Title
Fine particulate air pollution and the progression of carotid intima-medial thickness: a prospective cohort study from the multi-ethnic study of atherosclerosis and air pollution.

Permalink
https://escholarship.org/uc/item/709909bp

Journal
PLoS medicine, 10(4)

ISSN
1549-1277

Authors
Adar, Sara D
Sheppard, Lianne
Vedal, Sverre
et al.

Publication Date
2013

DOI
10.1371/journal.pmed.1001430

Peer reviewed
Fine Particulate Air Pollution and the Progression of Carotid Intima-Medial Thickness: A Prospective Cohort Study from the Multi-Ethnic Study of Atherosclerosis and Air Pollution

Sara D. Adar1,2,*, Lianne Sheppard2,3, Sverre Vedal2, Joseph F. Polak4, Paul D. Sampson5, Ana V. Diez Roux1, Matthew Budoff6,7, David R. Jacobs, Jr.8, R. Graham Barr9, Karol Watson7, Joel D. Kaufman2,10

1 Department of Epidemiology, University of Michigan, Ann Arbor, Michigan, United States of America, 2 Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington, United States of America, 3 Department of Biostatistics, University of Washington, Seattle, Washington, United States of America, 4 Department of Radiology, Tufts Medical Center, Boston, Massachusetts, United States of America, 5 Department of Statistics, University of Washington, Seattle, Washington, United States of America, 6 Los Angeles Biomedical Research Institute, Los Angeles, California, United States of America, 7 Division of Cardiology, University of California Los Angeles, Los Angeles, California, United States of America, 8 Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota, United States of America, 9 Departments of Medicine and Epidemiology, Columbia University Medical Center, New York, New York, United States of America, 10 Departments of Epidemiology and Medicine, University of Washington, Seattle, Washington, United States of America

Abstract

Background: Fine particulate matter (PM2.5) has been linked to cardiovascular disease, possibly via accelerated atherosclerosis. We examined associations between the progression of the intima-medial thickness (IMT) of the common carotid artery, as an indicator of atherosclerosis, and long-term PM2.5 concentrations in participants from the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods and Results: MESA, a prospective cohort study, enrolled 6,814 participants at the baseline exam (2000–2002), with 5,660 (83%) of those participants completing two ultrasound examinations between 2000 and 2005 (mean follow-up: 2.5 years). PM2.5 was estimated over the year preceding baseline and between ultrasounds using a spatio-temporal model. Cross-sectional and longitudinal associations were examined using mixed models adjusted for confounders including age, sex, race/ethnicity, smoking, and socio-economic indicators. Among 5,362 participants (5% of participants had missing data) with a mean annual progression of 14 µm/y, 2.5 µg/m³ higher levels of residential PM2.5 during the follow-up period were associated with 5.0 µm/y (95% CI 2.6 to 7.4 µm/y) greater IMT progressions among persons in the same metropolitan area. Although significant associations were not found with IMT progression without adjustment for metropolitan area (0.4 µm/y [95% CI −0.4 to 1.2 µm/y] per 2.5 µg/m³), all of the six areas showed positive associations. Greater reductions in PM2.5 over follow-up for a fixed baseline PM2.5 were also associated with slowed IMT progression (−2.8 µm/y [95% CI −1.6 to −3.9 µm/y] per 1 µg/m³ reduction). Study limitations include the use of a surrogate measure of atherosclerosis, some loss to follow-up, and the lack of estimates for air pollution concentrations prior to 1999.

Conclusions: This early analysis from MESA suggests that higher long-term PM2.5 concentrations are associated with increased IMT progression and that greater reductions in PM2.5 are related to slower IMT progression. These findings, even over a relatively short follow-up period, add to the limited literature on air pollution and the progression of atherosclerotic processes in humans. If confirmed by future analyses of the full 10 years of follow-up in this cohort, these findings will help to explain associations between long-term PM2.5 concentrations and clinical cardiovascular events.

Please see later in the article for the Editors’ Summary.

Citation: Adar SD, Sheppard L, Vedal S, Polak JF, Sampson PD, et al. (2013) Fine Particulate Air Pollution and the Progression of Carotid Intima-Medial Thickness: A Prospective Cohort Study from the Multi-Ethnic Study of Atherosclerosis and Air Pollution. PLoS Med 10(4): e1001430. doi:10.1371/journal.pmed.1001430

Academic Editor: Simon Hales, University of Otago, New Zealand

Received November 7, 2012; Accepted March 15, 2013; Published April 23, 2013

Copyright: © 2013 Adar et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This work was supported by awards R01ES015195 and R01ES014309 from the EPA; N01-HC-95159 through N01-HC-95165, N01-HC-95169, R01-HL-069003, and R01-HL-081352 from the NHLBI; and K24ES013195, P50ES015915, and P30ES07033 from the NIEHS. The funders had no role in study design, data analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Abbreviations: HDL, high-density lipoprotein; IMT, intima-medial thickness; LDL, low-density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air); PM2.5, fine particulate matter.

* E-mail: sadar@umich.edu
Introduction

Long-term exposure to fine particulate air pollution (PM\textsubscript{2.5}) has been associated repeatedly with cardiovascular and ischemic heart disease [1]. Several biological processes underlying these associations have been proposed, including oxidative stress and systemic inflammation, endothelial dysfunction, and alterations in autonomic tone. Toxicological data also indicate that PM\textsubscript{2.5} can initiate or accelerate atherosclerosis [2–6], yet there is little information to confirm this relation in humans.

