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Original Contribution

Long-term Exposure to Ambient Particulate Matter and Prevalence of Subclinical Atherosclerosis in the Multi-Ethnic Study of Atherosclerosis

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Exposure to airborne particulate matter has been linked to cardiovascular events. Whether this finding reflects an effect of particulate matter exposure on the triggering of events or development of atherosclerosis remains unknown. Using data from the Multi-Ethnic Study of Atherosclerosis collected at baseline (2000–2002), the authors investigated associations of 20-year exposures to particulate matter with measures of subclinical disease (coronary calcium, common carotid intimal-medial thickness, and ankle-brachial index) in 5,172 US adults without clinical cardiovascular disease. Particulate matter exposures for the 20 years prior to assessment of subclinical disease were obtained from a space-time model of Environmental Protection Agency monitor data linked to residential history data for each participant. Intimal-medial thickness was weakly, positively associated with exposures to particulate matter <10 μm in aerodynamic diameter and <2.5 μm in aerodynamic diameter after controlling for age, sex, race/ethnicity, socioeconomic factors, diet, smoking, physical activity, blood lipids, diabetes, hypertension, and body mass index (1–4% increase per 21-μg/m^3 increase in particulate matter <10 μm in aerodynamic diameter or a 12.5-μg/m^3 increase in particulate matter <2.5 μm in aerodynamic diameter). No consistent associations with other measures of atherosclerosis were observed. There was no evidence of effect modification by sociodemographic factors, lipid status, smoking, diabetes, body mass index, or site. Results are compatible with some effect of particulate matter exposures on development of carotid atherosclerosis.

atherosclerosis; cardiovascular diseases; carotid artery diseases; environmental exposure; particulate matter

Abbreviations: ABI, ankle-brachial index; CIMT, common carotid intimal-medial thickness; MESA, Multi-Ethnic Study of Atherosclerosis; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; PM_{10}, particulate matter <10 μm in aerodynamic diameter.

Several studies have shown that exposure to airborne particulate matter <10 μm in aerodynamic diameter (PM_{10}) and particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) is related to the occurrence of clinical cardiovascular events (1). In time-series analyses, particulate matter exposures have been found to be associated with cardiovascular deaths (2) and hospital admissions for congestive heart failure, ischemic heart disease, and cerebrovascular disease (3). Residing in areas with high levels of particulate matter has also been associated with greater cardiovascular disease incidence and mortality (4–8). The biologic mechanisms responsible for these associations remain a subject of research.

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One possibility is that exposure to particulate matter triggers cardiovascular events in persons with underlying atherosclerotic disease (9–11) through mechanisms involving effects of air pollution on arrhythmias, coagulation, or vascular resistance (12–16). A second possibility is that long-term exposure to particulate matter causes the development of atherosclerosis. There are plausible biologic mechanisms through which such an effect could be mediated, including effects on systemic inflammation, blood pressure, and autonomic function (1, 17–19). In addition, animal experiments have linked particulate matter exposures to atherosclerosis progression in small mammals with risk factors for atherosclerosis (20, 21).

Studies that focus on the relation between particulate matter exposure and clinical events or deaths are unable to determine whether particulate matter exposure is related to only the triggering of acute events or to the development of atherosclerosis. Investigating the role of particulate matter exposures in the development of atherosclerosis requires studies that focus on measures of subclinical atherosclerotic disease. Because any effects of particulate matter exposure on the development of atherosclerosis are likely to accumulate slowly over very long periods, measures of long-term exposures are also required. However, only two studies to date are known to have directly assessed the relation between exposure to airborne particles ($PM_{2.5}$) and subclinical atherosclerotic disease in human population samples (22, 23). Neither study had true long-term measures of exposure.

Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), we investigated associations of 20-year exposures to particulate matter with several measures of subclinical disease in a large sample of healthy adults. The aims of the analyses were 1) to examine the relation between long-term (20-year) exposure to particulate matter (PM_{10} and $PM_{2.5}$) and the prevalence of subclinical atherosclerotic disease measured by coronary artery calcification, carotid intimal-medial thickness, and ankle-brachial index (ABI); and 2) to determine whether any potential atherogenic effects of particulate matter exposure vary by characteristics that may make individuals more vulnerable to these effects, including age, sex, smoking, diabetes, blood lipid levels, education, and geographic location.

MATERIALS AND METHODS

MESA is a longitudinal study of subclinical atherosclerosis. Cohort members are 6,814 men and women aged 44–84 years who were free of clinical cardiovascular disease at baseline. Individuals were recruited from six field centers: Baltimore, Maryland (Johns Hopkins University); Chicago, Illinois (Northwestern University); Forsyth County, North Carolina (Wake Forest University); Los Angeles, California (University of California-Los Angeles); New York, New York (Columbia University); and St. Paul, Minnesota (University of Minnesota) (24). The present analyses are based on data collected at the baseline visit (June 2000–August 2002).

Three measures of subclinical atherosclerosis (common carotid intimal-medial thickness (CIMT), coronary artery calcification, and ABI) previously shown to be related to incident cardiovascular events (25–27) were investigated. Each measures atherosclerosis in a different vascular bed (the coronary arteries, the carotids, and the peripheral arterial circulation, respectively). Images of the right and left common and internal carotid arteries were captured by using high-resolution B-mode ultrasound (28). CIMT assessed as the mean of all available maximum wall thicknesses across the near and far walls of the left and right common carotids was used in analyses. Coronary calcium was assessed by chest computed tomography with a cardiac-gated electron-beam computed tomography scanner at three field centers or with a prospectively electrocardiogram-triggered scan acquisition at 50 percent of the R-R interval with multidetector scanners at the other three field centers (29). Two scans were obtained for each participant, and the mean Agatston score (30) for the two scans was used in analyses. The presence of calcification was defined as an Agatston score of >0. We also examined logged Agatston score as a continuous variable in persons with nonzero calcification.

