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Vascular Responses to Long- and Short-Term Exposure to Fine Particulate Matter:

MESA Air (Multi-Ethnic Study of Atherosclerosis and Air Pollution)

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Abstract

Objectives—This study evaluated the association of long- and short-term air pollutant exposures with flow-mediated dilation (FMD) and baseline arterial diameter (BAD) of the brachial artery using ultrasound in a large multicity cohort.

Background—Exposures to ambient air pollution, especially long-term exposure to particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$), are linked with cardiovascular mortality. Short-term exposure to $PM_{2.5}$ has been associated with decreased FMD and vasoconstriction, suggesting that adverse effects of $PM_{2.5}$ may involve endothelial dysfunction. However, long-term effects of $PM_{2.5}$ on endothelial dysfunction have not been investigated.

Methods—FMD and BAD were measured by brachial artery ultrasound at the initial examination of the Multi-Ethnic Study of Atherosclerosis. Long-term $PM_{2.5}$ concentrations were estimated for the year 2000 at each participant's residence (n = 3,040) using a spatio-temporal model informed by cohort-specific monitoring. Short-term $PM_{2.5}$ concentrations were based on daily central-site monitoring in each of the 6 cities.

Results—An interquartile increase in long-term $PM_{2.5}$ concentration (3 $\mu g/m^3$) was associated with a 0.3% decrease in FMD (95% confidence interval [CI] of difference: −0.6 to −0.03; p =

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APPENDIX For supplementary tables, please see the online version of this article.

0.03), adjusting for demographic characteristics, traditional risk factors, sonographers, and 1/BAD. Women, nonsmokers, younger participants, and those with hypertension seemed to show a greater association of $PM_{2.5}$ with FMD. FMD was not significantly associated with short-term variation in $PM_{2.5}$ (−0.1% per 12 $\mu g/m^3$ daily increase [95% CI: −0.2 to 0.04] on the day before examination).

Conclusions—Long-term $PM_{2.5}$ exposure was significantly associated with decreased endothelial function according to brachial ultrasound results. These findings may elucidate an important pathway linking air pollution and cardiovascular mortality.

Keywords

air pollution; atherosclerosis; cardiovascular mortality; endothelial function; flow-mediated dilation; traffic

Air pollution is a complex mixture of particulate matter, volatile organic compounds, and gaseous pollutants such as oxides of nitrogen. Epidemiological analyses have demonstrated an association between short- and long-term exposures to air pollution, especially particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) and increased cardiovascular morbidity and mortality (1,2). It is postulated that this adverse cardiovascular effect is related to systemic inflammation, oxidative stress, or autonomic nervous system imbalance effects in the artery wall (3). Hence, one of the intermediate steps by which $PM_{2.5}$ exposure increases cardiovascular morbidity and mortality may be via functional changes in the endothelium–smooth muscle complex.

Previous studies have shown associations between short-term exposure to $PM_{2.5}$ and nitric oxide (NO)-mediated endothelial dysfunction measured by using forearm plethysmography (4) or flow-mediated dilation (FMD) using brachial ultrasound (5,6). In a study of healthy volunteers situated for 2 h at different urban bus stops, a 30-$\mu g/m^3$ increase in $PM_{2.5}$ exposure corresponded to a 0.5% reduction in FMD (7). In contrast, other experimental studies have shown associations with vasoconstriction measured as a decrease in baseline arterial diameter (BAD) but not FMD (8,9). These studies provide different conclusions: $PM_{2.5}$ exposure may primarily affect NO-mediated endothelial dysfunction or it may alter elaboration of vasoconstrictors.

Observations from short-term exposure studies provide only limited insight into effects of pollutants and mechanisms. Are the vascular responses transient or do lasting effects accrue after long-term exposure? We hypothesized that repeated short-term insults to the vasculature result in persistent endothelial dysfunction related to long-term exposures. To test this hypothesis, we investigated the relationship between $PM_{2.5}$ exposures and changes in the brachial artery in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort. Leveraging the detailed exposure assignment of the MESA Air Pollution (MESA Air) study, we examined whether long- and short-term exposure to $PM_{2.5}$ is associated with decreased FMD and/or decreased BAD in this cohort.

