI: 0.019, 0.034), respectively. Findings were generally similar using the national spatial model predictions but were often sensitive to adjustment for city. We did not find strong evidence of associations with coronary artery calcium. Long-term concentrations of sulfur and OC, and possibly silicon, were associated with CIMT using 2 distinct exposure prediction modeling approaches.

atherosclerosis; cardiovascular diseases; carotid intima-media thickness; cohort studies; particulate matter

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; CIMT, carotid intima-media thickness; EC, elemental carbon; IQR, interquartile range; MESA, Multi-Ethnic Study of Atherosclerosis; MESA Air, Multi-Ethnic Study of Atherosclerosis and Air Pollution; NPACT, National Particle Component Toxicity; OC, organic carbon; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm.

There is good evidence for an association between long-term exposure to particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$), also called fine participate matter, and cardiovascular events (1–3). Because atherosclerosis may be an underlying cause, there has been interest in using subclinical measures of atherosclerosis such as carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) to study the association. CIMT is related to cardiovascular risk factors (4, 5) and incident cardiovascular diseases, including myocardial infarction and stroke (6–9). Higher annual average $PM_{2.5}$ concentrations have been associated with increased CIMT in the United States and Germany (10–14). CAC is also related to cardiovascular risk factors (15) and incident cardiovascular diseases (16–18). CAC has not been found to be associated with long-term $PM_{2.5}$ concentrations (12) but was found to be associated with proximity to traffic in Germany (19).

Because $PM_{2.5}$ is a complex mixture of a large number of chemical species emitted from various pollution sources, there has been a call for research to gain insight into the chemical components of $PM_{2.5}$ that could be responsible for the association with cardiovascular outcomes (20). Most observational studies of $PM_{2.5}$ components and cardiovascular health have assessed associations between short-term exposures and mortality or morbidity using the time-series design (21–23). Associations with long-term exposures to $PM_{2.5}$ chemical components have been examined in a few studies that focused on mortality (24–26). Recently, we considered associations of 4 $PM_{2.5}$ components with subclinical measures of atherosclerosis using common and relatively simple exposure prediction approaches, including area-averaging, nearest-monitor, and inverse-distance-weighting methods, in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort as part of the National Particle Component Toxicity (NPACT) Initiative (27, 28). We found that sulfur and organic and elemental carbon were associated with increased CIMT.

In the present study, we examined the cross-sectional associations of long-term $PM_{2.5}$ component concentrations at MESA cohort participants' residences with CIMT and CAC using advanced exposure prediction approaches from 2 distinct models: a spatiotemporal model and a national spatial model (29, 30). Administrative monitoring data commonly used in studies that assess associations between air pollution and health are particularly limited for $PM_{2.5}$ components as compared with other pollutants such as total $PM_{2.5}$ and oxides of nitrogen in a given study area (31). This limitation in the monitoring data has been identified as a challenge for epidemiologic studies of $PM_{2.5}$ components (32). To overcome this limitation, the NPACT study (28) obtained $PM_{2.5}$ component measurements from a monitoring campaign focusing on MESA participants in the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). These data were used in developing the city-specific spatiotemporal models, while national administrative monitoring data were used for our national spatial model. This allowed for assessment of the consistency of the findings across 2 exposure prediction models.

Of the many $PM_{2.5}$ components measured in NPACT, we specifically focused on 4 that we considered to reflect important sources of $PM_{2.5}$. Elemental carbon (EC) and organic carbon (OC) were chosen as markers of primary emissions from combustion processes, with OC in addition including contributions from organic aerosols formed secondarily from atmospheric chemical reactions; silicon was chosen as a marker of crustal dust; and sulfur was chosen as a marker of sulfate, an inorganic aerosol formed from atmospheric chemical reactions, primarily reactions with sulfur dioxide.

METHODS

MESA cohort and measures of subclinical atherosclerosis

MESA recruited 6,814 participants aged 45–84 years without preexisting clinically apparent cardiovascular disease on a population basis in 6 US metropolitan areas: Los Angeles, California; Chicago, Illinois; Minneapolis-St. Paul, Minnesota; Baltimore, Maryland; New York, New York; and Winston-Salem, North Carolina (33). These participants underwent the first MESA examination (examination 1) between 2000 and 2002. CIMT was measured by B-mode ultrasound using a General Electric Logiq scanner (GE Healthcare, Little Chalfont, United Kingdom). An image acquisition and analysis protocol was followed in order to obtain reproducible intima-media thickness measurements of the common carotid artery (5). The transducer was positioned relative to the patient's neck and artery in a consistent location defined by the plane of the internal jugular vein as it lines up on the top of the common carotid artery. The mean CIMT of the right far common carotid wall from examination 1 was used for the analyses. CAC was measured using cardiac-gated electron-beam computed tomography or retrospectively gated multidetector-row computed tomography. Calibration of the CAC scores in MESA was performed by scanning torso phantoms with each scanner regularly. Two scans were obtained for each participant; the mean Agatston score of the 2 scans was used. The presence of CAC was defined as an Agatston score greater than zero. Continuous CAC values were log-transformed because of their right-skewed distribution.

Geocoding

The residential addresses of MESA participants who consented to use of their addresses were geocoded according to standardized procedures. Geocoded locations of MESA Air and agency monitoring sites were obtained from geocoding and hand-held global positioning system devices and from agency sources, respectively.