Human investigations of prevalent atherosclerosis and air pollution have suggested a relation but are inconclusive. In cross-sectional analyses of older adults, 10 \mu g/m\textsuperscript{3} greater long-term concentrations of PM\textsubscript{2.5} were associated with a 1%–10% larger intima-medial thickness of the common carotid artery (IMT) [7–9]. In young adults, a positive but non-significant association has also been reported [10]. Other atherosclerosis measures such as coronary artery calcium and ankle brachial index have been linked to traffic exposures [11,12], a source of PM\textsubscript{2.5}, but have shown less consistent associations with PM\textsubscript{2.5} itself [7]. Conversely, prevalent aortic calcium was linked to PM\textsubscript{2.5} but not traffic [13]. Only one investigation to date has examined relations between air pollution and the progression of atherosclerosis in humans: both closer proximity to traffic sources and higher PM\textsubscript{2.5} [14] were linked to greater progression of IMT in 1,483 older adults from Los Angeles. Replication of these findings in a more general population is needed, however, as participants of that study originated from five different clinical trials of vitamin, hormone, and anti-diabetes therapies and associations with IMT were limited to those in the treated groups. In addition, that investigation relied exclusively on regulatory monitoring data for assignment of air pollution concentrations and may have had insufficient information to fully capture fine-scale variability in pollution across different locations.

The Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) was designed to investigate associations between long-term PM\textsubscript{2.5} exposures and the progression of atherosclerosis over a 10-y follow-up period using information from the large population-based MESA cohort who were without pre-existing cardiovascular disease at baseline [15]. In this report, we present associations between individual-level PM\textsubscript{2.5} estimated using measurements and models specific to this project and IMT progression over the first three MESA examinations. We hypothesized that persons living in areas with high PM\textsubscript{2.5} during the follow-up period would experience a faster rate of progression than other individuals and that PM\textsubscript{2.5} preceding the baseline exam would be related to baseline IMT.

Methods

Study Population

Participants of MESA with any IMT measurements in the first three clinical visits (2000–2005) who consented to having their home addresses geocoded were examined. While IMT measurements were also collected in later clinical visits of the MESA study, these data were collected from a different portion of the vessel and must be explored separately. At baseline, MESA was composed of 6,814 white, African-American or black, Spanish/Hispanic/ Latino, and Chinese adults (aged 45–84 y) without clinical cardiovascular disease from six US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan and Southern Bronx, NY; and St Paul, MN) [16]. Each field center developed recruitment procedures according to the characteristics of its community, past experience, available resources, and site-specific logistics. Recruitment sources included lists from county assessors, the Department of Motor Vehicles, local labor unions, commercial mailers, and random digit dialing. Friends, family, and persons serviced by the Centers for Medicare and Medicaid Services were also contacted to facilitate the target recruitment in upper age groups. This study met with the guidelines of the Declaration of Helsinki. Institutional review board approval was granted at each study site and written informed consent was obtained from all participants. We restricted our primary analyses to participants with complete covariate information.

Common Carotid IMT

Trained technicians captured images of the right common carotid artery from supine participants using high resolution B-mode ultrasound (Logiq 700, 13MHz; GE Medical Systems). Images collected over a distance 10 mm proximal to the common carotid bulb were transferred from each study center to the Tufts Medical Center for quantification [16]. This analysis examined the mean far wall thickness of the right common carotid, retrospectively gated to end-diastole. Blinded replicate readings gave inter-reader intra-class correlation coefficients of 0.84 and 0.86 for two separate sets of readers [17]. IMT was collected from all participants at baseline with follow-up measures collected on a subset in exam 2 and a different subset in exam 3.

Participant Characteristics

Information regarding participant demographics, medical history, and medications were obtained at each MESA exam through interviewer-administered questionnaires. Race/ethnicity was assessed by participant questionnaire where they were asked to report if they were best described as African-American or black, Asian (Chinese, Filipino, Japanese, Korean, Vietnamese, Asian Indian), white, Native Hawaiian or other Pacific Islander (Guamanian or Chamorro, Samoan, Micronesan, Tahitian), or American Indian or Alaska Native. Participants were also asked if they described themselves as Spanish/Hispanic/Latino and they were permitted to select more than one group. Participants reporting African-American or black, white, Spanish/Hispanic/ Latino, or Chinese were eligible for participation. Measurements of anthropometry as well as serum levels of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, glucose, homocysteine, and inflammatory markers were also collected [16]. Residential addresses were gathered and assigned geographic coordinates using ArcGIS v9.1 (ESRI) on the basis of the Dymap 2000 street network (TeleAtlas).

Air Pollution Concentrations

Individual-level, long-term PM\textsubscript{2.5} concentrations were estimated by MESA Air for the MESA cohort using area-specific hierarchically spatio-temporal models described elsewhere [18,19]. Predictions were derived from 2-wk average PM\textsubscript{2.5} concentrations from the Environmental Protection Agency’s Air Quality System (AQS) and supplemental monitoring specific to MESA Air [20]. These models decompose the space-time field of concentrations into spatially varying long-term averages, spatially varying seasonal and long-term trends, and spatially correlated but temporally independent residuals. Each model utilized spatial covariates such as proximity to roadways and local land uses to predict outdoor concentrations at subjects’ homes between 1999 and 2007. City-specific cross-validated root mean square errors for these
predictions ranged between 4.7% and 9.5% of long-term average concentrations at MESA Air monitoring locations.

Historical exposures accounting for residential history were estimated for each participant on the basis of concentrations for the year preceding their baseline exam. Exposure between ultrasounds was estimated by taking the time-weighted average of concentrations at a participant’s residence or residences for the period between baseline and the follow-up exam. We also explored associations of IMT progression with the difference in exposures between the follow-up period and baseline levels as well as with average concentrations of PM$_{2.5}$, measured at the nearest AQS monitor over the year before baseline and with living near a major roadway (i.e., within 100 m of an interstate or US highway or within 50 m of a state or county highway as defined by the US Census Feature Class Codes A1, A2, and A3).

Statistical Analysis

A longitudinal mixed model [21] was fit with random slopes and intercepts for each subject in R v.2.10.1 [22]. As discussed in detail in Text S1, this model simultaneously examined the association between IMT at baseline and PM$_{2.5}$ levels preceding the baseline exam (henceforth referred to as “cross-sectional association”) as well as IMT progression as a function of the average concentration over follow-up (henceforth referred to as “longitudinal association”). We also fit the same model examining cross-sectional and longitudinal associations and baseline PM$_{2.5}$ as well as longitudinal associations with the change in PM$_{2.5}$ between follow-up and baseline, defined as the average PM$_{2.5}$ over follow-up minus baseline PM$_{2.5}$. This specification allowed us to independently assess the associations of IMT progression with each of these two distinct exposures.