Methods

Study design

MESA is a prospective study designed to investigate the prevalence and progression of subclinical atherosclerosis in participants aged 45 to 84 years who were free of clinical cardiovascular disease at the time of enrollment (10). The study includes 6,814 participants of white, African American, Hispanic, and Chinese descent from 6 US communities. The institutional review boards of each study site approved this study, and all participants gave

written informed consent. Demographic characteristics, medical history, anthropometry, laboratory data, and brachial ultrasound measurements for the current analysis were taken at the first examination (July 2000 to August 2002). For this study, we included all participants with reliable brachial ultrasound measurements for whom complete covariate information and exposure estimates were available (N = 3,040).

Vascular outcomes

The brachial examination procedure, inclusion and exclusion criteria, and reproducibility measures are reported in detail elsewhere (11). Briefly, participants were examined in the supine position after at least a 6-h fast and 15 min of rest. A standard blood pressure cuff was positioned around the right arm, 2 inches below the antecubital fossa, and the brachial artery was imaged 5 to 9 cm above the antecubital fossa by using a linear-array multifrequency transducer operating at 9 MHz and the LOGIQ 700 ultrasound (General Electric Logic 700 Device General Electric Medical Systems, Waukesha, Wisconsin). After the baseline images were obtained continuously for 30 s to obtain the BAD, the cuff was inflated to 50 mm Hg for 5 min above the participant's systolic blood pressure (SBP). After cuff deflation, the maximum arterial diameter (MAD) was measured. Image analysis was performed at the Wake Forest University Cardiology Image Processing Laboratory by using a previously validated semiautomated system that uses media-adventitial interfaces (12).

$$\text{FMD\% was computed as: } \frac{(\text{MAD} - \text{BAD}) \times 100}{\text{BAD}}$$

BAD (in millimeters) and FMD% were our main outcome measures and are based on recent guidelines (13). The number of sonographers acquiring images varied between the cities, ranging from 1 in St. Paul to 9 in Chicago. Each sonographer underwent central training, performed a supervised examination, and acquired at least 5 examinations acceptable to the core laboratory before certification. Intrareader reproducibility for BAD and FMD, evaluated by comparing an original and a blinded quality control reread of ultrasounds from 40 participants, was reported previously (11).

Exposure assessment. LONG-TERM $PM_{2.5}$ EXPOSURE ASSESSMENT

Estimates of long-term average ambient $PM_{2.5}$ concentrations were computed for each participant by using a hierarchical spatio-temporal model fit with an estimation procedure described elsewhere (14–16). Monitoring data came from the U.S. Environmental Protection Agency's Air Quality System regulatory monitoring stations supplemented by several fixed-site monitoring stations in each MESA community and home-monitoring at 10% of MESA participant homes, in campaigns specifically deployed for the MESA Air cohort (17). The hierarchical model decomposed the space-time field of concentrations into 3 components: 1) spatially varying long-term averages; 2) spatially varying seasonal and long-term trends; and 3) spatially correlated but temporally independent residuals. The spatially varying long-term averages and seasonal trends were modeled by using land-use regression and spatial smoothing of residuals using universal kriging. A large suite of spatial covariates such as proximity to major roadways and local land-use were used as predictors in the universal kriging models, after dimension reduction by partial least-squares. The spatially correlated but temporally independent residuals were predicted by using ordinary kriging. These components were combined to predict concentrations at each subject's home location for every 2-week period starting in January 1999. An average of exposures for the calendar year 2000 were used for this analysis. We used ArcGIS 9.1 software (Esri, Redlands, California);

Dynamap/2000 street network and geocoding database (TeleAtlas, Boston, Massachusetts) were used to determine participants' residential addresses.

SHORT-TERM $PM_{2.5}$ EXPOSURE ASSESSMENT

We assessed each participant's short-term exposure to $PM_{2.5}$ concentrations on the day of the examination (day 0), 1 day prior, 2 days prior, and the average of days 0 to 2. Daily average $PM_{2.5}$ concentrations were derived from an air quality system central-site monitoring station with complete daily average information available for the study city during the examination period (14).

