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Fine Particulate Matter Air Pollution, Proximity to Traffic, and Aortic Atherosclerosis

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Abstract

Background—The initiation and acceleration of atherosclerosis is hypothesized as a physiologic mechanism underlying associations between air pollution and cardiovascular effects. Despite toxicologic evidence, epidemiologic data are limited.

Methods—In this cross-sectional analysis we investigated exposure to fine particulate matter ($PM_{2.5}$) and residential proximity to major roads in relation to abdominal aortic calcification a sensitive indicator of systemic atherosclerosis. Aortic calcification was measured by computed tomography among 1147 persons, in 5 U.S. metropolitan areas, enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). The presence and quantity of aortic calcification were modeled using relative risk regression and linear regression, respectively, with adjustment for potential confounders.

Results—We observed a slightly elevated risk of aortic calcification (RR = 1.06; 95% confidence interval = 0.96–1.16) with a 10-μg/m^3 contrast in $PM_{2.5}$. The $PM_{2.5}$-associated risk of aortic calcification was stronger among participants with long-term residence near a $PM_{2.5}$ monitor (RR = 1.11; 1.00–1.24) and among participants not recently employed outside the home (RR = 1.10; 1.00–1.22). $PM_{2.5}$ was not associated with an increase in the quantity of aortic calcification (Agatston score) and no roadway proximity effects were noted. There was indication of $PM_{2.5}$ effect modification by lipid-lowering medication use, with greater effects among users, and $PM_{2.5}$ associations were observed most consistently among Hispanics.

Conclusions—Although we did not find persuasive associations across our full study population, associations were stronger among participants with less exposure misclassification.

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These findings support the hypothesis of a relationship between particulate air pollution and systemic atherosclerosis.

Epidemiologic studies have demonstrated that long-term exposure to ambient air pollution, especially fine particulate matter ($PM_{2.5}$), is associated with cardiovascular morbidity and mortality.[1] Recent evidence suggests that particles and other pollutants generated by traffic may be important contributors to the cardiovascular effects of air pollution.[2–4]

The initiation and acceleration of atherosclerosis has been hypothesized as a physiologic pathway through which particles exert cardiovascular effects.[1,5,6] Acute air pollution exposure has been linked to pulmonary and systemic inflammation[7,8] and repeated inflammatory responses may lead to accelerated atherosclerosis.[5,9]

There is toxicologic evidence of a link between PM exposure and atherosclerosis.[10–12] However, there is only limited cross-sectional epidemiologic evidence of a relationship between air pollution and atherosclerosis in humans. In Los Angeles, Künzli et al[13] studied 859 adult participants from the baseline assessment of 2 clinical trials and examined carotid intima-media thickness in relation to $PM_{2.5}$ concentrations interpolated to participants' zip code centroids. They reported a 4% increase in intima-media thickness associated with a 10-$\mu g/m^3$ contrast in $PM_{2.5}$. Greater effect estimates were reported for those taking lipid-lowering medications, women, and those 60 years or older. A recent investigation of 4494 persons in Germany found that proximity to major roads was associated with increases in coronary artery calcium, and $PM_{2.5}$ was associated with coronary artery calcium among individuals who had not worked full-time in the previous 5 years.[4] The strongest roadway associations with mcoronary artery calcium were among men and less-educated participants. Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), we recently analyzed $PM_{2.5}$ and PM_{10} exposure in relation to coronary artery calcium, carotid intima-media thickness, and ankle–brachial index.[14] We found significant associations only for carotid intima-media thickness.

Our objective was to build on this nascent understanding of the relationship between air pollution and atherosclerosis in humans. Here we report the results of a cross-sectional analysis of the relationship between both $PM_{2.5}$ concentrations and residential proximity to major roadways and atherosclerosis of the abdominal aorta among a multiethnic group of individuals in 5 metropolitan areas in the United States.

Although initially investigated as a marker of peripheral vascular disease, calcification of the aorta has emerged as a measure of systemic atherosclerosis.[15] Atherosclerosis of the aorta is associated with atherosclerosis of the carotid and coronary arteries[16–18] and with cardiovascular mortality and morbidity.[19–22] In addition, aortic calcification is associated with many traditional cardiovascular risk factors including age, smoking, total cholesterol, hypertension, and diabetes metillus.[18,23–26] Lipid-lowering therapy has been found to slow the progression of abdominal aortic plaques,[27] and there is evidence that the development of atherosclerosis in women accelerates after menopause.[18] The prevalence and extent of abdominal aortic calcium is generally greater than coronary artery calcium for both sexes after age 50.[18,28] The lower frequency of 0 values for aortic calcification makes it a useful measure in epidemiologic studies.

METHODS

Aortic calcification data, information on potential confounders, and participants' residence locations were collected as part of MESA[29] and 2 MESA ancillary studies: the MESA Aortic Calcium Study and the MESA Neighborhood Study. The study design and data collection methods for MESA have been previously described.[29] In summary, 6814 men and

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women aged 45–84 years and without clinical cardiovascular disease representing 4 ethnic groups (black, Chinese, Hispanic, and white) were recruited starting in 2000 from 6 areas in the U.S.: Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County (Winston-Salem), NC; Los Angeles County, CA; Manhattan and the Bronx, NY; and St. Paul, MN. Participants were recruited using a variety of population-based approaches including lists of area residents (all sites), Health Care Financing Administration lists of area residents (for participants 65 years and older at all sites), area residents enrolled in a union health plan (New York), and random digit dialing (New York and Los Angeles). Four clinical examinations were conducted at about 18-month intervals. Each examination included a variety of assessments and measurements of cardiovascular risk factors, as well as the administration of questionnaires to assess personal history, behaviors, and socioeconomic characteristics. All of the participating centers' institutional review boards approved the study and all study participants gave informed consent.

Abdominal Aortic Calcium

A group of 1965 MESA participants were randomly selected from all but the Maryland center for enrollment in the MESA Aortic Calcium Ancillary Study. Scanning centers assessed aortic calcification by computed tomography (CT) using either an electron-beam CT or multidetector CT scanner. Certified technologists scanned all participants over phantoms of known physical calcium concentration. Scanning teams attempted to include the segment of the aorta between its bifurcation and a point 8 cm cephalad to the bifurcation by scanning between the superior plate of the first sacral vertebra and a point 15 cm cephalad.