All models were constructed in a staged manner to assess the sensitivity of our results to control for different risk factors, including some that may possibly be mediators of the association between air pollution and IMT. In our minimally adjusted models, we explored confounding by age, sex, and race/ethnicity. Our moderately adjusted models added control for education, a neighborhood socio-economic score (derived from census tract level data on education, occupation, median home values, and median household income) [23], adiposity (1/height, 1/height$^2$, weight, waist, and 1/hip), and pack-years at baseline as well as a time-varying smoking status. Our main models further adjusted for time-varying HDL, total cholesterol, statin use, diabetes mellitus (using the 2003 ADA fasting criteria algorithm [24]), systolic blood pressure, diastolic blood pressure, hypertensive diagnosis, and hypertensive medications. For sensitivity analyses, we tested an extended model that also included physical activity, alcohol use, second-hand smoke exposures, C-reactive protein, creatinine, fibrinogen, occupation, and neighborhood noise. Although we also considered changes in healthy food stores over the follow-up period from the National Establishment Time Series database (Walls & Associates) as an indicator of neighborhood change, it was uncorrelated with changes in pollution ($p = 0.03$ to $0.13$) and thus not included in our models. All covariates were included as possible confounders of associations of PM$_{2.5}$ with baseline IMT (cross-sectional associations) and with progression in IMT (longitudinal associations). Since metropolitan area was also considered to be an important potential confounder, models were constructed with and without fixed effects for clinic.

Although our models control for baseline IMT by including key predictors of IMT at baseline, we also explored a model of the change in IMT between the baseline and follow-up exams as the outcome normalized by the time between visits. Effect modification was also examined by age, gender, race/ethnicity, education, obesity, diabetes, hypertension, statin therapy, and baseline IMT.

Standard model diagnostics were explored including graphics of residuals for evidence of non-normality, influential outliers, and omitted covariates.

Results

Between exams 1 and 3, 11,270 valid IMT measurements were collected from 5,660 participants. By design, approximately half of the participants were sampled in exam 2 ($n = 2,907$) and half in exam 3 ($n = 2,726$), with 99% contributing two samples per person. Excluding 645 observations with missing covariate information, and 513 with missing exposures resulted in 10,220 observations for this analysis. The 5,362 included participants (52% female) had a mean age of 62 y and were 40% white, 27% black, 21% Hispanic, and 12% Chinese (Table 1). Overall, 44% had hypertension, 12% had diabetes, and nearly 50% were former or current smokers at baseline. Some differences were observed between the MESA clinics with respect to race, ethnicity, and socio-economic features. New York and Los Angeles had a higher fraction of their populations without high school educations whereas Baltimore, Chicago, and Winston-Salem had larger fractions of participants with graduate degrees.

Among the whole population, we observed a mean baseline IMT of 678 μm and progression of 14 μm/y over a mean follow-up of 2.5 y. The mean long-term PM$_{2.5}$ concentration was 16.6 μg/m$^3$ ± 3.7 μg/m$^3$ with a range of 9.4 to 27.5 μg/m$^3$. Concentrations were substantially more variable across areas (standard deviation: 3.5 μg/m$^3$) than within areas (average standard deviation: 1.11 μg/m$^3$). As shown in Table 1, all areas exhibited a decrease in PM$_{2.5}$ concentrations over the follow-up period (mean change: $-1.1 \pm 1.1$ μg/m$^3$) but regions with higher baseline PM$_{2.5}$ concentrations experienced the largest reductions over the follow-up period (overall $p$ for baseline and change in PM$_{2.5}$: $-0.32$ and average within-area $p$: $-0.54$). Concentrations at regulatory monitors also demonstrated similar patterns. While Chicago and New York had large fractions of their cohort living near major roadways (30% and 57%, respectively), in the other areas approximately 20% of the cohort resided in close proximity to a major roadway. Virtually no participants (<0.1%) changed residential proximity to roadways over follow-up.

Average PM$_{2.5}$ concentrations over follow-up showed consistent positive associations with IMT progression in all models following adjustment for metropolitan area, with areas of higher concentrations showing steeper progressions of IMT over time (Figure 1). Living at a residence with a 2.5 μg/m$^3$ higher concentration (inter-quartile range [IQR]) during the follow-up period was associated with a 5.0 μm/y (95% CI 2.6 to 7.4 μm/y) faster change in IMT over time when compared to others in the same metropolitan area (Table 2). Models that simultaneously explored associations with baseline PM$_{2.5}$, and the change in PM$_{2.5}$ over the follow-up period similarly indicated that a 2.5 μg/m$^3$ larger baseline PM$_{2.5}$ was associated with a 3.8 μm/y (95% CI 1.2 to 6.4 μm/y) faster rate of progression among persons with the same change since baseline. In addition, a 1 μg/m$^3$ greater reduction in PM$_{2.5}$ over follow-up was associated with a 2.8 μm/y (95% CI 1.6 to 3.9 μm/y) slower rate of IMT progression (Table 3) after control for metropolitan area and concentration preceding the baseline exam.
Without control for metropolitan area, associations between IMT progression and the average PM 2.5 concentration over follow-up (0.4 μm/y [95% CI 20.4 to 1.2 μm/y per 2.5 μg/m³]) were positive but could not be distinguished from no association. The same was true for associations between progression and baseline PM2.5 in models controlled for the change in pollution over follow-up (0.3 μm/y [95% CI 0.6 to 1.1 μm/y] per 2.5 μg/m³). In all of the six metropolitan areas, however, increased IMT progression was observed with larger PM 2.5 concentrations (Figure 2). Also, the change in PM2.5 over the follow-up period remained associated with IMT progression (1.3 μm/y reduction [95% CI 0.4 to 2.2 μm/y] per μg/m³ reduction in PM2.5), even without control for metropolitan area.