COVARIATES

A number of covariates were considered in the multivariate analysis. These included age, gender, ethnicity, education, income, body surface area, smoking status, alcohol consumption, dietary fat intake, emotional distress derived from a standardized anxiety scale, and physical activity. We also adjusted for waist to hip ratio, blood glucose, SBP, diastolic blood pressure, high-density lipoprotein, total cholesterol, triglycerides, homocysteine, fibrinogen, and C-reactive protein. We also adjusted for specific medications, including anti-inflammatory agents, antihypertensives, lipid-lowering medications, and antioxidants (vitamin C).

Statistical analysis

Using Stata version 10.1 (Stata Corp., College Station, Texas) and SAS version 9.1.3 (SAS Institute, Inc., Cary, North Carolina), summary statistics were calculated and analyses performed. We tested for differences between the full cohort and those with complete data by using a *t* test for continuous covariates and chi-square test for the categorical covariates. Linear regression modeling was performed to examine associations between $PM_{2.5}$ estimates and the main vascular outcomes. Because the sonographers vary by study location and can influence these outcomes, the analyses were adjusted by using an indicator variable for sonographer. Each sonographer worked in only 1 study site; in effect, our analysis controls for study site as well.

The ratio outcome (FMD%) requires careful statistical consideration because the denominator (BAD) may itself be associated with the exposure. In our primary approach, we included 1/BAD as a covariate in regression models to obtain unbiased effect estimates and to increase precision (18). We also evaluated the FMD% outcome without adjusting for 1/BAD and have referred to it as "FMD% without adjustment for 1/BAD." In a sensitivity analysis, we also used simple extent of dilation ("FMDmm"), calculated as MAD-BAD, as reported in the Framingham Heart Study (13,19). Results are reported per interquartile range (IQR) change in $PM_{2.5}$.

The role of all the aforementioned covariates, including secondhand smoke exposures, family history of myocardial infarction, serum cotinine, and forced expiratory volume in 1 s, were examined. However, these were not included in the final model due to a large amount of missing data.

To control for temporal and meteorological confounding in short-term analyses, B-splines were used for city-specific trends in calendar time (12 df/year), temperature (6 df), and relative humidity (6 df) and included a city-specific day of the week indicator. In addition, long- and short-term exposures were evaluated jointly, including the temporal and meteorological confounders.

In another sensitivity analysis, the final model was not controlled for sonographer (or city) to determine between-city estimates. In separate city-specific analyses, the influence of within-city exposure contrasts was estimated in the final model controlled for sonographer. Differential susceptibility was investigated by stratifying for age categories, gender, ethnicity, diabetes mellitus status, hypertension categories (using the criteria of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, as derived from the blood pressure variables from examination 1) (20), antihypertensive use, obesity (obese if body mass index [BMI] ≥30 kg/m^2), smoking status, and residential stability (people who lived in the same address for ≥5 versus <5 years' duration). In addition, we tested for interaction for age, BMI, SBP, and diastolic blood pressure as continuous variables.

The effect of lipid-lowering medications and the antihypertensive medications classified as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, and vasodilators was investigated. Analysis was conducted by using stratification and by evaluating effect modification through interaction terms for the respective categories.

Results

Characteristics of the study population

Of the 6,814 MESA participants, only a subset of images from the brachial ultrasound examinations was analyzed due to quality control and funding reasons and also only in 5 of the 6 MESA study sites. Similar to the main cohort, our study population of 3,040 subjects included 50% female patients and 18% with less than a high school education. The exclusion of 1 site resulted in a lower proportion of African Americans and higher proportion of Chinese Americans than in the overall MESA cohort. Fifteen percent of the study population used lipid-lowering drugs, and 34% were treated for hypertension (Table 1). Approximately 21% of the participants had moved residential location within 5 years before their brachial examination. Estimated long-term $PM_{2.5}$ concentrations ranged from 10.6 to 24.7 $\mu g/m^3$, with an IQR of 3 $\mu g/m^3$. Short-term $PM_{2.5}$ concentrations ranged from 1 to 74 $\mu g/m^3$, with an IQR of 12 $\mu g/m^3$ (Fig. 1). The mean BAD and FMD% in this cohort were 4.3 ± 0.8 mm and 4.4 ± 2.8%, respectively (Table 2).