A single radiologist read and assessed all CT scans at a central reading center (LA Biomedical Research Institute at Harbor-UCLA in Torrance, CA) by using an interactive scoring system similar to that used by Yaghoubi et al.[30] The reader–work station interface identified and quantified calcification from images calibrated using readings of the calcium phantom. The quantitative measure of interest for analysis was the Agatston score of the abdominal aorta.[31]

Although aortic calcification was quantified from only a single scan, Budoff et al[32] recently reported on the reproducibility of calcium scores from the thoracic aorta in MESA. Interscan variability (ie, different scan, same reader) was 17%–18%, interreader variability (ie, same scan, different reader) was 3%–7%, and intrareader variability (ie, same scan, same reader) was 0.4%–1.4%.

Residence Locations

A subset of MESA participants who agreed to participate in the MESA Neighborhood ancillary study had their residential addresses at baseline geocoded into a latitude/longitude location. Geocoding was conducted using the year 2006 TeleAtlas Dynamap/2000 road network. The percentage of addresses that were successfully geocoded was 97%, and ranged from 93% in New York to 99% in St. Paul.

Exposure Assessment

Our exposure assessment approach was intended to capture exposure to both urban background $PM_{2.5}$ and traffic-generated pollutant concentrations.[3] The background $PM_{2.5}$ concentration within urban areas is generally spatially homogeneous,[33] whereas the concentrations of traffic-generated pollutants vary on a much smaller spatial scale.[34,35] Due to a lack of routine pollution monitoring near roads, residential proximity to major roads is frequently used as a surrogate for traffic exposure in epidemiologic studies of cardiovascular and respiratory effects.[2–4] This approach is supported by data showing that the

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concentrations of traffic pollutants decay sharply as a function of distance from the roadway's edge.[36,37]

We assigned $PM_{2.5}$ exposure based on the average concentrations over the 2-year period from October 2000 through September 2002. Concentrations over this period are assumed to be representative of longer-term past exposures. This averaging period was selected because the U.S. national $PM_{2.5}$ monitoring network was fully deployed beginning in 2000 and aortic CT scans were begun in September 2002. $PM_{2.5}$ data were obtained from the Environmental Protection Agency's Aerometric Information Retrieval System. Monitoring sites were included if they met the following criteria: 1) a monitoring objective of "population exposure," "regional transport," or "general/background;" and 2) at least 50% data reporting in each of the 8 3-month periods over the averaging time of interest. The number of $PM_{2.5}$ monitors meeting the above criteria and located within 50 km of a study participant's residence ranged from 3 in Forsyth County, NC to 21 in Chicago. In cities with at least 10 monitoring sites (Chicago, Los Angeles, and New York), we used universal kriging to interpolate the 2- year average $PM_{2.5}$ concentration to the participants' residence locations. Exposures in St. Paul and Forsyth County were assigned based on inverse distance weighting ($1/d^2$). The average (± standard deviation [SD]) distance from participants' residences to the nearest $PM_{2.5}$ monitor in each city ranged between 2.2 ± 1.1 km in New York and 7.1 ± 4.5 km in Forsyth County. The maximum distance from any participant's residence to the closest $PM_{2.5}$ monitor was 21.0 km; therefore, no participants were excluded based on distance to the nearest monitor.

We assigned traffic exposure by using a binary variable based on residential proximity to major roads. Participants were considered exposed to traffic pollution if they resided within 100 m of the centerline of a highway or within 50 m of the centerline of a major arterial road, where road types were defined using the TeleAtlas road network's classification system. We defined highways as those with feature class codes A1 or A2 and major arterial roads as those with feature class A3. Our roadway distance criteria of 50 and 100 m were selected to be consistent both with 2 previous investigations of traffic pollution–related health effects[2,3] and with data on pollutant concentrations as a function of distance from roads. All roadway proximity calculations, interpolation of $PM_{2.5}$ concentrations, and $PM_{2.5}$ exposure assignments were conducted using ArcGIS 9 (ESRI, Redlands, CA).

Data Reduction

A total of 1879 participants had a valid abdominal aortic CT scan and an address that was successfully geocoded. We removed 196 participants without complete data on the following potential confounders: age, sex, race/ethnicity, body mass index (BMI), smoking status, smoking history (ie, pack-years), diabetes, education, income, blood pressure, blood lipid concentrations, and medication use. To minimize exposure misclassification under the assumption that our exposure assignments represent long-term past exposures, we excluded an additional 555 participants who had not lived in the same area for at least 10 years prior to MESA examination 1, when addresses for geocoding were obtained. The final group of residentially stable participants included 1147 persons (Table 1). In our sensitivity analysis we used multiple imputation methods (SAS PROC MI and PROC MIANALYZE) to include the 122 residentially stable participants with missing covariate data and to estimate $PM_{2.5}$ and roadway proximity effects among the full group of 1269 residentially stable participants.

Data Analysis

Because abdominal aortic calcification was not detectable in every study participant we selected a priori a 2-part modeling approach consistent with previous MESA analyses.[38] First, we modeled the relative risk of having any detectable calcification among the full

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group of participants. For common outcomes, relative risk regression is desirable because it prevents misinterpretation of odds ratios.[39] The probability of a nonzero calcification score was modeled using the GENMOD procedure in SAS (SAS 9.1, Cary, NC). We used a log link and a Gaussian error model with robust standard errors; this approach was necessary to avoid convergence problems associated with a binomial error model. Relative risks are based on the exponent of the model's coefficients. In our sensitivity analysis we also used a modified Poisson regression with robust error variance.[40]

The second analysis step was a multiple linear regression of the log-transformed Agatston score among those with any calcification (Table 2). We report these results as the percent change in the Agatston score. All $PM_{2.5}$ effect estimates for both modeling steps are reported per 10-μg/m^3 exposure contrast. In our sensitivity analysis we also modeled the Agatston score among all participants by adding 1 prior to log-transforming.