Exposure prediction modeling approach

The 2 exposure prediction modeling approaches have been described in detail elsewhere (28–30). $PM_{2.5}$ component monitoring data used for the 2 models are also described in published papers (28, 31) and in the Web Appendix (available at http://aje.oxfordjournals.org/). The spatiotemporal model for each of the $PM_{2.5}$ components used 2-week samples collected from the NPACT/MESA Air fixed and home-outdoor sites and was constructed separately for each city. In this model, we assumed that the 2-week average component concentration consists of a spatially varying long-term mean, a spatially varying single temporal trend, and spatially varying but temporally independent spatiotemporal residuals. Each of these 3 model components was modeled in a universal kriging framework that included a mean model characterized by land-use regression using selected geographical variables and a variance model characterized by a covariance function (34). Annual averages of predicted $PM_{2.5}$ component concentrations at baseline participant addresses were computed for 1 year from May 2007 to April 2008 when data on all 4 $PM_{2.5}$ components were available.

The national spatial model used annual averages of $PM_{2.5}$ component concentrations for 2009 and 2010 from the Environmental Protection Agency's Chemical Speciation Network and the Interagency Monitoring of Protected Visual

Table 1. Subclinical Atherosclerosis-Related, Individual, and Biological Characteristics of 5,488 Multi-Ethnic Study of Atherosclerosis Participants in 6 US Metropolitan Areas at Examination 1, 2000–2002

Variable	Mean (SD)	No. of Participants	%[a]
Subclinical atherosclerosis			
Carotid intima-media thickness, mm	0.68 (0.19)		
Presence of CAC[b]		2,683	48.9
No CAC		2,805	51.1
CAC Agatston score[c]	281.7 (519.4)		
Individual characteristics			
Age, years	61.9 (10.1)		
Sex			
Female		2,868	52.3
Male		2,620	47.7
Race/ethnicity			
White or Caucasian		2,179	39.7
Chinese-American		671	12.2
Black or African-American		1,450	26.4
Hispanic		1,188	21.6
Study site			
Winston-Salem, North Carolina		892	16.3
New York, New York		855	15.6
Baltimore, Maryland		774	14.1
Minneapolis-St. Paul, Minnesota		897	16.3
Chicago, Illinois		999	18.2
Los Angeles, California		1,071	19.5
Education			
Incomplete high school		906	16.5
Complete high school		988	18.0
Some college		1,567	28.6
Complete college		2,014	36.7
Annual income			
<$12,000		561	10.2
$12,000–24,999		1,016	18.5
$25,000–49,999		1,532	27.9
$50,000–74,999		903	16.5
≥$75,000		1,279	23.3
Smoking status			
Never smoker		2,760	50.3
Former smoker		2,021	36.8
Current smoker		695	12.7
Hypertension			
No		3,099	56.5
Yes		2,389	43.5
Diabetes			
Normal		4,080	74.3
Impaired fasting glucose		745	13.6
Untreated diabetes		139	2.5
Treated diabetes		510	9.3
Lipid-lowering medication use			
No		4,594	83.7
Yes		891	16.2
Statin use			
No		4,670	85.1
Yes		815	14.9
Biological characteristics			
Waist circumference, cm	97.8 (14.1)		
Body surface area	1.9 (0.2)		
Body mass index[d]	28.2 (5.3)		
Total cholesterol, mg/dL	194.3 (35.3)		
HDL cholesterol, mg/dL	51.1 (14.7)		
LDL cholesterol, mg/dL	117.3 (31.0)		
Triglycerides, mg/dL	130.7 (85.2)		

Abbreviations: CAC, coronary artery calcium; HDL, high density lipoprotein; LDL, low density lipoprotein; SD, standard deviation.

[a] Missing data were included in the denominator when percentages were calculated.

[b] Defined as an Agatston score greater than zero.

[c] Computed for 2,683 (48.9%) people who had CAC measurements greater than zero.

[d] Weight (kg)/height $(m)^2$.

Environments (IMPROVE) Program. We constructed the single national spatial model in a universal kriging framework along with spatial predictors estimated by partial least squares and a specified covariance function and predicted annual average concentrations at MESA participants' homes in all 6 study areas. We restricted the prediction area to participants living within 10 km of any NPACT monitors to avoid extrapolation. Predicted sulfur dioxide and nitrogen dioxide levels used for adjustment in our health model were also obtained using the national modeling approach (28).

Statistical analysis

We used multiple linear regression models to investigate the associations of CIMT and log-transformed CAC with long-term concentrations of $PM_{2.5}$ and 4 $PM_{2.5}$ components predicted from the spatiotemporal and national spatial models. Since approximately 50% of the cohort had no measureable CAC at baseline, we conducted 2 separate analyses: 1) a linear regression of log-transformed CAC among persons with measureable CAC and 2) a relative risk regression for the presence of CAC (35). Although associations with