Measurements to calculate ABI were obtained by using a hand-held Doppler instrument with a 5-mHz probe. Systolic blood pressure measurements were obtained from bilateral brachial, dorsalis pedis, and posterior tibial arteries (31). Brachial artery pressures were averaged to obtain the ABI denominator. When the two brachial artery pressures differed by 10 mmHg or more, the highest brachial artery pressure was used as the denominator. For each lower extremity, the ABI numerator used was the highest pressure (dorsalis pedis or posterior tibial) from that leg. Ratios were calculated separately for the left and right sides, and the minimum was used for analyses.

Long-term (20-year) exposure to particulate matter was estimated on the basis of a residential history reported retrospectively by each participant. Participants reported all addresses at which they lived since January 1982, including move dates. All addresses were geocoded, creating a file containing the residential location of each participant each month between August 1982 and the date of the baseline examination. The test-retest reliability of the 20-year PM_{10} exposure measure was 0.95 in a subset of 505 participants who repeated the residential history questionnaire 1 year apart. Data on levels of air pollution from community monitors were obtained from the US Environmental Protection Agency's Aerometric Information Retrieval Service database. Monthly mean PM_{10} and $PM_{2.5}$ measures were created for each monitor and month by averaging all available readings for a given month.

A spatio-temporal model was used to predict PM_{10} (and subsequently $PM_{2.5}$) exposures for each participant-month based on the geographic location of each participant's residence each month (32). The mean distance of participant residential addresses to the nearest PM_{10} monitor for all addresses reported was 13.1 km (standard deviation, 33.0 km; median, 5.6 km; 25th–75th percentile, 3.0–11.4 km). Monthly PM_{10} values for each monitor were modeled as a function of time and location effects. Time effects were modeled with trend, cyclic, and autoregressive components. Location effects were modeled by using thin-plate splines. We included temperature and airport visibility data obtained from the

National Climatic Data Center and total suspended particle, nitrogen dioxide, ozone, carbon monoxide, and sulfur dioxide measures from the Environmental Protection Agency's network (all predicted for monitor locations and months by using a similar modeling approach) as well as population density and geographic region as covariates to improve predictions. The model was cross-validated as follows: For a random sample of Environmental Protection Agency monitors, we deleted one monitor at a time and then predicted PM_{10} levels for that monitor by using the remaining monitors. We then computed the correlation between the predicted and the actual values across these monitors. The correlation coefficient was 0.86.

The spatio-temporal model was used to multiply impute exposure for each residential address and month. To impute $PM_{2.5}$ exposures, we used available data on colocated $PM_{2.5}$ and PM_{10} measures to develop a similar spatio-temporal model for $PM_{2.5}/PM_{10}$ ratios and then applied these ratios to predicted PM_{10} data to obtain predicted $PM_{2.5}$ data for each location and month. A total of 40 imputations were performed. These multiply imputed data sets were combined in analyses by using methods that appropriately account for uncertainty in the imputations (33). The imputed data were used to construct two measures of long-term exposure to PM_{10} and $PM_{2.5}$: an area under the curve measure (expressed as average monthly exposure over the 20-year period) and a measure of the percentage of months with mean values >50 μg/m^3 for PM_{10} (the 1997 Environmental Protection Agency annual standard) and the percentage of months with mean values >15 μg/m^3 for $PM_{2.5}$ (current annual standard).

Using potentially imprecise residential history data linked to often-sparse particulate matter monitoring data to estimate long-term exposures could lead to important measurement error. Therefore, in sensitivity analyses, we investigated the long-term exposure measures exclusively on the basis of observed (as opposed to multiply imputed) PM_{10} data by using exposures based on the monitor located closest to each participant for each month in the full sample as well as by restricting the analysis to persons who lived within 10 km of a monitor for the full 20 years of the study (68.8 percent of the sample). We also estimated associations between recently measured particulate matter exposures (in 2001, the midyear of the baseline examination) and subclinical disease measured at baseline. This procedure was performed to make our analyses directly comparable to prior work documenting associations of particulate matter exposure with CIMT (22) and because exposure levels for a given residential location are likely highly correlated over time; therefore, measures obtained in 2001 from the denser monitoring network may provide a better measure of long-term exposure than the imputed exposures based on historical monitoring data. Mean 2001 PM_{10} and $PM_{2.5}$ exposure was estimated for each participant by averaging all available daily values collected at the monitor nearest his or her residential address at baseline. Median distances to these "nearest" monitors were 6.9 km for PM_{10} and 4.4 km for $PM_{2.5}$.

Confounders investigated included age, sex, race/ethnicity, socioeconomic factors, and cardiovascular risks factors (body mass index, hypertension, high density lipoprotein and low density lipoprotein cholesterol, smoking, diabetes, diet, and physical activity). Several variables were also investigated as effect modifiers: age, sex, and lipid levels, because they were found to modify the particulate matter–CIMT association in prior work (22); site, because particle composition may vary by geographic region (3, 34); education, race/ethnicity, diabetes, and body mass index, because some prior work suggested that vulnerability to particulate matter effects may differ by these characteristics (7, 10, 35, 36); and smoking (personal and passive), because exposure to tobacco smoke may limit the ability to detect the comparatively small effects of inhaled particulate matter from other sources.