With the exception of residential location, which was collected only at study entry (examination 1), all subject-specific data used in this analysis were collected during the examination in which the abdominal CT scan was performed (2 or 3). Our fully adjusted models included age, sex, race/ethnicity, body mass index (BMI), smoking status (never, former, current), pack-years of smoking, diabetes (treated or untreated diabetes based on 2003 American Diabetes Association fasting criteria), education (< high school degree, high school graduate or equivalent, and college graduate), annual income (<$20,000, $20,000–$49,999, and ≥$50,000), blood lipid concentration (high-density, and low-density lipids), blood pressure (systolic and diastolic), and medications (lipid lowering and antihypertensives).

From the literature we identified potential effect modifiers, and as part of our exploratory analyses we tested for heterogeneity in the $PM_{2.5}$ and near road effects by sex,[13,41] age,[13,41] diabetes,[8,42] obesity (BMI ≥ 30 kg/m^2),[8] the use of lipid-lowering medications,[13] education,[43] and income.[44] In addition, the inclusion of multiple race/ethnicities is a major strength of this cohort, and we explored effects within each race/ethnic group. We conducted several sensitivity analyses to evaluate the impact on the effect estimates of our modeling approach, exposure assessment methods, and participant inclusion criteria. We also evaluated the impact of employment status on our estimates; since we used residence location to assign exposure, our exposure estimates may have been more accurate for those not working outside the home. Participants were considered employed if they reported working or volunteering at any study examination up to the time of the abdominal CT scan. Participants who were unemployed, retired, or homemakers at each study examination up to the time of the abdominal CT scan were considered not employed.

RESULTS

Summary statistics of participant characteristics and exposure variables are presented in Table 1. The average age (± SD) of study participants was 65.9 ± 9.4 years (range, 46–88) and was similar across cities. Whites comprised approximately 40% of the cohort and were the only racial/ethnic group represented in all cities. Blacks and Hispanics each comprised about one quarter of the cohort, and Chinese-Americans about 10%. Los Angeles was the only city with a significant number of participants from all four racial/ethnic groups. Some differences in socioeconomic status ([SES] as indicated by income and education) among cities were observed, with the lowest overall SES in Los Angeles and the highest in Chicago. About 40% of the participants were former smokers and 10% were current smokers. Employment/volunteer status was assessed from baseline to the time of the abdominal CT scan (an average duration of 2.7 years; range, 1.1–4.8 years); 63% of all participants (68% of men and 58% of women) worked or volunteered during this period.

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Estimates of individual $PM_{2.5}$ exposure ranged from 10.6 to 24.7 μg/m^3 (the U.S. National Ambient Air Quality Standard for annual average $PM_{2.5}$ concentration is 15 μg/m^3). There was considerable variability in estimated $PM_{2.5}$ exposure between cities (ranging from a mean of 10.9 μg/m^3 in St. Paul to 22.8 μg/m^3 in Los Angeles) but very little within-city variability (Table 1). In fact, 98% of the total variance in $PM_{2.5}$ exposure was between cities. This lack of within-city variability in exposure is due to both the spatial homogeneity of $PM_{2.5}$ concentrations and the fact that the study participants were clustered in relatively small geographic areas. Because not all racial/ethnic groups were present in St. Paul, blacks (14.4–23.2 μg/m^3) and Chinese (14.3–24.4 μg/m^3) had smaller ranges of $PM_{2.5}$ exposure than Hispanics (10.7–24.7 μg/m^3) and whites (10.6–24.3 μg/m^3). Overall, 31% of the cohort was classified as living near a major road, ranging from 16% in Los Angeles to 58% in New York. $PM_{2.5}$ exposures were similar for participants living "near" (n = 350; mean $PM_{2.5}$ = 15.6 ± 2.8 μg/m^3) and "far" (n = 797; mean $PM_{2.5}$ = 15.9 ± 3.9 μg/m^3) from major roads because our PM prediction approach did not account for roadway proximity.

CT Scanner Technology

Overall, abdominal aortic calcification was detected on 74% of the CT scans (Table 2). The electron-beam scanners detected calcium on 71% (489 of 694) of scans, whereas 80% (362 of 453) of scans from the multidetector CT scanners detected calcium (χ^2 = 12.8; P < 0.001). The mean ± SD log-transformed Agatston score from electron-beam and multidetector scanners were 6.27 ± 1.86 and 6.60 ± 1.79, respectively (P < 0.01, 2-sample t-test). These differences in both calcium prevalence and Agatston score persisted after adjustment for important risk factors. We therefore determined it was necessary to adjust for scanner technology in all models. Adjusting for scanner technology was preferable to adjusting for individual scanner because the former allowed us to retain the full between-city $PM_{2.5}$ exposure contrast. Participants scanned using electron-beam technology had higher mean $PM_{2.5}$ concentrations (17.7 ± 3.2 μg/m^3 vs. 13.0 ± 2.2 μg/m^3) and resided more frequently near a major road (36% vs. 23%) than those scanned on multidetector CT machines.

Detectable Abdominal Aortic Calcium

We estimated the risk of nonzero Agatston score in 6 models with increasing adjustment for confounders (Fig. 1). In the crude model (adjusting only for CT scanner technology) $PM_{2.5}$ was associated with elevated risk of calcification (RR = 1.15; 95% confidence interval [CI] = 1.02–1.29; P < 0.05). The $PM_{2.5}$ effect estimate remained elevated (RR = 1.09–1.11) under increasing adjustment for covariates until blood lipids, blood pressure, and medications were included in the model (models 1–4 in Fig. 1). The inclusion of blood lipids and lipid-lowering medications attenuated the effect estimate to 1.07 (0.98–1.17), and the estimate relative risk was further attenuated (RR = 1.06; 0.96–1.16) after also adjusting for blood pressure and use of antihypertensive medications. Adjustment for age and antihypertensive medications caused the greatest attenuation of the $PM_{2.5}$ effect estimate from the crude (scanner technology only) model (Fig. 1). Use of a modified Poisson regression approach had little impact on the fully adjusted $PM_{2.5}$ (RR = 1.06; 0.95–1.19) and roadway proximity effect estimates. No associations were found between aortic calcification and proximity to roads.