Long-term exposure to $PM_{2.5}$ and its association with reduced NO-mediated endothelial function

We found a significant inverse association between long-term $PM_{2.5}$ concentrations and FMD% but not with BAD. For every 3-$\mu g/m^3$ increase in the annual average of $PM_{2.5}$, FMD % decreased by 0.3% (95% CI: −0.6 to −0.03; p = 0.03) independent of cardiovascular risk factors (Table 3, Fig. 2). A weaker but highly statistically significant relationship was observed between long-term $PM_{2.5}$ concentrations and FMD% (−0.1% [95% CI: −0.2 to −0.04]; p = 0.005) without adjustment for sonographer or city (Online Table 1). Exclusion of sonographers who performed 1 to 2 examinations did not affect these estimates. Restricting analysis to those with a stable residential address for ≥5 years did not affect the association (Online Table 2). In sensitivity analyses using the FMD% without adjustment for 1/BAD (−0.3% [95% CI: −0.5 to 0.01]; p = 0.06) or the simple FMDmm (−0.01 mm [95% CI: −0.02 to 0.001]; p = 0.07), this negative association persisted.

Short-term $PM_{2.5}$ concentrations were associated with a small but not statistically significant reduction in FMD% (−0.1% [95% CI: −0.2 to 0.04]; p = 0.4) and BAD (−0.01 mm [95% CI: −0.05 to 0.01]; p = 0.4) for the day 1 before examination when adjusted for risk factors, seasonality, and meteorology (Table 4). Associations with long-term $PM_{2.5}$ exposure did not

significantly change when short-term exposure estimates or temperature or season were included in the model (Online Table 3).

City-specific differences for vascular outcomes and $PM_{2.5}$ association

Models stratified according to city demonstrated that the relationship between long-term $PM_{2.5}$ concentration and reduced FMD% was consistently negative across the 5 communities, except for St. Paul, which had the lowest mean $PM_{2.5}$ concentrations. Chicago participants showed the largest decrease in FMD% per IQR increase in $PM_{2.5}$ (Table 3). Similar effect estimates were noted when sonographer was not included as a covariate.

Assessing effect modification of association between long-term $PM_{2.5}$ exposure and NO-mediated endothelial dysfunction

A significant interaction was found between age and the association between long-term $PM_{2.5}$ and the FMD% ($p < 0.001$) but not for BMI or blood pressure. Younger age was associated with a larger magnitude of effect of $PM_{2.5}$ on reduced endothelial function (FMD % −0.5% [95% CI: −0.8 to −0.2%]; $p = 0.001$). Stratified analyses suggest that women, never smokers, participants with stages 1 and 2 hypertension, and those not taking antihypertensive medications tend to have a slightly greater negative association of $PM_{2.5}$ with FMD% (Online Table 3). Although no category of medication usage demonstrated statistically significant effect modification, the association between long-term $PM_{2.5}$ and FMD% seemed to be ameliorated by ACE inhibitor use ($n = 163$); there was a 0.3% increase (95% CI: −1.04 to 1.6) in FMD% per 3-$\mu g/m^3$ annual increase in $PM_{2.5}$ (Online Table 4).

Discussion

In this large, multisite, multiethnic cohort, a significant association was observed between long-term residential $PM_{2.5}$ concentrations and NO-mediated endothelial dysfunction as assessed by FMD, independent of major cardiovascular risk factors. Although previous studies (5,6,21) have assessed the relation between short-term exposure to $PM_{2.5}$ and endothelial function, this is the first investigation of the relation between long-term $PM_{2.5}$ exposure and endothelial function. Our study provides unique insights into the mechanisms of long-term $PM_{2.5}$ exposure and increased cardiovascular mortality.

Increasing age, SBP, BMI, and smoking are inversely related to FMD (19). The magnitude of the long-term effect of an IQR (difference between the 25th and 75th percentile) increase in $PM_{2.5}$ on FMD% is comparable to the effect of 5 years' increase in age, or of active tobacco smoking, in this population. A 3-$\mu g/m^3$ increase in $PM_{2.5}$ concentration occurs as a contrast in residential exposure between less polluted and more polluted areas in most major U.S. metropolitan areas. Taken together, these data suggest that $PM_{2.5}$ exerts a clinically relevant degree of effect on endothelial dysfunction.