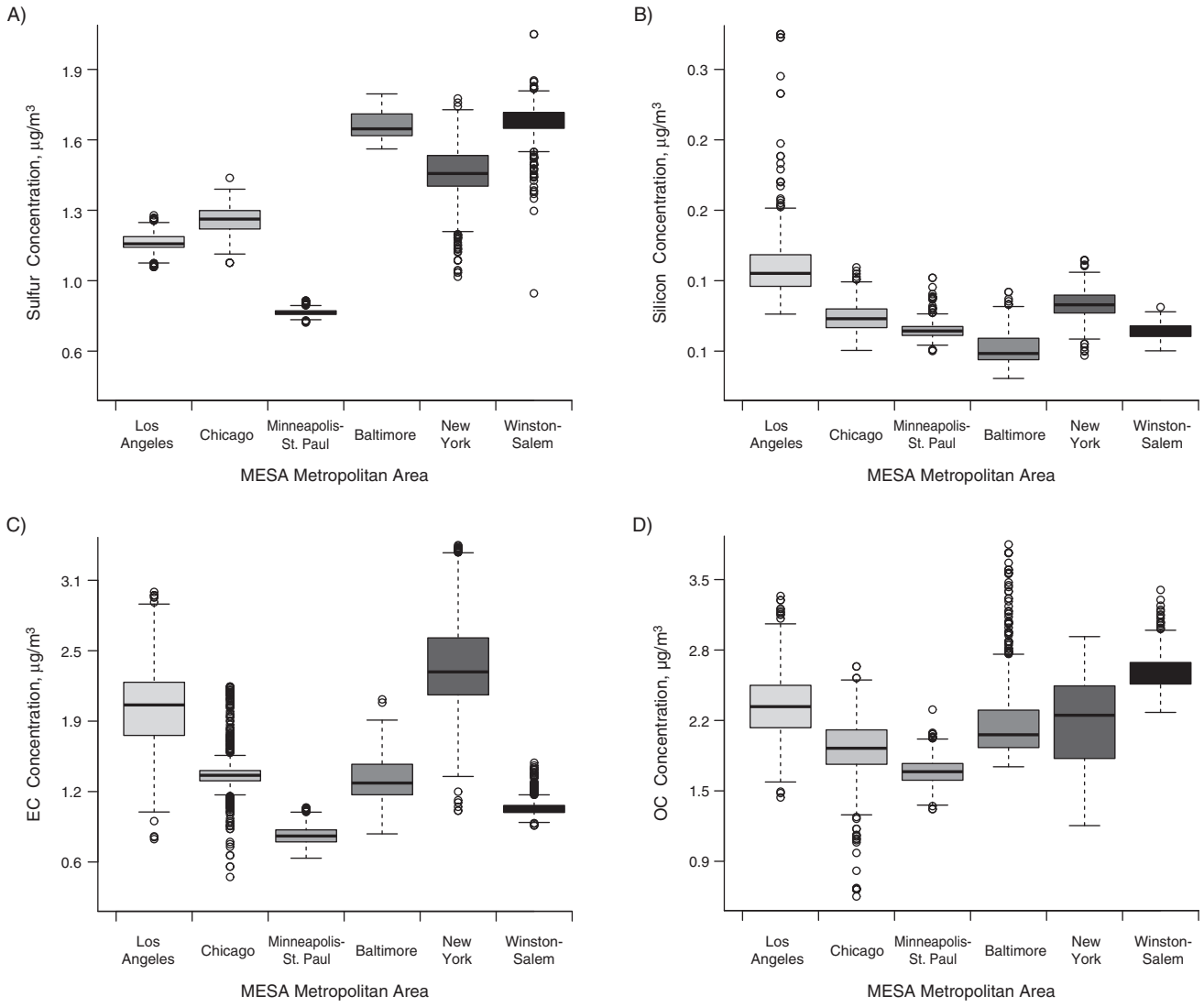

Figure 1. Predicted long-term concentrations of 4 components of particulate matter with an aerodynamic diameter less than or equal to 2.5 µm (sulfur (A), silicon (B), elemental carbon (EC) (C), and organic carbon (OC) (D)) at Multi-Ethnic Study of Atherosclerosis (MESA) participants' homes from a spatiotemporal model in 6 US metropolitan areas (Los Angeles, California; Chicago, Illinois; Minneapolis-St. Paul, Minnesota; Baltimore, Maryland; New York, New York; and Winston-Salem, North Carolina).

$PM_{2.5}$ were not of primary interest, we included $PM_{2.5}$ predictions (36, 37) to allow comparison of associations with those of the $PM_{2.5}$ components.

We examined 4 confounder models with a progressively larger number of covariates. Model 1, a minimally adjusted model, included terms for age, sex, and race/ethnicity. Model 2, our primary model, added terms based on the Framingham Risk Score (38), corresponding to the covariates used in the previous study for $PM_{2.5}$ components and subclinical atherosclerosis (27): total cholesterol, high-density lipoprotein cholesterol, smoking status, hypertension, and use of lipid-lowering medication. In model 3, variables considered potential confounders but not chosen for our primary model were added. This extended set of variables included education, income, waist circumference, body surface area, body mass index (weight (kg)/height $(m)^2$), squared body mass index, diabetes, low-density lipoprotein cholesterol, and triglycerides. In model 4, we added indicator variables for metropolitan area to our primary model (model 2). In the sensitivity analysis, we additionally adjusted for $PM_{2.5}$, other $PM_{2.5}$ components, and gaseous pollutants such as sulfur dioxide and nitrogen dioxide in 2-pollutant models. We also examined the sensitivity of our findings to exclusion of statin users, restriction of our prediction area to 5 km and 2 km from any MESA Air monitoring sites, and adjustment for neighborhood socioeconomic status using percentage of poverty by census tract area (39). We present measures of association for an interquartile-range (IQR) increase in the concentration