As part of our exploratory analyses we estimated $PM_{2.5}$ and roadway proximity effects after stratifying by several factors (Fig. 2). There was a trend of an increasing roadway proximity effect with increasing income (trend P value <0.01) and some indication of differences in $PM_{2.5}$ effect after stratifying by sex (greater effect among women, interaction P = 0.13) and lipid-lowering medication use (greater effect among users, interaction P = 0.13). $PM_{2.5}$ was associated with elevated risks of calcification among women (RR = 1.14; 1.00–1.30; n = 578), persons older than 65 years (RR = 1.10; 1.01–1.19; n = 602), users of lipid-lowering

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medications (RR = 1.14; 1.00–1.30; n = 293), and Hispanics (RR = 1.22; 1.03–1.45; n = 311). A near-road effect was found among participants earning over $50,000 per year (RR = 1.09; 1.00–1.19; n = 466).

We conducted several sensitivity analyses. After imputing missing covariates we estimated an elevated $PM_{2.5}$ relative risk among the complete group of 1269 residentially stable participants (RR = 1.08; 0.98–1.19). We also evaluated the sensitivity of the effect estimates to several factors hypothesized to affect $PM_{2.5}$ exposure accuracy, including our a priori criteria for residential stability (≥10 years) and proximity to a $PM_{2.5}$ monitor (all participants included) (Table 3). More restrictive criteria resulted in greater point estimates, and among participants residing at their current address for at least 20 years and within 10 km of a $PM_{2.5}$ monitor (n = 689) the estimated $PM_{2.5}$ relative risk was 1.11 (1.00–1.24). $PM_{2.5}$ relative risks were also elevated among participants who did not work from baseline to the time of the CT scan (RR = 1.10; 1.00–1.22; n = 424) and participants who did not reside near a major road (RR = 1.10; 0.99–1.23; n = 797).

As an alternative to kriging and inverse distance weighting, we estimated effects after assigning $PM_{2.5}$ exposure for all participants by using the concentration measured at the monitor nearest the residence. This approach had little impact on the estimates ($PM_{2.5}$ RR = 1.05; 0.96–1.15). We also modeled the relative risk of being in the top quartile of Agatston score (ie, Agatston score > 1806); the $PM_{2.5}$ (RR = 1.20; 0.94–1.53) and near roads (1.04; 0.89–1.22).

Agatston Score

Among the full group of persons with abdominal aortic calcification we found no $PM_{2.5}$ or near-road effects. As with the presence of calcification, increasing adjustment for confounders attenuated the estimate of $PM_{2.5}$ effect on Agatston score from 33% (−11%–76%) in the crude model to 8% (−30%–46%) in the fully adjusted model (Fig. 3). The greatest reductions in the $PM_{2.5}$ effect estimate resulted from adjustment for age and systolic blood pressure (Fig. 3). The point estimate of $PM_{2.5}$ effect on Agatston score was somewhat sensitive to selection criteria, interpolation method, and employment status (Table 3).

After stratifying, we noted a greater $PM_{2.5}$ effect on Agatston score among participants using lipid-lowering medications than among nonusers (interaction $P = 0.06$) (Fig. 4). Within strata we noted $PM_{2.5}$-associated increases in Agatson score among Hispanics (64%; −4%–133%; n = 224) and persons earning more than $50,000 per year (72%; 5%–139%; n = 318). There were no associations within strata between Agatston score and proximity to major roads.

In addition to our a priori model selection, we also modeled the Agatston score among the full study population (including those with Agatston score = 0) by adding 1 before log-tranforming. Because 25% of the cohort had no calcification, this transformation resulted in a nonnormal distribution, but the sample size was sufficient to accommodate this lack of normality in the regression.[45] Under this scenario $PM_{2.5}$ was associated with a 41% (−12%–93%) increase in Agatston score across all participants in the fully adjusted model (Fig. 5). Again, the $PM_{2.5}$ effect estimate was greater among lipid-lowering medication users than nonusers (interaction $P < 0.05$). There was also evidence of increasing roadway effect with increasing education (P for trend = 0.06) and income (P for trend < 0.05). Within strata we observed significant $PM_{2.5}$-related increases in Agatston score among persons older than 65 years (75%; 8%–143%; n = 602), diabetics (149%; 29%–270%; n = 174), users of lipid-lowering medications (121%; 25%–217%; n = 293), and Hispanics (141%; 45%–236%; n = 311) (Fig. 5). Roadway proximity was associated with a 63% increase in Agatston score (13%–112%; n = 466) among persons earning more than $50,000 per year.

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In sensitivity analyses, after imputing missing covariates $PM_{2.5}$ was associated with a 49% increase in Agatston score (1.3%–100.1%). The $PM_{2.5}$ effect estimates were sensitive to exposure misclassification. Among participants residing at their current address for at least 20 years and within 10 km of a $PM_{2.5}$ monitor (n = 689), $PM_{2.5}$ was associated with a 79% increase in Agatston score (10.1%–148%). Estimates of $PM_{2.5}$ effect were also elevated among participants not residing near a major road (51%; −8%–111%; n = 797) (Table 3).

DISCUSSION

This is the first effort to study the association between abdominal aortic calcification, a sensitive measure of systemic atherosclerosis, and an environmental exposure. We did not find consistent associations between $PM_{2.5}$ concentrations and the prevalence or extent of calcification across all participants in our fully adjusted models. However, there was evidence that our $PM_{2.5}$ effect estimates were affected by exposure misclassification. The increased point estimate for participants residing within 10 km of a $PM_{2.5}$ monitor suggests that exposure error introduced by spatially interpolating measured concentrations may have affected our estimates. Similarly, although we were able to assess employment status over only a relatively short period (from baseline to the CT scan), $PM_{2.5}$ point estimates were elevated among participants who did not work or volunteer outside the home during this period. This is consistent with the recent findings of Hoffmann et al,[4] who reported greater $PM_{2.5}$ and roadway effects on coronary artery calcium among participants who had not been working full-time during the previous 5 years. Our $PM_{2.5}$ effects using a residential stability criterion of 20 years suggest that our a priori criterion of 10 years may have been inadequate, given the long time scale over which atherosclerosis develops. Finally, $PM_{2.5}$ exposure may have been more accurate among participants not residing near a major road, as these participants' exposures may be less affected by local PM sources or street canyon effects.