Endothelial dysfunction measured by using FMD is a precursor for atherogenesis (22) and is associated with hypertension (23), passive smoking (24), and cardiovascular events (11,25). Although the role of FMD as a predictor is still controversial, it is consistently associated with future cardiovascular events (26). In a nested case-cohort study using MESA data, abnormal FMD was predictive of incident cardiovascular events independent of other major cardiovascular risk factors (11). Furthermore, a recent meta-analysis using pooled data from 14 studies (including 5,447 participants) found that a 1% decrease in FMD% was associated with an 8% increase in cardiovascular mortality independent of risk factors (26). In our study, a 10 $\mu g/m^3$ annual increase in $PM_{2.5}$ concentration was associated with a 1% decrease in FMD% (regardless of the adjustment for 1/BAD). Although we report our outcomes for an IQR increase in the $PM_{2.5}$ contrast, the equivalent of a 10-$\mu g/m^3$ exposure

contrast has previously been associated with a 9% increase in cardiopulmonary mortality in the American Cancer Society Cancer Prevention Study II (27) and a 24% increase in cardiovascular events in the Women's Health Initiative Observational Study (28).

Our finding regarding short-term exposures, although not statistically significant, is still notable given the prior association with endothelial dysfunction in both experimental (8,9) and observational (5,21) studies. Our results of larger associations with long-term compared with short-term associations (one-tenth of the effect estimate for short-term compared with long-term) parallel the larger magnitude of effect on cardiovascular mortality noted in previous population-based studies (27–29). For example, a 10-$\mu g/m^3$ increase in short-term exposure to particulate matter is typically associated with a 0.1% to 0.5% mortality increase in the large multicity studies (30) compared with 10% or greater mortality increases in long-term exposure cohort studies (1,27,28). The lack of more robust findings for short-term analysis may be due to limited statistical power or the simplified approach to short-term exposure estimation compared with long-term exposures.

Several mechanisms have been proposed to explain the potential cardiovascular risk associated with pollutants, involving oxidative stress, inflammation, and autonomic imbalance, each of which can affect the endothelium directly or indirectly. A recent study found an association between arterial stiffness and annual average concentrations of nitrogen dioxide and sulfur dioxide but not $PM_{2.5}$ (31). Reduced production and efficacy of NO in the vasculature is a hallmark of endothelial dysfunction. Previous studies in humans (8,9) have shown vasoconstriction and altered FMD with $PM_{2.5}$ but typically on an acute time scale. Stimulation of the angiotensin-1 receptor (32) or uncoupling of endothelial NO synthase (33) or generation of highly reactive oxygen species via nicotinamide adenine dinucleotide phosphate (reduced) oxidase and Toll-like receptor pathways (34) and Rho kinase activation (35) have been proposed as the relevant vascular mechanisms of $PM_{2.5}$. We found that long-term exposure to $PM_{2.5}$ might produce chronic changes in the brachial artery that negatively affects its ability to react to shear stress, primarily from NO-mediated endothelial dysfunction.

Insights into potential mechanisms of $PM_{2.5}$ exposure on endothelial function are further suggested by a subgroup analysis analyzing antihypertensive medication use. Although limited by subgroup sizes, we found that the use of ACE inhibitors, but not other classes of antihypertensive agents (including angiotensin receptor blockers) or lipid-lowering drugs, seemed to abrogate the association between long-term $PM_{2.5}$ concentrations and FMD%. Elevated endothelial kinins and NO from ACE inhibition could play a role in mitigating $PM_{2.5}$-induced endothelial dysfunction (36,37). Recently, we found that the genetic variation in the renin-angiotensin-aldosterone pathway seemed to modify the effect of traffic-related air pollution on increased left ventricular mass in the MESA cohort (38).

Study strengths and limitations

Major strengths of our study include availability of vascular functional measurements in a large multiethnic cohort with high-quality control standards and excellent data on covariates. We took advantage of the specialized monitoring and sophisticated exposure models from MESA Air to predict spatially resolved, individual-specific estimates at each participant's home (15).

Our study has several limitations. Most importantly, this is a cross-sectional evaluation of images collected on 1 occasion; important information might be gained by a longitudinal study of vascular function. Our findings also may not be generalizable to either normal younger individuals or those with recognized clinical disease. It should be noted that although our long-term exposure estimates are derived from sophisticated exposure

modeling methods, they are subject to measurement error and may not fully reflect an individual's long-term exposure because information on specific microenvironments, time-activity patterns, or periods of exposure >1 year before testing is lacking. Future MESA Air exposure metrics will be able to incorporate individual-level data on pollutant infiltration efficiencies and time spent indoors, which will improve these estimates.