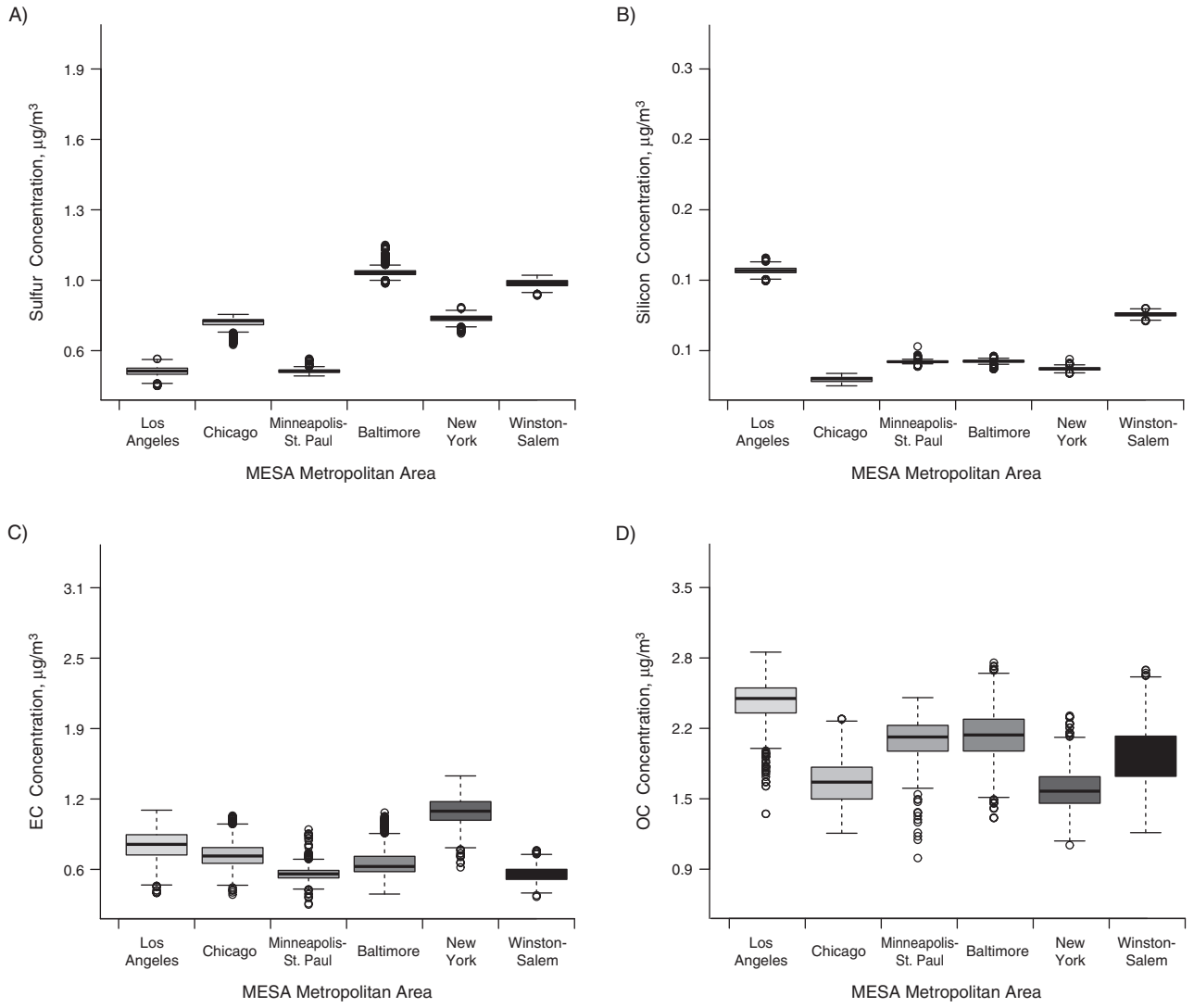

Figure 2. Predicted long-term concentrations of 4 components of particulate matter with an aerodynamic diameter less than or equal to 2.5 µm (sulfur (A), silicon (B), elemental carbon (EC) (C), and organic carbon (OC) (D)) at Multi-Ethnic Study of Atherosclerosis (MESA) participants' homes from a national spatial model in 6 US metropolitan areas (Los Angeles, California; Chicago, Illinois; Minneapolis-St. Paul, Minnesota; Baltimore, Maryland; New York, New York; and Winston-Salem, North Carolina).

of each pollutant from each of the 2 exposure prediction models to allow comparison of findings between pollutants and exposure models.

RESULTS

Table 1 shows summary statistics for individual characteristics, CIMT, and CAC for 5,488 of the 6,814 MESA examination 1 participants who lived within the prediction area and had CAC and CIMT measures. Participants had a mean age of 62 (standard deviation, 10.1) years, included 52% females, and were 40% Caucasian, 26% African-American, 22% Hispanic, and 12% Chinese-American. Forty-four percent had hypertension, 12% had diabetes, and 15% currently used a statin drug. The mean CIMT was 0.68 (standard deviation, 0.19) mm. The 49% of participants with Agatston scores greater than zero had a mean Agatston score of 281.7 (standard deviation, 519.4) Agatston units. Web Table 1 shows that the characteristics of the 1,326 participants excluded, mostly due to no CIMT measurements, were generally similar to those of the 5,488 included participants.