We conservatively adjusted for several factors that may be on the physiologic pathway between air pollution and atherosclerosis, including blood lipids[6] and blood pressure,[46,47] and, as surrogates, the use of lipid-lowering and antihypertensive medications. Thus, our conservative a priori model choice may have overadjusted the coefficients; a model that did not adjust for these variables (model 4 in Fig. 1) estimated the $PM_{2.5}$-associated relative risk of aortic calcification to be 1.09 (1.00–1.20).

Unlike Hoffmann and colleagues,[4] who reported an association between chronic exposure to traffic pollution and coronary atherosclerosis,[4] we found no associations between residential proximity to major roads and presence or extent of AAC. If an association between traffic exposure and atherosclerosis does exist, there are at least 2 possible explanations for our inability to detect it. First, we relied on the road classification system in the TeleAtlas database, which describes the type of road but not the traffic volume. Second, there is evidence that concentrations of traffic pollution decrease with elevation above the roadway.[48] Therefore, participants residing in high-rise buildings near major roads may have been misclassified. In summary, our lack of findings in relation to traffic may be due to exposure misclassification inherent in the relatively crude roadway category and residential proximity approach.

In exploratory stratified analyses the most consistent evidence of $PM_{2.5}$ effect modification across modeling scenarios was the use of lipid-lowering medications (interaction *P* values: 0.03–0.13), with greater effects among users. This result is consistent with the previous study of air pollution and atherosclerosis in Los Angeles,[13] although no such effect modification was observed in a previous analysis of coronary artery calcification, carotid intima-media thickness, and ankle–brachial index in the MESA cohort.[14] The use of lipid-

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lowering medication may act as a surrogate for risk of atherosclerosis even in a cohort without prior cardiovascular disease, although interpretation of this finding in a cross-sectional analysis is complicated by the fact that duration of medication use was not considered, and lipid-lowering medication slows the progression of abdominal aortic plaques and may therefore reduce progression of calcification.[27]

Within some subgroups we noted stronger $PM_{2.5}$ associations with detectable AAC and Agatston score. The most robust effects were among Hispanics. Although racial or ethnic differences in air pollution exposure have been investigated,[49,50] there is little prior evidence that race or ethnicity modify air pollution cardiovascular effects.[41,51] In this analysis not all ethnic groups were represented in every city, although whites and Hispanics had similar exposure gradients. No $PM_{2.5}$ effects were noted for whites under any modeling scenario. Hispanics had the highest rates of obesity (45% vs. 27% of non-Hispanics) and diabetes (22% vs. 13%) of any racial/ethnic group; both of these characteristics are hypothesized to modify PM effects on cardiovascular outcomes. In a panel study, Dubowsky et al[8] reported that diabetes and obesity both modified the effect of short-term $PM_{2.5}$ exposures on systemic inflammation, and time-series studies provide evidence that diabetes modifies the effect of PM on cardiovascular hospitalizations[42] and mortality.[52] It is possible that in our analysis Hispanic ethnicity acted as a surrogate for combinations of other potentially important effect modifiers. The $PM_{2.5}$-associated relative risk of aortic calcification among participants who are both obese and diabetic was 1.38 (0.98–1.95; n = 84), and Hispanics were disproportionately represented in this subgroup (39 of 84 participants). Exposure misclassification is another possible explanation for heterogeneity in $PM_{2.5}$ effect estimates. Hispanic participants lived closer to $PM_{2.5}$ monitors than any other racial/ethnic group (average distance: 4.2 ± 2.7 km for Hispanics vs. 5.7 ± 3.2 km for non-Hispanics), and 67% of non-Hispanics were employed between baseline and CT scan, compared with only 54% of Hispanics.

In a prior analysis of MESA data PM exposures were positively, but not significantly, associated with coronary artery calcification.[14] One important difference between aortic calcification and coronary artery calcium is that the former is generally more prevalent, especially among women and those older than 50.[18,28] In this analysis 74% of participants had detectable aortic calcification, whereas in the previous MESA air pollution analysis the prevalence of coronary artery calcification was only 50%.[14] Relative to coronary artery calcium, abdominal aortic calcification has not been as extensively studied as a cardiovascular risk factor. Nevertheless, an association between air pollution and aortic atherosclerosis would have important public health implications because aortic calcifications have been linked to increased risk of cardiovascular disease,[20] coronary heart disease,[20] stroke,[22] and congestive heart failure.[19] To put the magnitude of our point estimates into context, the relative risk of detectable aortic calcification (1.06 for a 10-$\mu g/m^3$ contrast in $PM_{2.5}$) is about equal to the point estimate associated with a 3-year increase in age but smaller than the risks among former smokers (RR = 1.15; 1.08–1.22) and current smokers (RR = 1.22; 1.11–1.34).

Limitations

Some limitations in our analysis should be noted. First, abdominal aortic calcification represents a different vascular bed than the coronary or carotid arteries, so associations between air pollution and calcification may not directly reflect processes in target organs associated with heart or cerebrovascular disease. Second, this was a cross-sectional analysis that relied primarily on exposure contrasts between cities. Although we made use of a rich dataset to control for potential confounders, we cannot rule out the possibility of residual confounding by other factors that vary regionally. Our exposure assessment approach relied on the strong assumption that the 2-year average $PM_{2.5}$ was representative of longer-term

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past exposures. We were able to assess the relationship only between calcification and this relatively recent exposure information, even though the development of calcification is a long-term process that may be affected by air pollution exposures over the full lifetime. Moreover, as previously mentioned, we attempted to capture within-city variations in traffic pollution concentrations by using a residential proximity approach. However, this approach is a fairly crude surrogate for actual traffic volumes, and errors in geocoded locations or vertical concentration gradients may have also contributed to uncertainty in the estimates of exposure to traffic-generated pollution. Finally, different CT scanners were used between, and in 2 cases within, field centers. We found that multidetector CT scanners were more likely to detect aortic calcification, and reported higher Agatston scores when calcification was detected, than electron-beam scanners. Although we attempted to correct for this effect in the statistical analyses, these technological differences may have had some impact on our results.