FMD is a commonly applied marker for NO-mediated endothelial dysfunction (39). We found consistent associations between $PM_{2.5}$ and reduced NO-mediated endothelial dysfunction, whether expressed as FMD% (with or without adjustment for 1/BAD) or the simple change in FMDmm. Because MESA did not include nitroglycerin administration, we could not rule out NO-independent endothelial dysfunction in this analysis.

Conclusions

This is the first epidemiological study to suggest that long-term exposure to $PM_{2.5}$ is associated with decreased endothelial function in a conduit artery independent of cardiovascular risk factors. This finding provides a clue that long-term perturbations of the endothelium–smooth muscle complex from $PM_{2.5}$ exposure lead to chronic functional changes. These functional changes may partly explain the risk of cardiovascular events previously associated with these environmental exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations and Acronyms

ACE	angiotensinconverting enzyme
BAD	baseline arterial diameter
BMI	body mass index
FMD	flow-mediated dilation
IQR	interquartile range
MAD	maximum arterial diameter
NO	nitric oxide
$PM_{2.5}$	particulate matter <2.5 μm in aerodynamic diameter
SBP	systolic blood pressure

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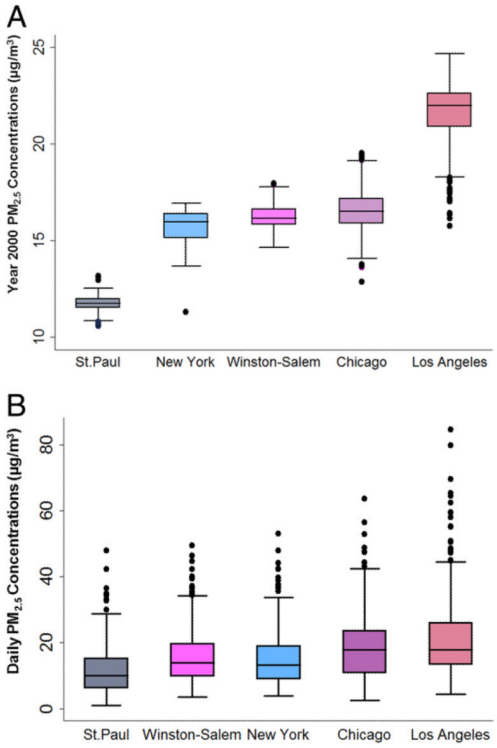

Figure 1. Distribution of the $PM_{2.5}$ Concentrations

(A) Long-term particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) concentrations estimated for the year 2000 annual average. **(B)** Short-term $PM_{2.5}$ concentrations for 2 days before the brachial examination. Similar distribution pattern was seen for all other averaging time points.

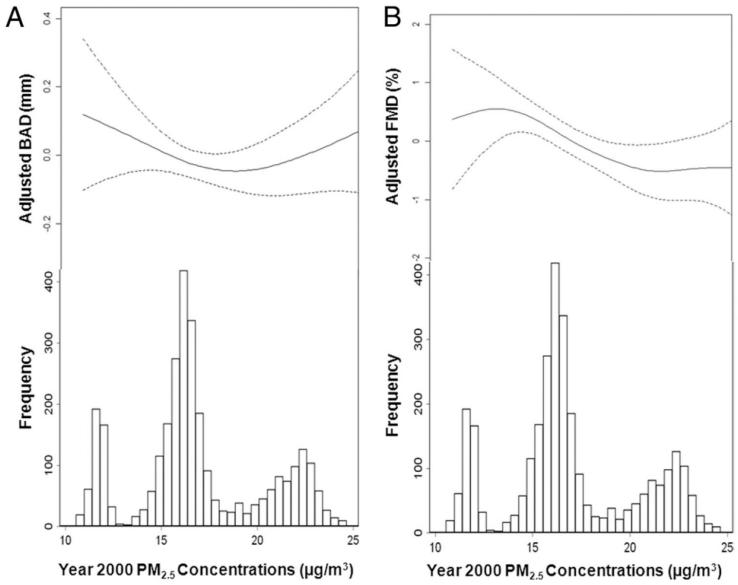

Figure 2. Dose-Response Associations Between Brachial Outcomes and Modeled Long-Term Pollutant Concentrations After Controlling for Covariates