Race/ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Hispanic, and Chinese. Education was classified as complete high school degree or less (34 percent), some college but no degree (29 percent), and bachelor's degree or more (37 percent). Annual family income was collected in 13 categories and was transformed into per capita income by taking the midpoint of each category and dividing by family size. High density lipoprotein and low density lipoprotein cholesterol were assessed by using standard methods (24). Use of lipid-lowering medications was assessed through questionnaire. Diabetes was defined as fasting glucose of $\geq$7.0 mmol/liter ($\geq$126 mg/dl) or use of hypoglycemic medication. Information on current and past smoking status, current exposure to passive smoking (at home or at work), and history of living with smokers over the 20-year period was assessed through questionnaires. Hypertension was defined as systolic blood pressure of $>$140 mmHg or diastolic blood pressure of $\geq$90 mmHg or taking antihypertensive medications. Physical activity and diet were assessed by using standard questionnaires and were summarized in indices (24, 37). Area socioeconomic characteristics were assessed by using a summary index previously shown to be related to cardiovascular risk (38).

Of the 6,814 MESA cohort members at baseline, 6,181 participated in the air pollution study and 5,871 provided information on all addresses reported since January 1982. Among these members, latitude/longitude coordinates in the United States for all addresses at which they had lived since January 1982 were available for 5,172. Final sample sizes were 5,172 for coronary calcium, 5,037 for CIMT, and 5,110 for ABI. Because of additional missing exposure data, analyses based on 2001 data were further restricted to 5,041 persons for calcium, 4,912 for CIMT, and 4,980 for ABI.

We initially examined the distribution of exposure measures by selected characteristics of the study sample. The form of the covariate-adjusted relation between exposures and the outcomes of interest was investigated by using generalized additive models (39). Binomial regression (40) was used to estimate associations between exposure and the presence of calcification before and after adjustment for covariates. Linear regression was used to estimate associations of exposures with CIMT, ABI, and amount of calcium (among persons with nonzero calcification). CIMT and Agatston score were log transformed for these analyses. For ease of interpretation, all measures of association were estimated for a difference in particulate matter exposure

equivalent to the differences between the 90th and the 10th percentiles in the full sample. Methods appropriate for imputed exposures were used in regression analyses (33).

Heterogeneity of effects was examined through stratified analyses and by including appropriate interaction terms in regression models. Sensitivity analyses included 1) contrasting results based on observed and imputed long-term PM_{10} exposures, 2) restricting observed PM_{10} analyses to persons for whom all addresses were within 10 km of a monitor for the full 20-year period, and 3) comparing results from long-term exposure estimates with those obtained by using 2001 estimates and restricting the sample to persons who had lived at the same address for 20 years.

RESULTS

The mean age of the sample was 62 years, 47 percent were men, and 43 percent were White, 7 percent were Chinese, 30 percent were Black, and 20 percent were Hispanic. Fifty percent of the sample had coronary calcification. The medians for subclinical measures were 0.85 mm (interquartile range, 0.23) for CIMT, 1.12 (interquartile range, 0.13) for ABI, and 90.3 units (interquartile range, 285.64) for Agatston score among persons with coronary calcification. Forty-three percent of participants reported only one address during the 20-year period, 26 percent reported two addresses, and 32 percent reported three or more addresses (table 1). Nearly 70 percent (68.8 percent) of the sample resided within 10 km of a PM_{10} monitor for the full 20-year period. Observed mean monthly PM_{10} levels for the 20 years prior to the clinic visit were positively associated with age, being Chinese or Hispanic, low income and educational level, and living in California (table 1). Similar patterns were generally observed for imputed historical PM_{10} and $PM_{2.5}$ and for year 2001 mean PM_{10} and $PM_{2.5}$.

As expected, observed and imputed long-term PM_{10} exposures were highly correlated ($r = 0.93$) (table 2). Imputed PM_{10} was also positively correlated with imputed $PM_{2.5}$ ($r = 0.73$). Long-term PM_{10} exposures were positively correlated with 2001 PM_{10} exposures (0.80 for observed and 0.75 for imputed). Imputed long-term $PM_{2.5}$ exposures were also positively (although not as strongly) correlated with 2001 $PM_{2.5}$ exposures ($r = 0.64$). Mean 20-year particulate matter exposures were highly correlated with the percentage of months above a threshold (all correlations >0.94). Therefore, results for only the mean 20-year exposures are reported here.