In conclusion, we did not find strong $PM_{2.5}$ or roadway associations with abdominal aortic calcium across our full study population. However, $PM_{2.5}$ associations among participants least affected by exposure misclassification (those living near PM_s monitors for at least 20 years and those not working outside the home) support the hypothesis of a relationship between particulate air pollution and systemic atherosclerosis.

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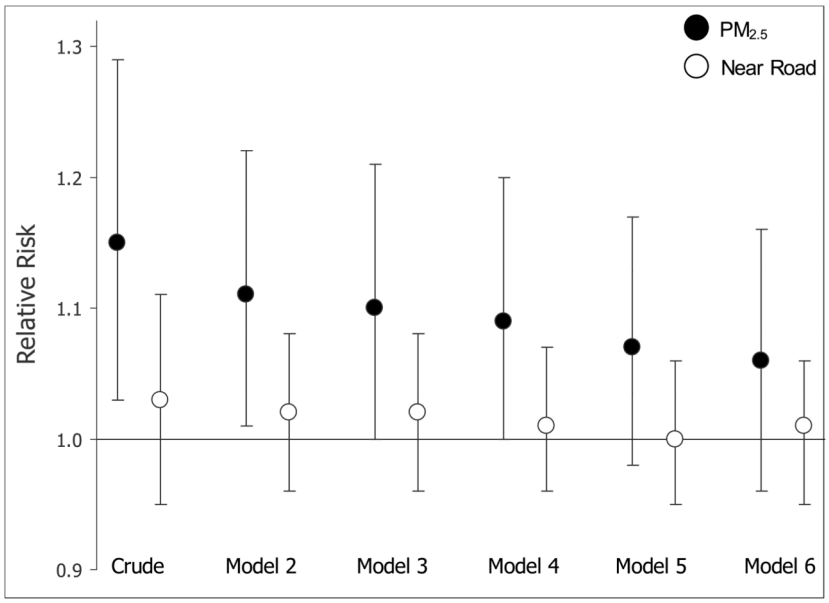

Figure 1.

Relative risks of detectable calcium for a 10-μg/m^3 contrast in $PM_{2.5}$ and for residing near a major road estimated from 6 models with increasing adjustment for confounders.

Crude: Adjusted for scanner technology only (see text).

Model 2: Adjusted for scanner technology + age, gender, ethnicity

Model 3: Model 2 + BMI (body mass index), smoking, diabetes

Model 4: Model 3 + education, income

Model 5: Model 4 + blood lipids, lipid-lowering medications

Model 6: Model 5 + blood pressure, anti-hypertensive medications

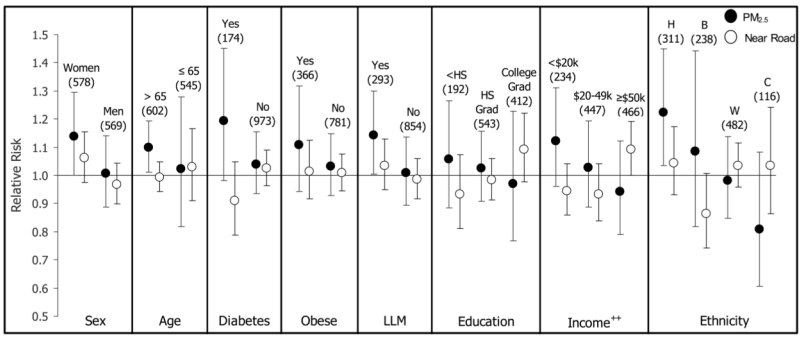

Figure 2.

Relative risks of detectable calcium for a 10-μg/m^3 contrast in $PM_{2.5}$ and residing near a major road estimated from the fully adjusted model after stratifying by sex, age, diabetes, obesity, lipid-lowering medication (LLM) use, education, income, and ethnicity. The number of participants within each stratum is given in parentheses.

* $PM_{2.5}$ interaction or trend p-value < 0.1.

** $PM_{2.5}$ interaction or trend p-value < 0.05.

+ Near Road interaction or trend p-value < 0.1.

++ Near Road interaction or trend p-value < 0.05.

H = Hispanic; B = Black; W = White; C = Chinese

<HS = less than high school education; HS Grad = high school education or equivalent

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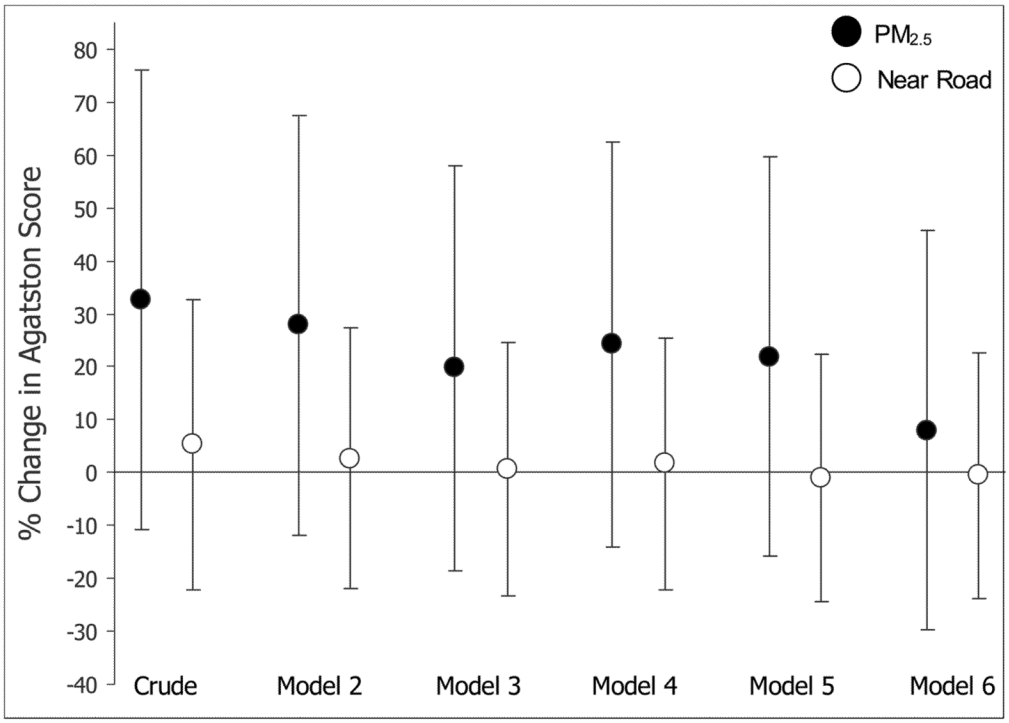