Cross-sectional associations with baseline IMT could not be differentiated from no effect (0.4 μm [95% CI 0.9 to 9.9 μm] [Table 2] to 2.7 μm [95% CI −6.9 to 12.4 μm] [Table 3]) after adjustment for the mean concentration for each metropolitan area. Associations with baseline IMT were stronger without

Table 1. Study population characteristics presented as mean (standard deviation) or percent.

| Characteristics          | Overall | Winston Salem | New York | Baltimore | St Paul | Chicago | Los Angeles |
|--------------------------|---------|---------------|----------|-----------|---------|---------|-------------|
| Number of samples        | 5,276   | 856           | 835      | 734       | 847     | 986     | 1,018       |
| Baseline (μm)            | 678 (189)| 725 (207)     | 677 (173)| 695 (191) | 641 (165)| 647 (180)| 690 (199)   |
| Progression (μm/y)       | 14 (53) | 13 (56)       | 9 (50)   | 19 (65)   | 15 (49) | 19 (55) | 12 (43)     |
| Follow-up time (y)       | 2.5 (0.8)| 2.4 (0.8)     | 2.6 (0.7)| 2.4 (0.8) | 2.4 (0.9)| 2.3 (0.8)| 2.5 (0.9)   |
| Air pollution concentrations |       |               |          |           |         |         |             |
| Baseline PM2.5 (μg/m³)   | 16.6 (3.7)| 15.5 (0.7)    | 15.5 (0.8)| 15.2 (0.9)| 11.9 (1.1)| 16.9 (1.2)| 23 (1.9)    |
| Average follow-up PM2.5 (μg/m³) | 15.5 (3.5)| 14.5 (0.7)    | 15.0 (0.7)| 14.9 (0.7)| 10.4 (0.7)| 15.3 (1.1)| 21.4 (1.8)  |
| Delta PM2.5 (μg/m³)      | −1.1 (1.1) | −1.1 (0.4)    | −0.5 (0.4)| −0.3 (0.5)| −1.4 (0.9)| −1.4 (0.8)| −1.6 (1.9)  |
| Personal characteristics  |       |               |          |           |         |         |             |
| Age (y)                  | 62 (10) | 62 (10)       | 62 (10)  | 63 (10)   | 60 (10) | 62 (10) | 63 (11)     |
| Female (%)               | 52      | 53            | 55       | 52        | 50      | 54      | 50          |
| Race/ethnicity (%)       |         |               |          |           |         |         |             |
| White                    | 40      | 53            | 20       | 51        | 60      | 49      | 12          |
| Black                    | 27      | 47            | 33       | 49        | 0       | 25      | 12          |
| Chinese                  | 12      | 0             | 0        | 0         | 0       | 26      | 38          |
| Hispanic                 | 21      | 0             | 47       | 0         | 40      | 0       | 39          |
| Education (%)            |         |               |          |           |         |         |             |
| Less than high school    | 16      | 7             | 25       | 10        | 16      | 7       | 31          |
| High school              | 18      | 22            | 18       | 19        | 22      | 8       | 19          |
| Higher education         | 47      | 52            | 41       | 51        | 49      | 49      | 41          |
| Advanced degree          | 19      | 19            | 16       | 22        | 11      | 36      | 9           |
| Smoking status (%)       |         |               |          |           |         |         |             |
| Never                    | 51      | 45            | 52       | 47        | 44      | 52      | 63          |
| Former                   | 37      | 43            | 34       | 40        | 41      | 37      | 28          |
| Current                  | 12      | 13            | 14       | 12        | 15      | 11      | 9           |
| General health characteristics |       |               |          |           |         |         |             |
| Body mass index (kg/m²)  | 28.2 (5.3)| 28.7 (5.2)    | 28.7 (5.3)| 29.3 (5.6)| 29.4 (5.1)| 26.7 (5) | 27 (5.2)    |
| Systolic BP (mm Hg)      | 126 (21)| 133 (21)      | 125 (21) | 128 (21)  | 122 (20) | 123 (21) | 126 (22)   |
| Diastolic BP (mm Hg)     | 72 (10) | 74 (10)       | 73 (10)  | 72 (10)   | 70 (10) | 71 (10) | 71 (10)    |
| HDL (mg/dl)              | 51 (15) | 51 (15)       | 53 (15)  | 52 (15)   | 49 (14) | 54 (16) | 49 (14)    |
| LDL (mg/dl)              | 117 (31)| 114 (30)      | 118 (32) | 118 (31)  | 121 (31) | 117 (31) | 117 (31)   |
| CRP (mg/dl)              | 3.7 (5.6)| 4.4 (6.6)    | 3.4 (4.2)| 4.0 (5.7) | 3.9 (5.5)| 3.1 (5.7)| 3.3 (5.4)  |
| Hypertension (%)         | 44      | 54            | 47       | 50        | 34      | 37      | 42          |
| Statin users (%)         | 15      | 16            | 16       | 19        | 12      | 15      | 13          |
| Diabetes (%)             | 12      | 11            | 13       | 13        | 10      | 8       | 15          |

Personal characteristics as reported at baseline. 86 participants had follow-up IMT measurements without valid baseline IMT measurements. Hypertension was defined by diastolic blood pressure ≥90, a systolic blood pressure ≥140 or self-reported history of hypertension with use of hypertensive medications.

CRP, C-reactive protein.
doi:10.1371/journal.pmed.1001430.t001
control for metropolitan area. In these models, a 2.5 \( \mu g/m^3 \) higher baseline \( PM_{2.5} \) concentration was associated with a 6.3 \( \mu m \) (95% CI 2.8–9.8 \( \mu m \) [Table 2]) to 6.7 \( \mu m \) (95% CI 3.2–10.2 \( \mu m \), [Table 3]) larger baseline IMT.