Web Figure 1 shows the maps of $PM_{2.5}$ component monitoring sites and MESA examination 1 participants' residences in the 6 MESA cities. Predicted concentrations of the 4 $PM_{2.5}$ components from the 2 prediction models had similar distributions across the 6 cities, with generally larger between-city variability than within-city variability (Figures 1 and 2 and Web Figure 2), with the exception of OC. Concentrations from the spatiotemporal model were generally higher than those from the national spatial model (Figures 1

Table 2. Predicted Long-Term Concentrations of Particulate Matter Less Than 2.5 μm in Diameter and 4 of Its Components From Spatiotemporal and National Spatial Models Among 5,488 Multi-Ethnic Study of Atherosclerosis Participants in 6 US Metropolitan Areas at Examination 1, 2000–2002

Prediction Model and Pollutant	Pollutant Level, μg/m^3			
	Minimum	Median (IQR)	Maximum	Mean (SD)
Spatiotemporal model				
$PM_{2.5}$	10.27	14.04 (1.51)	17.27	13.80 (1.44)
Sulfur	0.76	1.28 (0.51)	2.10	1.32 (0.32)
Silicon	0.06	0.10 (0.02)	0.31	0.11 (0.02)
EC	0.48	1.37 (0.88)	3.45	1.52 (0.58)
OC	0.58	2.13 (0.69)	3.81	2.16 (0.41)
National spatial model				
$PM_{2.5}$	8.35	10.38 (2.00)	13.13	10.81 (1.09)
Sulfur	0.46	0.77 (0.39)	1.12	0.74 (0.18)
Silicon	0.06	0.08 (0.04)	0.15	0.09 (0.03)
EC	0.29	0.69 (0.31)	1.45	0.75 (0.22)
OC	1.00	2.01 (0.54)	2.89	2.00 (0.35)

Abbreviations: EC, elemental carbon; IQR, interquartile range; OC, organic carbon; $PM_{2.5}$, particulate matter less than 2.5 μm in diameter; SD, standard deviation.

and 2). Average long-term concentrations of $PM_{2.5}$, sulfur, silicon, EC, and OC from the spatiotemporal model were 13.8 μg/m^3, 1.3 μg/m^3, 0.1 μg/m^3, 1.5 μg/m^3, and 2.2 μg/m^3, respectively; those from the national spatial model were 10.8 μg/m^3, 0.7 μg/m^3, 0.1 μg/m^3, 0.8 μg/m^3, and 2.0 μg/m^3, respectively (Table 2).

Figures 3 and 4, Web Table 2, and Web Figure 3 present measures of association for the relationship between IQR increases in $PM_{2.5}$ and $PM_{2.5}$ component predictions and CIMT, log(CAC), and the presence of CAC from the 4 confounder models. IQR increases in $PM_{2.5}$, sulfur, silicon, EC, and OC predictions were 1.51 μg/m^3, 0.51 μg/m^3, 0.02 μg/m^3, 0.88 μg/m^3, and 0.69 μg/m^3 for the spatiotemporal model, respectively, and 2.00 μg/m^3, 0.39 μg/m^3, 0.04 μg/m^3, 0.31 μg/m^3, and 0.54 μg/m^3 for the national spatial model, respectively. In our primary health model (model 2), IQR increases in sulfur and OC from the spatiotemporal model were associated with 0.022-mm (95% confidence interval (CI): 0.014, 0.031) and 0.026-mm (95% CI: 0.019, 0.034) increases in CIMT, respectively, while an IQR increase in silicon was associated with a borderline increase of 0.006 mm (95% CI: 0.000, 0.012) (Figure 3). The findings were broadly similar in analyses using the national spatial model predictions (Figure 4), with the exception that silicon measures of association were larger; IQR increases in sulfur, silicon, and OC were associated with 0.016-mm (95% CI: 0.004, 0.028), 0.023-mm (95% CI: 0.016, 0.030), and 0.013-mm (95% CI: 0.006, 0.020) increases in CIMT, respectively. There was little evidence of associations with EC using either exposure model. The association of $PM_{2.5}$ with CIMT was found only in the spatiotemporal model predictions. The associations for sulfur, silicon, and OC in our primary model and with both exposure model predictions were essentially unchanged after adjustment for the extended set of variables in model 3. However, the associations for OC and silicon were sensitive to adjustment for city in model 4, although the OC measure of association was only slightly attenuated using national model exposure predictions. The corresponding results of the 2 sets of predictions for the same IQRs are shown in Web Figure 4.

Neither $PM_{2.5}$ nor $PM_{2.5}$ components were associated with log(CAC). The presence of CAC was associated only with OC using exposure predictions from the national spatial model (relative risk = 1.043, 95% CI: 1.007, 1.081).

In further sensitivity analyses for associations with CIMT, the associations for sulfur and OC were not sensitive to the addition of $PM_{2.5}$ or another $PM_{2.5}$ component in 2-pollutant models when using exposure predictions from the spatiotemporal model (Web Figure 5). Using national spatial predictions, the associations for sulfur and silicon were not sensitive to inclusion of other pollutants, whereas that for OC was sensitive to inclusion of silicon. Primary model findings for sulfur and OC were also not sensitive to inclusion of predicted sulfur dioxide or nitrogen dioxide, to restriction to smaller prediction areas or to non–statin users (Web Figure 6), or to addition of neighborhood socioeconomic status (results not shown).