Analyses of the relation between particulate matter exposures and subclinical measures using generalized additive models did not yield clear evidence of threshold effects for any of the long-term exposures studied. Table 3 shows associations of 20-year particulate matter exposures prior to the MESA baseline examination with the presence of subclinical atherosclerosis. Analyses adjusted for age, sex, race/ethnicity, and socioeconomic status revealed no consistent evidence of positive associations between $PM_{2.5}$ or PM_{10} exposures (observed or imputed) and the presence of subclinical disease, with the exception of weak associations of PM_{10} exposures (20-year means and 2001 mean) and

TABLE 1. Selected characteristics of 5,172 participants included in the analyses of long-term exposure to ambient particulate matter and prevalence of subclinical atherosclerosis, the Multi-Ethnic Study of Atherosclerosis, 2000–2002*

	Distribution (%)	PM_{10}† 20-year observed mean (SD†) (μg/m^3)	$PM_{2.5}$† 2001 mean (SD) (μg/m^3)
Sex			
Male	47.4	34.02 (6.96)	16.70 (3.88)
Female	52.6	33.88 (6.67)	16.67 (3.65)
p value		0.46	0.80
Age (years)			
45–54	27.9	33.64 (6.76)	16.39 (3.54)
55–64	28.4	33.88 (6.81)	16.56 (3.60)
65–74	30.0	34.11 (6.82)	16.84 (3.91)
75–84	13.6	34.35 (6.84)	17.18 (4.13)
p value		0.01	<0.0001
Race			
White	42.8	32.21 (5.10)	15.6 (2.40)
Chinese	6.9	41.14 (7.32)	19.49 (3.73)
Black	30.0	32.39 (4.66)	16.45 (2.83)
Hispanic	20.3	37.47 (9.12)	18.36 (5.74)
p value		<0.0001	<0.0001
Income ($)			
<12,000	8.6	36.06 (7.87)	17.81 (4.62)
12,000–24,999	17.2	35.42 (7.89)	17.67 (4.74)
25,000–49,999	28.9	33.46 (6.67)	16.39 (3.78)
50,000–74,999	17.4	32.85 (5.93)	15.96 (2.97)
≥75,000	24.1	33.94 (6.12)	16.54 (2.95)
Missing	3.9	31.33 (5.23)	16.13 (2.95)
p value		<0.0001	<0.0001
Education			
Incomplete high school	14.9	36.86 (8.58)	18.45 (5.03)
Complete high school	18.7	33.34 (6.79)	16.52 (4.05)
Some college	29.4	33.56 (6.65)	16.36 (3.72)
Complete college	36.8	33.40 (5.78)	16.33 (2.74)
Missing	0.3	32.15 (1.77)	15.28 (0.23)
p value		<0.0001	<0.0001
Site at MESA† baseline			
North Carolina	17.3	28.39 (1.91)	15.26 (0.68)
New York	16.1	31.39 (3.07)	15.74 (1.11)
Maryland	17.1	32.82 (1.26)	15.65 (0.95)
Minnesota	16.6	29.42 (2.49)	12.82 (0.71)
Illinois	17.4	34.98 (2.62)	17.05 (1.00)
California	15.6	47.66 (3.72)	24.10 (3.29)
p value		<0.0001	<0.0001

* All *p* values for comparison across categories. Correspond to *p* value for trend for age, income, and education; all other *p* values are based on analysis of variance.

† PM_{10}, particulate matter <10 μm in aerodynamic diameter; SD, standard deviation; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; MESA, Multi-Ethnic Study of Atherosclerosis.

TABLE 2. Correlations* between historical and 2001 PM_{10}† and $PM_{2.5}$† exposures, Multi-Ethnic Study of Atherosclerosis, 2000–2002

	PM_{10} 20-year observed mean	PM_{10} 20-year imputed mean	PM_{25} 20-year imputed mean	PM_{10} 2001 mean	$PM_{2.5}$ 2001 mean
Mean (SD†) (μg/m^3)	34.0 (6.8)	34.1 (7.5)	21.7 (5.0)	29.5 (7.5)	16.7 (3.8)
PM_{10} 20-year observed mean		0.93	0.64	0.80	0.82
PM_{10} 20-year imputed mean			0.73	0.75	0.86
PM_{25} 20-year imputed mean				0.43	0.64
PM_{10} 2001 mean					0.69

* All *p* values for correlation coefficients <0.0001.

† PM_{10}, particulate matter <10 μm in aerodynamic diameter; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; SD, standard deviation.

20-year $PM_{2.5}$ exposures with CIMT (a 1–3 percent increase in CIMT per 21-μg/m^3 increase in PM_{10} or 12.5-μg/m^3 increase in $PM_{2.5}$). Higher 2001 PM_{10} exposures were associated with higher ABI, indicating less subclinical disease among persons with greater exposure. Similar results were obtained when ABI $\leq$0.9 was modeled as a dichotomous outcome. Most particulate matter exposures were weakly and positively associated with the presence of coronary calcification (1–10 percent increase), but all confidence intervals included the null value. Additional adjustment for cardiovascular risk factors slightly increased associations of particulate matter exposures with CIMT, resulting in weak, but statistically significant positive associations of nearly all particulate matter exposures investigated with CIMT (1–4 percent increase in CIMT for a 21-μg/m^3 increase in PM_{10} or a 12.5-μg/m^3 increase in $PM_{2.5}$). This slight increase resulted primarily from adjustment for body mass index and diet. Additional adjustment for area socioeconomic characteristics did not substantially modify results (not shown).

We found no clear evidence of systematic differences in associations of 20-year PM_{10} or $PM_{2.5}$ with subclinical atherosclerosis by age, sex, lipid status, smoking status, diabetes status, body mass index, education, or study site (all *p* for interactions > 0.05) (table 4).

DISCUSSION

We found evidence of associations between long-term exposure to particulate matter over a 20-year period and subclinical atherosclerosis for only one of the three outcomes investigated. Higher particulate matter exposures were associated with slightly higher CIMT after adjustment for demographic and cardiovascular risk factors, but no consistent associations with other measures of subclinical atherosclerosis were observed. We found no evidence that long-term particulate matter exposure was more strongly associated with subclinical disease in subgroups previously hypothesized to be more vulnerable to these effects, including women, older persons, persons with hyperlipidemia or diabetics, obese persons, and persons whose educational levels were low. Important innovations of our study include the availability of a measure of 20-year exposure, the large population sample, and simultaneous investigation of multiple measures of atherosclerosis.