The values for **(A)** baseline arterial diameter (BAD) and **(B)** flow-mediated dilation (FMD) represent partial residuals from a final model controlled for age, gender, ethnicity, body surface area, sonographer, income, education, smoking, alcohol use, dietary fat intake, emotional distress, physical activity, waist to hip ratio, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein, C-reactive protein, fibrinogen, homocysteine, fasting blood glucose, anti-inflammatory agents, antihypertensive agents, lipid-lowering drugs, and vitamin C. FMD% includes adjustment for 1/BAD. Data are plotted as penalized thin-plate regression splines with smoothness parameter selected by generalized cross-validation for BAD and FMD%.

Table 1

Demographic and Health Characteristics of the MESA Participants During Examination 1 (2000–2002)

Characteristic	All Participants (N = 6,814)	Participants With Complete Data (n = 3,040)	p Value
Age (yrs)	62.2 ± 10.2	61.2 ± 9.9	<0.001
Systolic blood pressure (mm Hg)	126.6 ± 21.5	125.5 ± 19.7	<0.001
Diastolic blood pressure (mm Hg)	72.0 ± 10.0	72.2 ± 10.3	0.45
Body mass index (kg/m^2)	28.3 ± 5.5	27.7 ± 5.1	0.01
Body surface area (m^2)	1.85 ± 2.3	1.86 ± 2.3	<0.001
Blood glucose (mg/dl) *	97.5 ± 30.2	96.2 ± 28.1	0.05
High-density lipoprotein (mg/dl) *	50.9 ± 14.8	50.6 ± 14.6	0.3
Total cholesterol (mg/dl) *	194.2 ± 35.7	194.4 ± 34.9	0.6
C-reactive protein (mg/l) *	3.8 ± 5.9	3.4 ± 5.4	0.002
Physical activity (MET min/week)	807.3 ± 793.3	821.3 ± 842.3	0.4
Less than high school education	1,225 (18.0)	559 (18.4)	0.4
Current alcohol users	3,749 (55.4)	1,681 (55.3)	0.001
Gender			
Men	3,601 (52.9)	1,545 (50.8)	0.06
Women	3,213 (47.2)	1,495 (49.2)	
Ethnicity			
White	2,622 (38.5)	1,023 (33.9)	<0.001
Chinese American	803 (11.8)	605 (19.8)	
African American	1,893 (27.8)	641 (21.1)	
Hispanic	1,496 (21.9)	765 (25.1)	
Smoking status *			
Never	3,418 (50.3)	1,654 (54.4)	0.001
Former	2,487 (36.6)	1,033 (33.9)	
Current	887 (13.1)	355 (11.6)	
Diabetes mellitus status (ADA 2003 criteria) *			
Normal	5,087 (74.9)	2,340 (76.9)	
Impaired fasting glucose	844 (12.4)	369 (12.1)	0.1
Nontreated DM	179 (2.6)	71 (2.3)	
Treated DM	680 (10.0)	260 (8.5)	
Drug use			
Antihypertensive medications *	2,536 (37.2)	1,042 (34.3)	0.01
Lipid-lowering drugs *	1,100 (16.1)	465 (15.3)	0.3

Values are mean ± SD or n (%), and p values were obtained from a *t* test or chi-square test for difference between all Multi-Ethnic Study of Atherosclerosis (MESA) participants and those with complete data.

* Indicates the covariates for which the total number of available participants was less due to missing information.

ADA = American Diabetes Association; DM = diabetes mellitus; MET = metabolic equivalent.

Table 2

Distribution of Brachial Artery Outcomes and Sonographers Among the MESA Participants Included in the Final Study Model (N = 3,040)

Outcome	Chicago (n = 681)	Los Angeles (n = 800)	New York (n = 584)	St. Paul (n = 473)	Winston-Salem (n = 502)	Total (N = 3,040)
Baseline arterial diameter (mm)	4.2 ± 0.8	4.4 ± 0.8	4.4 ± 0.8	4.3 ± 0.9	4.3 ± 0.9	4.3 ± 0.8
Flow-mediated dilation (mm)	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
Flow-mediated dilation (%)	4.8 ± 2.9	4.2 ± 2.5	4.2 ± 2.6	5.0 ± 3.2	4.0 ± 2.9	4.4 ± 2.8
No. of sonographers	9	5	7	1	2	24

Abbreviation as in Table 1.