Sensitivity analyses demonstrated that our findings were robust to increasing degree of control for an expanded covariate list (extended adjustment, Tables 2 and 3), restriction to residentially stable participants (no moves within 10 y, Figure 2), and alternate modeling strategies including a model of the change in IMT over the follow-up period as a function of the change in \( PM_{2.5} \) (see Text S1). Furthermore, qualitatively similar associations for baseline IMT and IMT progression were found for concentrations estimated by the nearest regulatory monitor. Living near a major roadway was not associated with a smaller baseline IMT or progression of IMT (Text S1).

Associations between \( PM_{2.5} \) and IMT and progression generally showed very little difference by risk factors examined, though stronger associations were suggested for some subgroups including women, diabetics, hypertensives, and residents of St Paul (Figure 2).

### Discussion

In a large prospective cohort study of adults without pre-existing cardiovascular disease, we found evidence that individuals with higher long-term residential concentrations of \( PM_{2.5} \) experience a faster rate of IMT progression as compared to other people within the same metropolitan area. Improvements in air quality over the duration of the study were similarly associated with changes in IMT progression, with greater reductions in \( PM_{2.5} \) showing slower IMT progression. These findings suggest that higher long-term \( PM_{2.5} \) exposures may be associated with an acceleration of vascular pathologies over time. As such, they may help explain why epidemiological studies have repeatedly found much larger associations between mortality and chronic air pollution exposures than can be explained by short-term triggering of cardiovascular events alone. Our findings furthermore bolster recent reports that falling pollution levels in the United States after the adoption of the Clean Air Act are associated with reduced mortality [25] and increased life expectancy [26,27].

Our results indicate that persons living in residences with a 2.5 \( \mu g/m^3 \) greater \( PM_{2.5} \) concentration could experience a 5.0 \( \mu m/y \) (95% CI 2.6–7.4 \( \mu m/y \)) faster rate of IMT progression than other persons in the same city. Similarly, a person who experienced a 1 \( \mu g/m^3 \) larger reduction in \( PM_{2.5} \) over the follow-up period would have a 2.8 \( \mu m/y \) (95% CI 1.6–3.9 \( \mu m/y \)) slower rate of IMT progression.
Air Pollution and Carotid IMT Progression

| Table 3. Mean differences (95% CI) in IMT at baseline and in IMT progression over time associated with PM$_{2.5}$ concentrations prior to baseline and change between follow-up and baseline, with and without control for metropolitan area. |
|---|
| **Model** | **Overall Associations** | **Within-City Associations** |
| **Mean IMT (µm) per 2.5 µg/m$^3$ of baseline PM$_{2.5}$** | | |
| Minimal adjustment | 6.4 (2.9 to 9.9) | 5.4 (−4.0 to 14.7) |
| Moderate adjustment | 7.0 (3.4 to 10.5) | 3.3 (−6.5 to 13.0) |
| Main model | 6.7 (3.2 to 12.2) | 2.7 (−6.9 to 12.4) |
| Extended adjustment | 6.0 (1.8 to 10.1) | 3.2 (−8.0 to 14.3) |
| **IMT progression (µm) per 2.5 µg/m$^3$ of baseline PM$_{2.5}$** | | |
| Minimal adjustment | 0.3 (−0.5 to 1.1) | 3.7 (1.3 to 6.2) |
| Moderate adjustment | 0.3 (−0.5 to 1.1) | 3.7 (1.1 to 6.3) |
| Main model | 0.3 (−0.6 to 1.1) | 3.8 (1.2 to 6.4) |
| Extended adjustment | 0.4 (−0.5 to 1.4) | 3.5 (0.5 to 6.5) |
| **IMT progression (µm) per 1 µg/m$^3$ of change in PM$_{2.5}$ over follow-up** | | |
| Minimal adjustment | 1.1 (0.2 to 2.0) | 2.7 (1.6 to 3.8) |
| Moderate adjustment | 1.2 (0.3 to 2.1) | 2.7 (1.6 to 3.9) |
| Main model | 1.3 (0.4 to 2.2) | 2.8 (1.6 to 3.9) |
| Extended adjustment | 1.0 (−0.1 to 2.0) | 2.5 (1.1 to 3.9) |

Change was defined as the average concentration over the follow-up period: concentration at baseline such that a reduction in concentrations over time would have a negative change and increases in concentrations over time would be manifest as a positive change. Minimal adjustment included age, sex, and race/ethnicity. Moderately adjustment added control for education, neighborhood socio-economic score (derived from census tract level data on education, occupation, median home values, and median household income), adiposity (1/height, 1/height$^2$, weight, waist, and 1/hip), and pack-years at baseline as well as a time-varying smoking status. Main models further adjusted for HDL total cholesterol, statin use, diabetes mellitus (using the 2003 ADA fasting criteria algorithms), systolic blood pressure, diastolic blood pressure, hypertension diagnosis, and hypertensive medications. In sensitivity analyses, we tested an extended model that also included physical activity, alcohol use, second-hand smoke exposures, C-reactive protein, creatinine, fibrinogen, occupation, and neighborhood noise among a smaller subset of the population with complete information.

doi:10.1371/journal.pmed.1001430.t003

The acceleration of atherosclerosis has been proposed as a possible mechanism linking chronic exposures to air pollution to clinical cardiovascular disease [30–32]; yet this is only the second publication to investigate the longitudinal relationships between air pollution and a surrogate of atherosclerosis in humans. Our findings support the hypothesis proposed by Künzli and colleagues [33] that persons living in areas with higher long-term concentrations of PM$_{2.5}$ may experience a more rapid development of vascular pathologies, which leads to the development of clinically relevant atherosclerosis at an earlier age, and increases the population at risk of cardiovascular events. Our findings that concentrations preceding baseline had slightly weaker associations with IMT progression per unit change than those during the follow-up period may indicate the importance of recent exposures or reduced exposure measurement error during the study period.