Evidence from animal experiments supports the notion that particulate matter exposure may accelerate progression of atherosclerotic lesions through mechanisms involving bone marrow stimulation, release of monocytes, altered vasomotor tone, and inflammation (20, 21, 41). Hyperlipidemic rabbits exposed to PM_{10} over 4 weeks experienced enhanced release of bone marrow macrophages and accelerated progression of atherosclerotic lesions. Among apolipoprotein E–/– mice, exposure to $PM_{2.5}$ was associated with altered vasomotor tone, vascular inflammation, and increased aortic atherosclerosis (21). Other biologic mechanisms linking particulate matter exposure to the development of atherosclerosis over long periods include effects of air pollution exposures on blood pressure, autonomic function, and low density lipoprotein oxidation (1, 17–19, 42). Kunzli et al. (22) investigated cross-sectional associations between CIMT and contemporaneously measured $PM_{2.5}$ exposure in a sample of 798 Los Angeles residents aged 40 years or older without clinical cardiovascular disease but with either elevated low density lipoprotein cholesterol or elevated homocysteine levels. Geostatistical methods were used to interpolate mean year 2000 $PM_{2.5}$ concentrations, and exposure was assigned to each subject on the basis of the postal code centroid for the home address. Each 10-μg/m^3 increase in $PM_{2.5}$ was associated with a 4.4 percent increase in CIMT after adjustment for age, sex, education, and income. Associations appeared to be stronger among persons older than 60 years of age, women, persons using lipid-lowering therapy, and never smokers.

Our results for mean annual $PM_{2.5}$ for 2001 adjusted for demographic and cardiovascular disease risk factors are consistent with those of Kunzli et al. (22), in that a 12-μg/m^3 increase in mean annual $PM_{2.5}$ for 2001 was associated with a 3 percent increase in CIMT (95 percent confidence interval: 1.01, 1.05). After adjustment for demographic factors and cardiovascular risks factors, all particulate matter exposures examined were positively, albeit weakly associated with CIMT (a 1–4 percent higher CIMT for an increase of 12 μg/m^3 in $PM_{2.5}$ or an increase of 21 μg/m^3 in PM_{10}),

TABLE 3. Differences in CIMT* and ABI,* relative prevalences of coronary calcification, and differences in amount of coronary calcium (in persons with calcium) associated with an increase in particulate matter exposure from the 10th to the 90th percentiles of exposure,† Multi-Ethnic Study of Atherosclerosis, 2000–2002

	CIMT		ABI		Coronary calcium		Coronary calcium (in those with calcium)	
	Relative difference‡	95% CI*	Mean difference	95% CI	Relative prevalence	95% CI	Relative difference‡	95% CI
PM_{10}* 20-year imputed mean								
Demographic and SES*,§	1.01	1.00, 1.02	0.002	−0.005, 0.009	1.02	0.96, 1.07	0.98	0.84, 1.13
+ Risk factors¶	1.02	1.00, 1.03	0.001	−0.006, 0.009	1.02	0.96, 1.08	1.01	0.86, 1.18
PM_{10} 20-year observed mean								
Demographic and SES	1.02	1.00, 1.03	0.001	−0.009, 0.012	1.06	0.98, 1.15	0.99	0.79, 1.24
+ Risk factors	1.03	1.01, 1.05	0.001	−0.010, 0.012	1.07	0.98, 1.17	1.02	0.81, 1.30
PM_{10} 20-year observed mean, restricted#								
Demographic and SES	1.00	0.98, 1.03	−0.001	−0.016, 0.015	1.10	0.98, 1.24	0.78	0.57, 1.07
+ Risk factors	1.02	0.99, 1.05	−0.003	−0.020, 0.013	1.11	0.98, 1.25	0.81	0.58, 1.13
$PM_{2.5}$* 20-year imputed mean								
Demographic and SES	1.01	1.00, 1.01	0.000	−0.006, 0.006	1.01	0.96, 1.05	0.99	0.88, 1.12
+ Risk factors	1.01	1.00, 1.02	−0.001	−0.006, 0.006	1.01	0.96, 1.06	1.01	0.89, 1.14
PM_{10} 2001 mean								
Demographic and SES	1.01	1.00, 1.03	0.012	0.002, 0.022	1.03	0.96, 1.12	0.93	0.75, 1.15
+ Risk factors	1.02	1.01, 1.04	0.013	0.002, 0.023	1.04	0.94, 1.15	0.95	0.75, 1.20
PM_{10} 2001 mean, restricted**								
Demographic and SES	1.03	1.01, 1.06	0.017	0.001, 0.032	1.02	0.92, 1.14	0.94	0.69, 1.28
+ Risk factors	1.04	1.01, 1.07	0.015	−0.002, 0.032	1.05	0.95, 1.15	0.91	0.65, 1.27
$PM_{2.5}$ 2001 mean								
Demographic and SES	1.01	0.99, 1.03	0.006	−0.006, 0.017	1.00	0.92, 1.09	0.86	0.68, 1.09
+ Risk factors¶	1.03	1.01, 1.05	0.006	−0.006, 0.018	1.03	0.93, 1.13	0.91	0.71, 1.17
$PM_{2.5}$ 2001 mean, restricted**								
Demographic and SES	1.02	0.99, 1.05	0.002	−0.016, 0.019	1.02	0.92, 1.14	0.84	0.61, 1.16
+ Risk factors	1.03	1.00, 1.06	−0.002	−0.020, 0.017	1.06	0.96, 1.17	0.83	0.58, 1.17

* CIMT, common carotid intimal-medial thickness; ABI, ankle-brachial index; CI, confidence interval; PM_{10}, particulate matter <10 μm in aerodynamic diameter; SES, socioeconomic status; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter.