Figure 3.

Change in Agatston score associated with a 10-μg/m^3 contrast in $PM_{2.5}$ and residing near a major road estimated from 6 models with increasing adjustment for confounders.

Crude: Adjusted for scanner technology only (see text).

Model 2: Adjusted for scanner technology + age, gender, ethnicity

Model 3: Model 2 + BMI (body mass index), smoking, diabetes

Model 4: Model 3 + education, income

Model 5: Model 4 + blood lipids, lipid-lowering medications

Model 6: Model 5 + blood pressure, anti-hypertensive medications

Note: outcome variable is log-transformed Agatston score among 851 participants with Agatston score > 0.

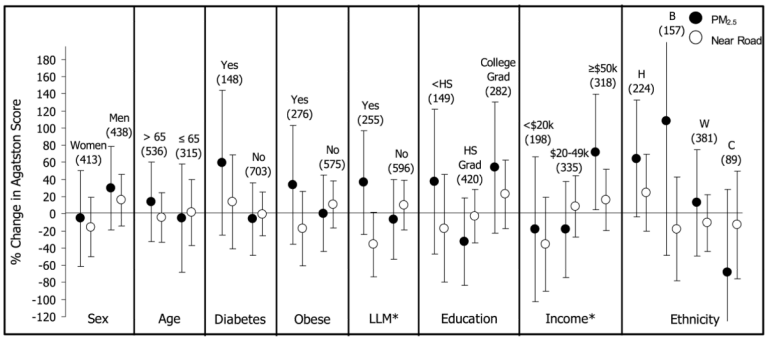

Figure 4.

Change in Agatston score associated with a 10-μg/m^3 contrast in $PM_{2.5}$ and for residing near a major road estimated from the fully adjusted model after stratifying by sex, age, diabetes, obesity, lipid-lowering medication (LLM) use, education, income, and ethnicity: participants with nonzero calcium. The number of participants within each stratum is given in parentheses.

* $PM_{2.5}$ interaction or trend p-value < 0.1.

** $PM_{2.5}$ interaction or trend p-value < 0.05.

+ Near Road interaction or trend p-value < 0.1.

++ Near Road interaction or trend p-value < 0.05.

H = Hispanic; B = Black; W = White; C = Chinese

<HS = less than high school education; HS Grad = high school education or equivalent

Note: outcome variable is log-transformed Agatston score among 851 participants with Agatston score > 0.

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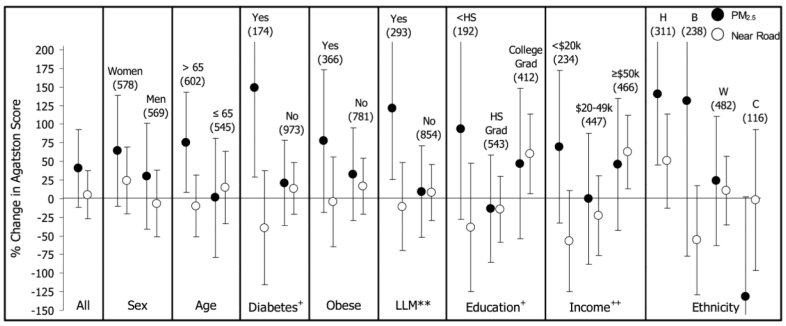

Figure 5.

Change in Agatston score associated with a 10-μg/m^3 contrast in $PM_{2.5}$ and for residing near a major road estimated from the fully adjusted model after stratifying by sex, age, diabetes, obesity, lipid-lowering medication (LLM) use, education, income, and ethnicity: all participants. The number of participants within each stratum is given in parentheses.

* $PM_{2.5}$ interaction or trend p-value < 0.1.

** $PM_{2.5}$ interaction or trend p-value < 0.05.

+ Near Road interaction or trend p-value < 0.1.

++ Near Road interaction or trend p-value < 0.05.

H = Hispanic; B = Black; W = White; C = Chinese

<HS = less than high school education; HS Grad = high school education or equivalent

Note: outcome variable is log(Agatston + 1) among 1,147 participants.

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Table 1

Summary Statistics (Mean ± SD or Percent) for Participant Characteristics and Exposure Variables