The magnitude of our findings are consistent with Künzli et al., which reported a 0.6 µm/y (95% CI −0.1 to 1.4 µm/y) larger IMT progression per 2.5 µg/m$^3$ of PM$_{2.5}$ and a 5.5 µm/y (95% CI 0.1–10.8 µm/y) larger progression for living within close proximity to a major roadway [14]. While we observed larger PM$_{2.5}$ associations, the 1,483 adult participants of that collection of studies were slightly younger, more white and Hispanic, better educated, and with lower overall rates of progression than our cohort. In addition, that study used a different exposure prediction modeling approach and relied on far fewer air pollution monitors than were available to us, resulting in nearly 5 times less variable PM$_{2.5}$ estimates for Los Angeles than in this investigation. Nevertheless, their PM$_{2.5}$ association was well within our confidence intervals for MESA participants in Los Angeles (3.4 µm/y; 95% CI −0.002 to 6.8 µm/y per 2.5 µg/m$^3$). Toxicological data also support our findings, with several studies documenting the growth of atherosclerotic lesions in the coronary arteries and aortas of rabbits and mice following controlled exposures to particulate matter [2–4,34].

We also demonstrated positive cross-sectional associations between baseline IMT and long-term exposure but these were blunted and could not be distinguished from no association after control for metropolitan area. Associations similar to our between-city results have been previously reported for long-term exposure to PM$_{2.5}$ among the older adults enrolled in the Los Angeles clinical trials [8], an earlier investigation of the MESA cohort at baseline [7], and a large population-based cohort of German older adults [9]. In fact, our result of a 3–10 µm difference in IMT at baseline is very consistent with the range of 5 to 17 µm predicted by these other studies for the same unit change in PM$_{2.5}$ and slightly higher than a recent investigation of young adults that reported a 2 µm larger IMT predicted per 2.5 µg/m$^3$ [10]. Associations between air pollution and other indicators of atherosclerosis extent have been somewhat suggestive but inconsistent [7,11–13]. Since our cross-sectional results were driven by differences in baseline IMT between the two areas with the highest (Los Angeles) and lowest (St Paul) concentrations of PM$_{2.5}$, however, and were not robust to control for metropolitan area, there is the possibility of residual confounding by regional factors.

In contrast to our cross-sectional results for baseline IMT, associations with IMT progression were strongest after control for metropolitan area. The reasons for the opposite effect of site adjustment on associations with baseline IMT and IMT progression remain to be determined. Because cross-sectional associations with baseline IMT are based on between-person contrasts, these relations may be more affected by confounding by personal factors than those in our progression models, which leverage information from the same individual. Within-area associations for IMT progression showed little change with control for neighborhood socio-economic characteristics, personal education, and perceived noise and demonstrated positive associations across all six metropolitan areas in stratified analyses. Changes in concentrations over the follow-up period were also associated with IMT progression in models with and without control for metropolitan area.
Thus, while some questions are raised as to the robustness of cross-sectional associations with baseline IMT, sensitivity analyses raise our confidence in the associations with IMT progression as potentially reflecting a causal association.

These data come from a well-defined prospective cohort study with an uncommonly rich set of air pollution measurements in participants’ communities and homes, including individual-level perceived noise exposures. The inclusion of noise data is a unique feature of this analysis as noise has generally not been accounted for in American epidemiological studies of air pollution to date. Although noise has been independently associated with cardiovascular disease and perceived noise was related to air pollution concentrations in MESA [35,36], interestingly, we found no evidence of confounding of the relationship between air pollution and IMT progression by perceived noise in this analysis.

Despite the many strengths of this study, this work is not without its weaknesses. First, IMT likely does not capture all of the relevant pathophysiology related to air pollution exposures [37]. Second, our exposure assignment is currently limited to predictions of pollution from ambient origin after 1999 but restriction of the analysis to non-movers (≥10 y at baseline address) did not alter our findings. Third, we did not achieve complete follow-up of all participants and data. The probability of being lost to follow-up over these first three exams was unrelated to baseline IMT levels, however, and the likelihood of missing covariate or exposure data was also unrelated to baseline IMT or IMT progression. Missing covariate information was similarly unrelated to baseline exposure concentrations. This finding suggests that bias in our primary associations due to selection is unlikely although it is always a possibility in any longitudinal study. Furthermore, we are currently not accounting for changes in neighborhood characteristics that also may have occurred during the study period. Control for time-varying vascular risk factors in our extended adjustment model, which may capture some time-varying socio-economic trends, did not substantially alter our findings so we might hypothesize that this is not a major source of confounding. The lack of an association between reductions in air pollution and changes in healthy food stores is further supportive of this hypothesis. Nevertheless, future work through MESA will address this question more thoroughly as they explore the impacts of changing neighborhoods on health. Similarly, our exposure assessment does not currently account for the penetration of outdoor particles into indoor air but correlations of outdoor and indoor PM2.5 of outdoor origin have been shown to be high [38]. Future analyses of MESA Air will confirm the findings of this early dataset using IMT data collected during MESA clinical visits 4 and 5. These analyses will furthermore incorporate estimates of air pollution infiltration into participant homes and participant time-activity information, as well as investigate other correlated pollutants that may explain some of this PM2.5 association and explore relationships with clinical events.

Overall, these results for IMT in the first three exams of a large, multi-center, population-based cohort study support the hypothesis that PM2.5 may be associated with the progression of atherosclerosis, even at levels below existing regulatory standards. Such a pathway would lend further support to reported associations between air pollution and the incidence of clinical cardiovascular disease.
Supporting Information

Text S1  Extended methods and results.  

(DOCX)

Acknowledgments

The authors acknowledge the other investigators, staff, and participants of MESA and MESA Air for their valuable contributions to this work. A full list of MESA investigators and institutions is located at http://www.mesa-nhlbi.org.