† The difference between the 90th and the 10th percentiles corresponds to 21 μg/m^3 for all PM_{10} exposures and 12.5 μg/m^3 for all $PM_{2.5}$ exposures (percentiles based on 20-year observed PM_{10} and 20-year imputed $PM_{2.5}$). Sample size for 20-year exposures is 5,172 for CIMT, ABI, and calcium prevalence and 2,586 for amount of calcium in persons with calcium (3,557 for CIMT, ABI, and calcium prevalence and 1,859 for amount of calcium in the "restricted" sample). Sample size for 2001 exposures is 5,041 for CIMT, ABI, and calcium prevalence and 2,526 for amount of calcium in persons with calcium (2,149 for CIMT, ABI, and calcium prevalence and 1,222 for amount of calcium in the "restricted" sample).

‡ A relative difference of 1.05 indicates that CIMT increases by 5% when exposure increases from the 10th to the 90th percentile.

§ Includes income (as a continuous variable) and education (three categories). Race/ethnicity was classified as non-Hispanic White, non-Hispanic Black, Chinese, and Hispanic.

¶ Adjusted for age, sex, race/ethnicity, SES, hypertension (yes/no), body mass index, low density lipoprotein and high density lipoprotein cholesterol, smoking status (current, former, never), diabetes (normal, impaired, diabetes), physical activity (time engaged in light, moderate, and vigorous activities), and four dietary indices (37).

Restricted sample refers to persons for whom all addresses were within 10 km of a monitor for the exposure assessment period ($N = 3{,}557$).

** Restricted sample refers to persons who reported living at the same address for the 20 years prior to the baseline examination ($n = 2{,}149$).

which is equivalent to the effects of a 1–4-year increase in age (in fully adjusted models, each 1-year increase in age was associated with an approximately 1 percent increase in intimal-medial thickness). The cardiovascular risk factors examined did not appear to mediate any particulate matter effects on CIMT because associations became stronger, rather than weaker, when cardiovascular risk factors were added to the regression models.

There was no evidence that particulate matter exposures were associated with greater atherosclerosis when other measures of subclinical disease were used, except for a weak, but not statistically significant, association of 20-year

TABLE 4. Mean differences in CIMT* and ABI* and relative prevalences of CAC* associated with an increase in 20-year particulate matter exposure from the 10th to the 90th percentile of exposure† stratified by selected individual-level covariates, Multi-Ethnic Study of Atherosclerosis, 2000–2002

	PM_{10}* 20-year mean				$PM_{2.5}$* 20-year mean			
	CIMT	ABI	CAC	Amount of calcium‡	CIMT	ABI	CAC	Amount of calcium‡
	Relative difference	Mean difference	Relative prevalence	Relative difference	Relative difference	Mean difference	Relative prevalence	Relative difference
Age 45–54 years	1.02	0.002	1.10	1.38	1.01	−0.001	1.02	1.14
Age 55–64 years	1.03	0.002	0.99	0.93	1.02	0.000	1.00	1.01
Age 65–74 years	1.01	0.001	0.99	0.92	1.01	−0.002	0.99	0.95
Age 75–84 years	1.00	−0.005	1.03	1.15	0.99	0.000	1.01	1.07
Female	1.02	0.006	1.00	1.03	1.01	0.001	0.99	1.01
Male	1.02	−0.005	1.04	0.99	1.01	−0.002	1.02	1.00
White	1.02	0.001	1.02	1.04	1.01	−0.006	1.01	1.04
Chinese	1.03	0.002	1.06	0.92	1.03	0.005	0.99	0.89
Black	1.01	−0.001	1.05	1.21	1.01	0.002	1.03	1.11
Hispanic	1.02	0.001	0.98	0.98	1.01	0.005	1.01	0.94
High school or less	1.02	0.002	0.99	0.97	1.01	−0.001	1.00	1.02
Some college, no degree	1.01	−0.007	1.10	1.08	1.00	−0.005	1.06	1.05
Complete college	1.02	0.007	1.00	0.97	1.01	0.003	0.98	0.95
North Carolina site§	1.01	−0.011	1.06	1.20	1.00	−0.007	0.98	1.26
New York site§	0.99	−0.001	0.97	1.05	0.99	−0.004	0.99	0.98
Maryland site§	1.00	0.005	1.07	1.08	1.00	0.005	1.04	0.91
Minnesota site§	1.01	−0.003	0.99	1.01	1.00	0.005	0.99	1.19
Illinois site§	1.01	0.001	1.03	0.93	1.01	0.004	1.03	0.97
California site§	1.01	−0.004	0.98	1.08	1.01	0.001	1.01	0.97
Cholesterol ≤240 mg/dl and no lipid-lowering medications	1.02	0.003	1.01	1.02	1.01	0.001	0.99	1.00
Cholesterol >240 or lipid-lowering medications	1.01	−0.004	1.06	1.00	1.00	−0.005	1.04	1.05
Normal glucose	1.02	0.003	1.05	1.11	1.01	0.001	1.02	1.10
Impaired glucose tolerance	1.02	−0.005	1.01	0.93	1.01	−0.007	1.01	0.87
Diabetes¶	1.02	0.000	0.96	0.85	1.01	0.006	0.97	1.02
Never smokers with no exposure to secondhand smoke who did not live with a smoker for the past 20 years	1.01	0.005	1.01	1.00	1.01	0.004	1.02	1.04
All others	1.02	−0.001	1.03	1.01	1.01	−0.002	1.01	1.00
Body mass index <30 kg/m^2	1.02	−0.001	1.01	1.02	1.01	−0.002	1.01	1.02
Body mass index ≥30 kg/m^2	1.01	0.005	1.03	0.97	1.00	0.002	1.01	0.97