DISCUSSION

In this study, we investigated the association between subclinical measures of atherosclerosis and long-term residential concentrations of 4 $PM_{2.5}$ chemical components predicted from 2 advanced exposure modeling approaches. We found that increased concentrations of sulfur and OC, and possibly silicon, were associated with an increase in CIMT using either of the 2 exposure predictions. The findings were robust to adjustment for an extended set of covariates, but some were very sensitive to adjustment for metropolitan area. There was little consistent evidence of associations between any of the 4 $PM_{2.5}$ components and CAC.

CIMT, being a predictor of cardiovascular events and being relatively easy to measure while exhibiting little short-term variation (5, 40), has been utilized in many air pollution studies. In MESA, Diez Roux et al. (12) and Adar et al. (10) found that long-term $PM_{2.5}$ concentrations were associated with CIMT at examination 1. Other investigators have also reported associations between CIMT and long-term $PM_{2.5}$ or black carbon in studies from Los Angeles, 3 cities in Germany, and the Greater Boston, Massachusetts, area (11, 13, 41). Ostro et al. (25) focused on $PM_{2.5}$ chemical components in the California Teachers Study cohort and found that silicon, sulfate, EC, and OC were associated with ischemic heart disease mortality.

Our intent was to obtain the most valid and precise measures of association possible, and therefore we predicted individual-level concentrations based on rigorous exposure modeling approaches. Simpler prediction approaches may result in poor performance of measures of association, particularly for $PM_{2.5}$ components that are dominated by fine-scale spatial variability from local sources and for which data are collected in spatially limited administrative monitoring networks. For

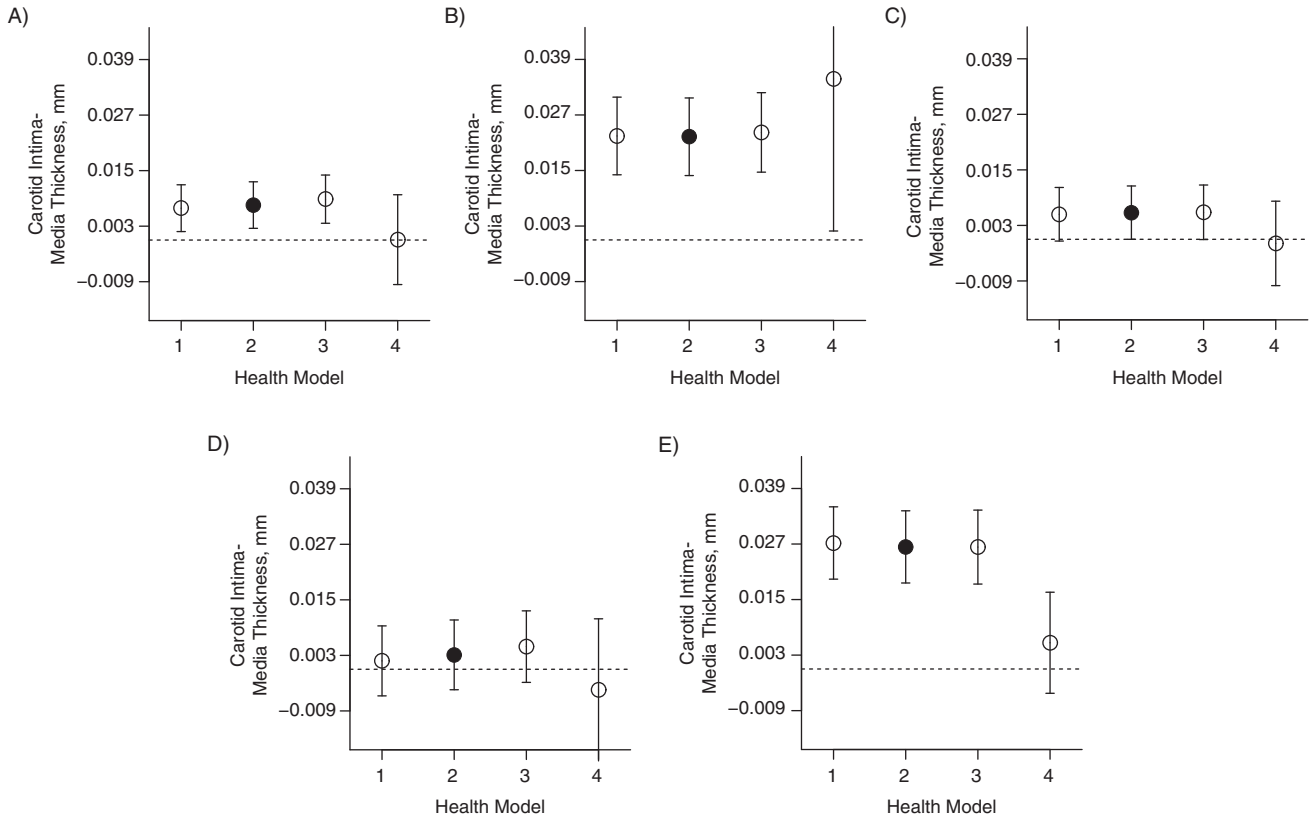

Figure 3. Cross-sectional associations of interquartile-range increases in predicted long-term concentrations of particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) (A) and 4 of its components (sulfur (B), silicon (C), elemental carbon (D), and organic carbon (E)) from a spatiotemporal model with carotid intima-media thickness in 6 US metropolitan areas in 4 health models, Multi-Ethnic Study of Atherosclerosis, 2000–2002. Solid dots represent estimates in the primary model; bars show 95% confidence intervals. Interquartile-range increases in the spatiotemporal model predictions were 1.51 μg/m^3, 0.51 μg/m^3, 0.02 μg/m^3, 0.88 μg/m^3, and 0.69 μg/m^3 for $PM_{2.5}$, sulfur, silicon, elemental carbon, and organic carbon, respectively.

example, we showed in simulations that predictions from a small monitoring network tended to produce more attenuated measures of association from nearest-monitor predictions than from kriging predictions (42). We interpret this attenuation as largely due to classical-type measurement error (43) induced by the small number of monitor locations.