References

1. Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, et al. (2010) Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 121: 2331–2378.
2. Suta T, Honig JC, Qumlan KB, Ogahmi A, Vincent R, et al. (2002) Particulate air pollution induces progression of atherosclerosis. J Am Coll Cardiol 39: 935–942.
3. Araujo JA, Nel AE (2009) Particulate matter and atherosclerotic role of particle size, composition and oxidative stress. Particle and Fiber Toxicology 6.
4. Sun QH, Wang AX, Jin XM, Natanzen A, Dusquinoi D, et al. (2005) Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. JAMA-Journal of the American Medical Association 294: 3003–3010.
5. Nica Y, Hiria Y, Murayama T, Yokoide M, Iwai N (2007) Nano-sized carbon black exposure exacerbates atherosclerosis in LDL- receptor knockout mice. Circ J 71: 1157–1161.
6. Chen LG, Quan CL, Hwang JN, Jin XM, Li QA, et al. (2010) Atherosclerosis lesion progression during inhalation exposure to environmental tobacco smoke: a comparison to concentrated ambient air fine particles exposure. Inhal Toxicol 22: 449–459.
7. Roux AVD, Auchinleck AH, Franklin TG, Raghunathan T, Barr RG, et al. (2008) Long-term exposure to ambient particulate matter and prevalence of subclinical atherosclerosis in the multi-ethnic study of atherosclerosis. Am J Epidemiol 167: 667–675.
8. Kunzli N, Jerrett M, Mack NJ, Beckerman B, LaBree L, et al. (2005) Ambient air pollution and atherosclerosis in Los Angeles. Environ Health Perspect 113: 201–206.
9. Bauer M, Mobius S, Mohlenkamp S, Dragano N, Nonnenmacher M, et al. (2010) Urban particulate matter air pollution is associated with subclinical atherosclerosis: results from the HNR-Heinz Nixdorf Recall study. J Am Coll Cardiol 56: 1803–1808.
10. Liviakis L, Pogue B, Paramsothy P, Bourne A, Gill EA (2010) Carotid intima-media thickness progression during inhalation exposure to environmental tobacco smoke: a comparison to concentrated ambient air fine particles exposure. Inhal Toxicol 22: 449–459.
11. Hoffmann B, Moebus S, Mohlenkamp S, Stang A, Lehmna N, et al. (2007) Residential exposure to traffic is associated with coronary atherosclerosis. Circulation 116: 489–496.
12. Allen RW, Criqui MH, Roux AVD, Allison M, Shera S, et al. (2009) Fine particulate matter air pollution, proximity to traffic, and aortic atherosclerosis. Epidemiology 20: 254–264.
13. Kunzli N, Jerrett M, Garcia-Esteban R, Basagana X, Beckerman B, et al. (2010) Ambient air pollution and the progression of atherosclerosis in adults. PLOS One 5: e9696. doi:10.1371/journal.pone.009696.
14. Kaufman JD, Adar SD, Allen RW, Barr RG, Budolf MJ, et al. (2012) Prospective study of particulate air pollution exposures, subclinical atherosclerosis, and clinical cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). J Am Coll Cardiol 176: 825–837.
15. Bult DE, Buremke DA, Burkc GL, Detrano R, Roux AVD, et al. (2002) Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 156: 671–681.
16. Miller MR, Hankinson J, Brussaco V, Burgos F, Casaburi R, et al. (2005) Standardisation of spirometry. Eur Respir J 26: 319–338.
17. Sampson PD, Sapiro A, Sheppard L, Lindstrom J, Kaufman JD (2009) Pragmatic estimation of a spatio-temporal air quality model with irregular monitoring data. UWB Biostatistics Working Paper Series Working Paper 353. Available: http://biostats.unirsepress.com/uwbiosstat/paper353.
18. Sapiro A, Sampson P, Sheppard L, Lamley T, Adar S, et al. (2010) Predicting intra-urban variations in air pollution with complex spatio-temporal dependencies. Environmetrics 21: 606–631.
19. Cohen MA, Adar SD, Allen RW, Avel E, Cuss CL, et al. (2009) Approach to estimating particulate pollutants in the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). Environ Sci Technol 43: 4676–4683.
20. Singer J, Willett J, editors (2005) Applied longitudinal data analysis. 1st edition. New York: Oxford University Press.
21. R Core Team (2012) R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computer.
22. Hajat A, Diex-Roux A, Adar S, Auchinleck A, Lovasi G, et al. (2015) The burden of air pollution on poor individuals and neighborhoods: evidence from the Multi-Ethnic Study of Atherosclerosis (MESA). Environ Health Perspect. In press.
23. Genuit S, Alberti K, Bennett P, Buse J, DeFronzo R, et al. (2003) Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 26: 3160–3167.
24. Laden F, Schwartz J, Speizer FE, Dockery DW (2006) Reduction in fine particulate air pollution and mortality - Extended follow-up of the Harvard six cities study. Am J Respir Crit Care Med 173: 667–672.
25. Pope CA, Ezzati M, Dockery DW (2009) Fine-particulate air pollution and life expectancy in the United States. N Engl J Med 360: 376–386.
26. Pope CA, Ezzati M, Dockery DW (2009) Fine-particulate air pollution and mortality - Extended follow-up of the Harvard six cities study. Am J Respir Crit Care Med 173: 667–672.
27. Correia AW, Pipe CAI, Dockery DW, Wang Y, Ezzati M, et al. (2015) Effect of air pollution control on life expectancy in the United States: an analysis of 545 U.S. counties for the period from 2000 to 2007. Epidemiology 24: 23–31.
28. Lim SS, Von T, Flaxman AD, Damaei G, Shibuya K, et al. (2013) A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380: 2224–2260.
29. USEPA (2010) Summary of expert opinions on the existence of a threshold in the concentration-response function of PM2.5-related mortality. Office of Air Quality Planning and Standards HaEID, editor. USEPA: Research Triangle Park (North Carolina).
30. Dockery DW, Pope CA, Srd, Xu X, Spengler JD, Ware JH, et al. (1993) An association between air pollution and mortality in six U.S. cities. N Engl J Med 329: 1753–1759.
31. Pope CA, Burnett RT, Thurston GD, Thun MJ, Calle EE, et al. (2004) Cardiovascular mortality and long-term exposure to particulate air pollution - Epidemiological evidence of general pathophysiological pathways of disease. Circulation 109: 71–77.
32. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, et al. (2007) Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 356: 447–458.
33. Kunzli N, Perez L, von Klot S, Balsebarre D, Bauer M, et al. (2011) Investigating air pollution and atherosclerosis in humans: concepts and outlook. Prog Cardiovasc Dis 53: 334–343.
34. Sun QH, Yue PB, Kirk RI, Wang AX, Moatti D, et al. (2008) Ambient air particulate matter exposure and tissue factor expression in atherosclerosis. Inhaled Toxicol 20: 127–137.
35. Allen R, Davies H, Cohen MA, Mallach G, Kaufman JD, et al. (2009) The spatial relationship between traffic-generated air pollution and noise in 2 US cities. Environ Res 109: 71–77.
36. Allen RW, Adar SD (2011) Are both air pollution and noise driving adverse cardiovascular health effects from motor vehicles? Environ Res 111: 184–185.
37. Livkais L, Pogue B, Paramsothy P, Bourne A, Gill EA (2010) Carotid intima-media thickness for the practicing cardiologist. J Clin Lipidol 4: 24–33.
38. Sarnat JA, Koustrakis P, Suh H (2000) Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. J Air Waste Manag Assoc 50: 1184–1198.