* CIMT, common carotid intimal-medial thickness; ABI, ankle-brachial index; CAC, coronary artery calcification; PM_{10}, particulate matter <10 μm in aerodynamic diameter; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter.

† The difference between the 90th and the 10th percentiles corresponds to 21 μg/m^3 for PM_{10} and 12.5 μg/m^3 for $PM_{2.5}$. Estimates were adjusted for age, sex, race/ethnicity, income, education, and cardiovascular risks factors (except when one of these was the stratification variable, in which case all variables except the stratification variable were included in the models).

‡ Restricted to participants with CAC.

§ Refers to site at recruitment into the Multi-Ethnic Study of Atherosclerosis.

¶ Based on American Diabetes Association criteria.

PM_{10} exposure with coronary calcification. To our knowledge, only one prior study has investigated coronary calcium in relation to air pollution exposures: living closer to a major road was associated with coronary calcification in a population-based study of 4,424 persons. Similar to our results, associations of $PM_{2.5}$ exposures with calcification were weakly positive and not statistically significant (23). In addition, we were unable to replicate the effect modification results for CIMT previously reported (22). We found no evidence that associations of particulate matter exposures with subclinical disease were stronger or present in only women, older persons, hyperlipidemics, or never smokers. Results also did not differ by diabetes status, body mass index, education, or study site. The mean levels and ranges of $PM_{2.5}$ exposure in our data were comparable (although slightly lower) to those observed in the Los Angeles sample, for which interactions with age, sex, and lipid status were reported (22).

All our measures of particulate matter exposure were based on ambient air monitors sited for regulatory purposes. Outdoor concentrations have been shown to be reasonable proxies for personal exposure to particles of outdoor origin (43, 44). Ambient levels are also the subject of regulation and are therefore of interest from the point of view of policy. However, the measures obtained at these outdoor locations may be poor proxies for personal exposures, which are affected by time spent indoors and in cars, as well as by air exchange rates between indoor and outdoor locations. We assigned exposure based on the participant's residential address. This approach does not capture differences in exposure that may occur as a result of travel to work and other daily activities. However, 37 percent of study participants were not employed at the time of the survey (retired and not working, unemployed, or homemakers), and 75 percent of the participants reported spending at least 60 percent of their time either in their home or within 1 mile (1.609 km) of their home.

Our approach to exposure assignment—using monitor data linked to participants based on their residence—is similar to that used in other work that has documented associations of particulate matter exposures with cardiovascular outcomes (7, 22). We improved on that work by incorporating historical exposures and imputing exposures based on a time-space model. We also conducted extensive sensitivity analyses in an attempt to assess the possible impact of some sources of measurement error on our results. These included working with only observed (as opposed to imputed) data, repeating analyses with PM_{10} and $PM_{2.5}$, restricting analyses to persons living within 10 km of a monitor for the full period over which exposure was assessed, and replicating analyses by using contemporaneously measured exposures from the denser monitor networks available in recent years. None of these sensitivity analyses resulted in substantially different results. Nevertheless, our approach may still be subject to important measurement error, limiting our ability to detect possibly small effects of particulate matter exposures on atherosclerosis development. Therefore, our null results for some outcomes do not rule out a possible effect of particulate matter exposures on subclinical atherosclerosis.

In summary, we found some evidence of associations between particulate matter exposure and CIMT, but associations with other measures of subclinical atherosclerosis were inconsistent. There was also no evidence that any associations were stronger or present in vulnerable groups only. Future work planned as part of the MESA cohort study will provide more precise measures of particulate matter and other pollutant exposures and will also allow direct examination of these exposures to changes in subclinical disease over time.

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REFERENCES

1. Brook RD, Franklin B, Cascio W, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 2004;109:2655–71.
2. Samet JM, Dominici F, Curriero FC, et al. Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. N Engl J Med 2000;343:1742–9.
3. Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA 2006;295:1127–34.
4. Dockery DW, Pope CA 3rd, Xu X, et al. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993;329:1753–9.
5. Pope CA 3rd, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 2002;287:1132–41.
6. Hoek G, Brunekreef B, Goldbohm S, et al. Association between mortality and indicators of traffic-related air pollution in The Netherlands: a cohort study. Lancet 2002;360:1203–9.
7. Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 2007;356:447–58.
8. Jerrett M, Burnett RT, Ma R, et al. Spatial analysis of air pollution and mortality in Los Angeles. Epidemiology 2005; 16:727–36.