Variable	Chicago (n = 270)	Los Angeles (n = 188)	New York (n = 275)	St. Paul (n = 234)	Winston-Salem (n = 180)	All (n = 1,147)
Age (y)	65.9 ± 9.3	65.8 ± 9.9	65.9 ± 9.4	65.5 ± 9.2	66.2 ± 9.7	65.9 ± 9.4
Female (%)	51	48	56	46	51	50
Ethnicity (%)						
Black	26	8	29	0	41	21
Chinese	27	23	<1	0	0	10
Hispanic	0	47	50	37	0	27
White	47	22	21	63	59	42
Annual Income (%)						
<$20,000	8	34	31	17	14	20
$20,000–49,999	30	36	42	50	38	39
≥$50,000	62	31	28	33	48	41
Education (%)						
<High school grad.	4	30	30	12	7	17
High school grad.	34	45	42	64	57	47
College grad.	62	25	28	24	36	36
BMI (kg/m^2)	26.4 ± 4.7	28.2 ± 5.4	28.9 ± 5.7	29.6 ± 4.7	28.5 ± 5.2	28.3 ± 5.3
BMI ≥ 30 (%)	16	30	38	43	34	32
Diabetes (%)	10	21	16	16	15	15
SBP (mm Hg)	121.2 ± 19.9	124.4 ± 21.2	125.1 ± 20.9	123.3 ± 20.5	129.4 ± 22.3	124.4 ± 21.0
DBP (mm Hg)	69.2 ± 10.2	67.8 ± 10.1	70.6 ± 9.5	70.0 ± 9.4	69.9 ± 9.5	69.6 ± 9.8
HDL (mg/dL)	57.8 ± 17.9	50.1 ± 15.4	52.6 ± 15.1	49.6 ± 13.2	50.3 ± 14.0	52.4 ± 15.6
LDL (mg/dL)	110.1 ± 30.2	114.6 ± 31.4	111.1 ± 33.4	115.3 ± 31.7	107.9 ± 29.6	111.8 ± 31.5
Lipid-lowering medications (%)	22	26	27	29	24	26
Antihypertension medications (%)	40	48	49	42	54	46

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Variable	Chicago (n = 270)	Los Angeles (n = 188)	New York (n = 275)	St. Paul (n = 234)	Winston-Salem (n = 180)	All (n = 1,147)
Smoking (pack-y)	12.3 ± 23.9	7.1 ± 15.4	10.7 ± 19.5	13.3 ± 21.1	21.5 ± 53.4	12.7 ± 28.6
Smoking Status (%)						
Never	50	55	52	47	45	50
Former	40	37	39	39	42	39
Current	9	9	10	14	13	11
$PM_{2.5}$ (μg/m^3)	16.0 ± 0.3	22.8 ± 0.9	15.5 ± 0.4	10.9 ± 0.1	15.3 ± 0.3	15.8 ± 3.6
Near road (%)	29	16	58	21	19	31

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Table 2

Abdominal Aortic Calcium Summary Statistics by City and CT Scanner

City	Scanner	Scanner Technology	No. of Participants Scanned	Scans with Detectable Calcium (%)	Median (25%–75%) Agatston Score (if > 0)	Mean (± SD) Log-transformed Agatston Score (if > 0)
Chicago	Imatron C-150	EBT	270	191 (71)	634 (149–2361)	6.25 ± 1.86
Los Angeles	Imatron C-150	EBT	188	145 (77)	994 (234–2877)	6.51 ± 1.74
New York	Imatron C-150	EBT	236	153 (65)	557 (126–2003)	6.08 ± 1.95
	Siemens Sensations 64	MDCT	39	33 (85)	626 (282–2180)	6.58 ± 1.66
St. Paul	Siemens S4 Volume Zoom	MDCT	137	108 (79)	1199 (162–3740)	6.64 ± 1.82
	Siemens Sensations 16	MDCT	97	80 (82)	812 (209–3032)	6.57 ± 1.76
Winston-Salem	GE Lightspeed	MDCT	180	141 (78)	1297 (248–3129)	6.60 ± 1.83
All EBT		EBT	694	489 (71)	750 (151–2293)	6.27 ± 1.86
All MDCT		MDCT	453	362 (80)	1026 (233–3129)	6.60 ± 1.79
All			**1147**	**851 (74%)**	**836 (166–2680)**	**6.41 ± 1.84**

EBT indicates electron-beam CT; MDCT indicates multidetector CT.

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Table 3

Results per 10-μg/m^3 Contrast in $PM_{2.5}$ for Fully Adjusted Models Under Different Participant Inclusion, Employment Status, and Roadway Proximity Criteria

Inclusion Criteria	Presence/Absence of Calcium		Log-transformed Agatston Score (Agatston > 0)		Log-transformed Agatston Score (All)	
	No.	RR (95% CI)	No.	% Change (95% CI)	No.	% Change (95% CI)
< 10 y at address	555	1.04 (0.89–1.22)	366	−6.6 (−64.0 to 50.9)	555	−8.5 (−81.3 to 64.2)
10+ y at address[a]	1147	1.06 (0.96–1.16)	851	8.0 (−29.7 to 45.7)	1147	40.7 (−11.5 to 92.8)
10+ y at address and <10 km from $PM_{2.5}$ monitor	1067	1.08 (0.98–1.18)	788	19.7 (−19.6 to 58.9)	1067	60.7 (5.9 to 115.4)**
20+ y at address	731	1.10 (0.99–1.22)+	552	14.4 (−32.8 to 61.7)	731	64.1 (−1.73 to 129.9)*
20+ y at address and <10 km from $PM_{2.5}$ monitor	689	1.11 (1.00–1.24)*	518	24.6 (−24.6 to 73.8)	689	79.2 (10.1 to 148.3)**
10+ y at address and employed[b]	723	1.02 (0.87–1.20)	491	29.1 (−25.7 to 83.8)	723	33.5 (−35.9 to 102.9)
20+ y at address and employed[b]	440	1.07 (0.89–1.27)	306	43.8 (−32.4 to 119.9)	440	55.8 (−37.2 to 148.7)
10+ y at address and not employed[c]	424	1.10 (1.00–1.22)*	360	−15.1 (−66.3 to 36.1)	424	54.8 (−23.8 to 133.4)
20+ y at address and not employed[c]	291	1.16 (1.02–1.31)**	246	−14.1 (−72.6 to 44.4)	291	89.3 (−3.7 to 182.3)*
10+ y at address and near major road	350	0.85 (0.69–1.05)	259	34.0 (−44.2 to 112.1)	350	−30.6 (−141.3 to 80.1)
10+ y at address and not near major road	797	1.10 (0.99–1.23)*	592	3.9 (−39.9 to 47.8)	797	51.3 (−8.3 to 110.8)+

[a] Criterion selected a priori.

[b] Participants who reported working or volunteering at any study examination up to the time of the abdominal CT scan.

[c] Participants who reported being unemployed, retired, or a homemaker at each study examination up to the time of the abdominal CT scan.

+ $p<0.10$;

* $p = 0.06$;

** $p < 0.05$