Table 3

Associations Between Brachial Artery Outcomes and the Long-Term Exposures to $PM_{2.5}$

Final Model	BAD (mm)		FMD (%)	
Final Model	**β-Coefficient (95% CI)**	**p Value**	**β-Coefficient (95% CI)**	**p Value**
Total population (n = 3,040)	−0.002 (−0.06 to 0.06)	1.0	−0.3 (−0.6 to −0.03)	0.03
Chicago (n = 681)	−0.1 (−0.3 to 0.002)	0.05	−0.6 (−1.1 to 0.01)	0.05
Los Angeles (n = 800)	0.1 (−0.02 to 0.2)	0.13	−0.2 (−0.6 to 0.2)	0.3
New York (n = 584)	−0.2 (−0.4 to −0.02)	0.03	−0.3 (−1.1 to 0.4)	0.4
St. Paul (n = 473)	0.02 (−0.4 to 0.5)	0.9	0.2 (−1.9 to 2.4)	0.8
Winston-Salem (n = 502)	0.2 (−0.1 to 0.5)	0.2	−0.1 (−1.5 to 1.3)	0.9

All associations reported for baseline arterial diameter (BAD) as millimeters and for flow-mediated dilation (FMD) as percentage per interquartile range of 3 $\mu g/m^3$ in particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) for the long-term exposure. Effect estimates (β-coefficients) and 95% confidence intervals (CIs) are shown for these associations derived from the multiple regression modeling. Final model includes age, gender, body surface area, sonographer, income, education, smoking, alcohol use, dietary fat intake, emotional distress, physical activity, waist to hip ratio, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein, C-reactive protein, fibrinogen, homocysteine, fasting blood glucose, anti-inflammatory agents, antihypertensive agents, lipid-lowering drugs, and ascorbate (also 1/BAD for FMD). p Values are based on the final model of the multiple regression analysis controlled for all the these covariates for the total population and the city-specific analysis. Interaction testing did not reveal any significant effect modification for the city-specific analysis.

Table 4

Association Between Short-Term $PM_{2.5}$ Concentrations and the Brachial Artery Outcomes

	BAD (mm)		FMD (%)	
Outcome	**β-Coefficient (95% CI)**	**p Value**	**β-Coefficient (95% CI)**	**p Value**
Day 0 (n = 2,695)	−0.02 (−0.06 to 0.01)	0.1	−0.06 (−0.2 to 0.08)	0.4
Day 1 (n = 2,715)	−0.01 (−0.05 to 0.01)	0.4	−0.10 (−0.2 to 0.04)	0.2
Day 2 (n = 2,709)	−0.001 (−0.04 to 0.04)	0.9	−0.08 (−0.2 to 0.05)	0.2
Average of 3 days (n = 2,550)	−0.02 (−0.06 to 0.02)	0.3	−0.1 (−0.3 to 0.05)	0.3

All associations reported for BAD as millimeters and for FMD as percentage for a daily interquartile range increase of 12 $\mu g/m^3$ of $PM_{2.5}$ concentrations derived from central-site monitors on days 0, 1, and 2, and the average of these 3 days, before the brachial ultrasound examination. Effect estimates (β-coefficients) and 95% CIs are shown for these associations derived from the multiple regression modeling. Final model includes age, gender, body surface area, sonographer, income, education, smoking, alcohol use, dietary fat intake, emotional distress, physical activity, waist to hip ratio, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein, C-reactive protein, fibrinogen, homocysteine, fasting blood glucose, anti-inflammatory agents, antihypertensive agents, lipid-lowering drugs, and ascorbate (also 1/BAD for FMD %). In addition, we also included interaction for each city and day of the week as well as B-splines of temporal variables temperature (4 df/year), seasonality (12 df/year), and humidity (6 df/year) for these short-term exposures.

Abbreviations as in Table 3.