9. Peters A, Dockery DW, Muller JE, et al. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 2001;103:2810–15.
10. Zanobetti A, Schwartz J. Are diabetics more susceptible to the health effects of airborne particles? Am J Respir Crit Care Med 2001;164:831–3.
11. Goldberg MS, Burnett RT, Bailar JCD 3rd, et al. Identification of persons with cardiorespiratory conditions who are at risk of dying from the acute effects of ambient air particles. Environ Health Perspect 2001;109(suppl 4):487–94.
12. Zanobetti A, Canner MJ, Stone PH, et al. Ambient pollution and blood pressure in cardiac rehabilitation patients. Circulation 2004;110:2184–9.
13. Baccarelli A, Zanobetti A, Martinelli I, et al. Effects of exposure to air pollution on blood coagulation. J Thromb Haemost 2007;5:252–60.
14. Sarnat SE, Suh HH, Coull BA, et al. Ambient particulate air pollution and cardiac arrhythmia in a panel of older adults in Steubenville, Ohio. Occup Environ Med 2006;63:700–6.
15. Dockery DW, Luttmann-Gibson H, Rich DQ, et al. Particulate air pollution and nonfatal cardiac events. Part II. Association of air pollution with confirmed arrhythmias recorded by implanted defibrillators. Res Rep Health Eff Inst 2005,Jun:83–126; discussion 127–48.
16. Brook RD, Brook JR, Urch B, et al. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. Circulation 2002;105:1534–6.
17. Donaldson K, Stone V, Seaton A, et al. Ambient particle inhalation and the cardiovascular system: potential mechanisms. Environ Health Perspect 2001;109(suppl 4):523–7.
18. Brook RD. You are what you breathe: evidence linking air pollution and blood pressure. Curr Hypertens Rep 2005;7:427–34.
19. Creason J, Neas L, Walsh D, et al. Particulate matter and heart rate variability among elderly retirees: the Baltimore 1998 PM study. J Expo Anal Environ Epidemiol 2001;11:116–22.
20. Suwa T, Hogg JC, Quinlan KB, et al. Particulate air pollution induces progression of atherosclerosis. J Am Coll Cardiol 2002;39:935–42.
21. Sun Q, Wang A, Jin X, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. JAMA 2005;294:3003–10.
22. Kunzli N, Jerrett M, Mack WJ, et al. Ambient air pollution and atherosclerosis in Los Angeles. Environ Health Perspect 2005;113:201–6.
23. Hoffmann B, Moebus S, Mohlenkamp S, et al. Residential exposure to traffic is associated with coronary atherosclerosis. Circulation 2007;116:489–96.
24. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.
25. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. Am J Epidemiol 1997;146:483–94.
26. Detrano RC, Wong ND, Doherty TM, et al. Prognostic significance of coronary calcific deposits in asymptomatic high-risk subjects. Am J Med 1997;102:344–9.
27. Criqui MH, Langer RD, Fronek A. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;120:721–9.
28. O'Leary DH, Polak JF, Kronmal RA, et al. Thickening of the carotid wall. A marker for atherosclerosis in the elderly? Cardiovascular Health Study Collaborative Research Group. Stroke 1996;27:224–31.
29. Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) Study. Radiology 2005;234:35–43.
30. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
31. McDermott MM, Criqui MH, Liu K, et al. Lower ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial arterial pressures, and association with leg functioning in peripheral arterial disease. J Vasc Surg 2000;32:1164–71.
32. Raghunathan T, Diez-Roux A, Chen W. Predicting cumulative particulate matter exposure using space-time models and historical monitor data. (Abstract). Epidemiology 2006;17(suppl):S250.
33. Raghunathan TE. What do we do with missing data? Some options for analysis of incomplete data. Annu Rev Public Health 2004;25:99–117.
34. Schlesinger RB, Kunzli N, Hidy GM, et al. The health relevance of ambient particulate matter characteristics: coherence of toxicological and epidemiological inferences. Inhal Toxicol 2006;18:95–125.
35. O'Neill MS, Jerrett M, Kawachi I, et al. Health, wealth, and air pollution: advancing theory and methods. Environ Health Perspect 2003;111:1861–70.
36. Jerrett M, Burnett RT, Brook J, et al. Do socioeconomic characteristics modify the short term association between air pollution and mortality? Evidence from a zonal time series in Hamilton, Canada. J Epidemiol Community Health 2004;58:31–40.
37. Nettleton JA, Steffen LM, Mayer-Davis EJ, et al. Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr 2006;83:1369–79.
38. Diez Roux AV, Merkin SS, Arnett D, et al. Neighborhood of residence and incidence of coronary heart disease. N Engl J Med 2001;345:99–106.
39. Hastie T, Tibshirani R. Generalized additive models for medical research. Stat Methods Med Res 1995;4:187–96.
40. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. Am J Epidemiol 2005;162:199–200.
41. Fujii T, Hayashi S, Hogg JC, et al. Interaction of alveolar macrophages and airway epithelial cells following exposure to particulate matter produces mediators that stimulate the bone marrow. Am J Respir Cell Mol Biol 2002;27:34–41.
42. Sharman JE, Coombes JS, Geraghty DP, et al. Exposure to automotive pollution increases plasma susceptibility to oxidation. Arch Environ Health 2002;57:536–40.
43. Janssen NA, Hoek G, Brunekreef B, et al. Personal sampling of particles in adults: relation among personal, indoor, and outdoor air concentrations. Am J Epidemiol 1998;147:537–47.
44. Dockery DW, Spengler JD. Indoor-outdoor relationships of respirable sulfates and particles. Atmos Environ 1981;15:335–43.