Sun et al. (27) performed an analysis parallel to ours but adopted relatively simple prediction approaches based on the same NPACT monitoring data. Our findings were largely consistent with those of Sun et al. for OC and sulfur, apart from differences in magnitude and precision of measures of association (Web Figure 7). However, findings differed for EC and silicon; while we found evidence of associations with silicon but not EC, they found evidence of associations with EC but not silicon. Increased measurement error and inability to capture fine-scale spatial variability might have driven the somewhat different findings in the study by Sun et al. (27). As has been observed in simulation (42), any single estimate could be an underestimate or overestimate of the average pattern of negative bias; this could apply to any individual epidemiologic study. In addition, their use of measurements from a single near-road site in each area for predicting the residential exposures of participants living near roads could have introduced some differential measurement error that affected the measures of association.

Despite differences in the monitoring data and modeling approaches used in our spatiotemporal and national spatial prediction models, findings from our primary health model using these 2 predictions were generally consistent. Part of the explanation for this consistency may be the larger between-city variability than within-city variability in the predictions and the consistent ranking of cities by the 2 approaches (Figures 1 and 2). Larger between-city variability also led to sensitivity to adjustment for city. When we adjusted for city, we removed much of the exposure variability, particularly for sulfur and silicon, which had relatively small within-city variability and large between-city variability, resulting in often greatly attenuated and/or more uncertain measures of association. For OC, which had relatively large within-city variability in both prediction models, the widths of the confidence intervals were similar to those in the primary model (model 2). In addition, measures of association in the city-adjusted model (model 4) decreased slightly using national spatial model predictions, but more substantially with spatiotemporal model predictions. We remain