Author Contributions

Conceived and designed the experiments: SA LS SV JP ADR MB DJ RGB KW. Performed the experiments: JP MB DJ RGB KW. Analyzed the data: SA. Contributed reagents/materials/analysis tools: PS. Wrote the first draft of the manuscript: SA. Contributed to the writing of the manuscript: SA LS SV JP PS ADR MB DJ RGB KW. JCMJE criteria for authorship read and met: SA LS SV JP PS ADR MB DJ RGB KW. Agree with manuscript results and conclusions: SA LS SV JP PS ADR MB DJ RGB KW. Enrolled patients: DJ RGB KW.
Editors’ Summary

Background. Cardiovascular disease (CVD)—disease that affects the heart and/or the blood vessels—is a major cause of illness and death worldwide. In the US, for example, the leading cause of death among adults is coronary artery disease, a CVD in which narrowing of the heart’s arteries by atherosclerotic plaques (fatty deposits that build up with age inside arteries) slows the blood supply to the heart and may eventually cause a heart attack (myocardial infarction). The fourth leading cause of death in the US is stroke, a CVD in which atherosclerotic plaques interrupt the brain’s blood supply. Smoking, high blood pressure, high blood cholesterol levels, diabetes, being overweight, and being physically inactive all increase an individual’s risk of developing CVD. Treatments for CVD include lifestyle changes and taking drugs that lower blood pressure or blood cholesterol levels.

Why Was This Study Done? Another risk factor for CVD is long-term exposure to fine particulate air pollution. Fine particulate matter (PM$_{2.5}$)—particles with a diameter of less than 2.5 μm or 1/30th the width of a human hair—is mainly produced by motor vehicles, power plants, and other combustion sources. Why PM$_{2.5}$ increases CVD risk is unclear, but one hypothesis is that it initiates or accelerates atherosclerosis. In this prospective cohort study, which is part of the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air), the researchers investigate whether there is an association between long-term PM$_{2.5}$ exposure and the progression of intima-medial thickness (IMT; the tunica intima and media are the innermost layers of the arterial wall) in the right common carotid artery (one of the arteries that supplies the head and neck with blood). A prospective cohort study enrolls a group of individuals and follows them to see whether exposure to certain risk factors affects their risk of developing a specific disease; progression of IMT—thickening of the arterial wall with time—in the common carotid artery is a surrogate measure of atherosclerosis.

What Did the Researchers Do and Find? MESA Air enrolled nearly 7,000 45–84-year-old individuals without symptoms of CVD from different ethnic backgrounds living in six US metropolitan areas beginning in 2000. Carotid IMT was measured using ultrasound in all the participants at baseline and at the second or third planned examination of MESA Air for most participants. The researchers modeled the outdoor concentration of PM$_{2.5}$ at each participant’s house for the year preceding baseline and for the years between ultrasound examinations using data collected by regulatory monitoring stations and data derived from study-specific air samples collected outside the homes and in the communities of study participants. Among the 5,362 study participants eligible for the current analysis, the average annual progression of carotid IMT was 14 μm/year. Higher average levels of residential PM$_{2.5}$ between ultrasound examinations were associated with increased IMT progression among people living in the same metropolitan area after adjusting for other factors that might have affected each participant’s risk of CVD such as smoking and age. Living at a residence with 2.5 μg/m$^3$ higher levels of PM$_{2.5}$ levels at baseline, greater reductions in PM$_{2.5}$ between ultrasound examinations were associated with a slower rate of IMT progression.

What Do These Findings Mean? These findings suggest that higher long-term PM$_{2.5}$ concentrations are associated with increased IMT progression—a surrogate for atherosclerosis progression—and that larger reductions in PM$_{2.5}$ are associated with slower IMT progression. By combining these findings with other results from MESA Air, the researchers estimate that individuals living in parts of town with 2.5 μg/m$^3$ higher PM$_{2.5}$ levels may have a 2% increased risk of stroke compared to people living in less polluted regions of the same metropolitan area. Because of study limitations such as the use of a surrogate marker for atherosclerosis and the failure to account for changes in other factors that might also have affected CVD risk, the findings reported here should be interpreted cautiously. Nevertheless, these findings support the hypothesis that long-term exposure to PM$_{2.5}$ is associated with the progression of atherosclerosis and consequently with an increased risk of CVD, even at PM$_{2.5}$ levels below existing regulatory standards.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1001430.

- The American Heart Association provides information for patients and caregivers on all aspects of cardiovascular disease (in several languages), including information on air pollution and cardiovascular disease
- The AirNow site provides information about US air quality and about air pollution and health
- The Air Quality Archive has up-to-date information about air pollution in the UK and information about the health effects of air pollution
- The US Environmental Protection Agency has information on particulate matter pollution
- Information on MESA and on MESA Air is available