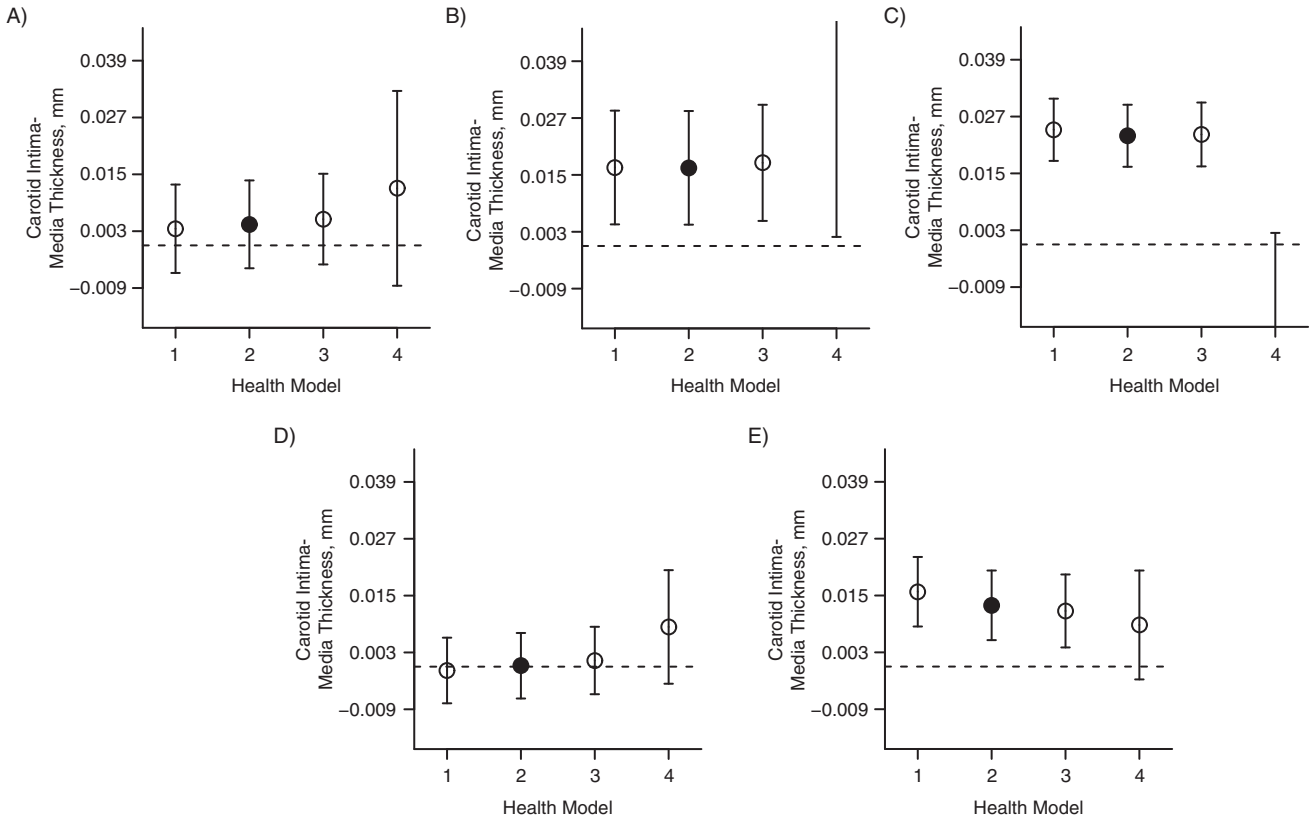

Figure 4. Cross-sectional associations of interquartile-range increases in predicted long-term concentrations of particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) (A) and 4 of its components (sulfur (B), silicon (C), elemental carbon (D), and organic carbon (E)) from a national spatial model with carotid intima-media thickness in 6 US metropolitan areas in 4 health models, Multi-Ethnic Study of Atherosclerosis, 2000–2002. Solid dots represent estimates in the primary model; bars show 95% confidence intervals. Interquartile-range increases in the national spatial model predictions were 2.00 μg/m^3, 0.39 μg/m^3, 0.04 μg/m^3, 0.31 μg/m^3, and 0.54 μg/m^3 for $PM_{2.5}$, sulfur, silicon, elemental carbon, and organic carbon, respectively.

puzzled as to why the measures of association for OC were attenuated after control for city (at least using the spatiotemporal model predictions) in contrast to those for sulfur, which had large between-city variability. Potential explanations include differences in source contributions to OC across cities or area-level confounding.

We have reported our primary findings without adjustment for metropolitan area. Our spatiotemporal model was developed to capture fine-scale spatial variability of $PM_{2.5}$ components in each city which might allow us to assess within-city associations. To characterize within-city variability, we originally intended to use all available data, combining the administrative monitoring data with the NAPCT monitoring data. However, these monitoring data were not sufficiently consistent and we made a scientific choice to use the NPACT monitoring data only for the spatiotemporal model (31). This data limitation contributed to predicting relatively small within-city variability compared with between-city variability of predicted long-term concentrations for all $PM_{2.5}$ components except OC; in turn, these yielded uncertain measures of association when we adjusted for metropolitan area. The national spatial model and the nearest-monitor method produced even smaller within-city variability compared with between-city variability for sulfur and silicon than the spatiotemporal model (Web Figure 2). This pattern indicates that our spatiotemporal model generally represented more within-city spatial variability than the nationwide prediction model or a relatively simple prediction approach. However, for most $PM_{2.5}$ components, this within-city variability may not have been adequate for assessing the within-city association with health outcomes.

Of the 4 $PM_{2.5}$ components that we focused on, the strongest evidence was obtained for the associations of sulfur and OC with CIMT, with relatively less evidence for silicon and little for EC. These associations per IQR for sulfur and OC were larger than the association for $PM_{2.5}$. Source apportionment based on NPACT monitoring data showed that sulfur had large contributions from a secondary organic factor and/or a sulfate factor. These secondary mixtures suggest impacts from regionally transported emission sources such as coal-fired power plants or urban particulate matter air pollution (44, 45). OC had large contributions from combustion sources such as biomass, as well as secondary sulfate and/or organics, depending on the metropolitan area (28).

We found little consistent evidence of associations of CAC with the 4 $PM_{2.5}$ components, apart from that between the presence of CAC and OC based on the national spatial model predictions. Previous studies also found little evidence of associations of CAC in the MESA cohort with long-term $PM_{2.5}$ concentrations (12, 27). CIMT is a measure of general atherosclerosis and can reflect early arterial wall changes, whereas CAC generally reflects later stages of plaque formation (40). Our null findings for CAC could be due to a relatively low prevalence of advanced atherosclerosis in the MESA examination 1 participants, who did not have clinically apparent cardiovascular disease at the time of recruitment.

This study had limitations, with implications for the design of future studies. Our CIMT and CAC measurements were made before the monitoring data on which we based the $PM_{2.5}$ component predictions were collected. NPACT monitoring was performed between 2005 and 2009 and the regulatory monitoring data were obtained in 2009 and 2010, while MESA examination 1 took place between 2000 and 2002. We assumed a consistent pattern of $PM_{2.5}$ component concentrations over time and linked $PM_{2.5}$ component predictions to the earlier measured health data. A lack of available $PM_{2.5}$ component monitoring data in the early 2000s did not allow us to test this assumption. Instead, we used $PM_{2.5}$ predictions for MESA participants from the MESA Air spatiotemporal prediction model (36) for the years 2000 and 2007–2008 and found smaller measures of association in 2007–2008 than in 2000, possibly resulting from different decreasing patterns of $PM_{2.5}$ predictions across cities (28). Future cohort studies will allow us to assess the impact of changes in $PM_{2.5}$ component concentrations with outcome measures that are more temporally aligned with our exposures. In addition, measurement error in the exposure predictions may have introduced bias or additional variability in the measures of association. A measurement error correction approach developed and applied in a pure spatial exposure model (30, 43) needs to be generalized to a spatiotemporal modeling structure and a multicity setting to be applicable to our study. Finally, as a cross-sectional study, our study did not allow us to examine associations with progression of CIMT or CAC. Longitudinal analyses using CIMT and CAC measurements from follow-up examinations will provide better evidence on the relationship between long-term exposure to $PM_{2.5}$ components and atherosclerosis.

This study's findings support the notion that some components in the ambient $PM_{2.5}$ mix are more associated with worsened atherosclerosis than other components. In particular, the evidence was strongest for OC and sulfur, suggesting that long-term exposure to $PM_{2.5}$ related to secondary inorganic or secondary organic aerosol or to combustion emissions that contribute to OC may be important sources of more toxic $PM_{2.5}$.

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