



# Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study

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## Summary

**Background** Long-term exposure to fine particulate matter less than 2.5 µm in diameter (PM<sub>2.5</sub>) and traffic-related air pollutant concentrations are associated with cardiovascular risk. The disease process underlying these associations remains uncertain. We aim to assess association between long-term exposure to ambient air pollution and progression of coronary artery calcium and common carotid artery intima-media thickness.

**Methods** In this prospective 10-year cohort study, we repeatedly measured coronary artery calcium by CT in 6795 participants aged 45–84 years enrolled in the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) in six metropolitan areas in the USA. Repeated scans were done for nearly all participants between 2002 and 2005, for a subset of participants between 2005 and 2007, and for half of all participants between 2010 and 2012. Common carotid artery intima-media thickness was measured by ultrasound in all participants at baseline and in 2010–12 for 3459 participants. Residence-specific spatio-temporal pollution concentration models, incorporating community-specific measurements, agency monitoring data, and geographical predictors, estimated concentrations of PM<sub>2.5</sub> and nitrogen oxides (NO<sub>x</sub>) between 1999 and 2012. The primary aim was to examine the association between both progression of coronary artery calcium and mean carotid artery intima-media thickness and long-term exposure to ambient air pollutant concentrations (PM<sub>2.5</sub>, NO<sub>x</sub>, and black carbon) between examinations and within the six metropolitan areas, adjusting for baseline age, sex, ethnicity, socioeconomic characteristics, cardiovascular risk factors, site, and CT scanner technology.

**Findings** In this population, coronary calcium increased on average by 24 Agatston units per year (SD 58), and intima-media thickness by 12 µm per year (10), before adjusting for risk factors or air pollutant exposures. Participant-specific pollutant concentrations averaged over the years 2000–10 ranged from 9.2–22.6 µg PM<sub>2.5</sub>/m<sup>3</sup> and 7.2–139.2 parts per billion (ppb) NO<sub>x</sub>. For each 5 µg PM<sub>2.5</sub>/m<sup>3</sup> increase, coronary calcium progressed by 4.1 Agatston units per year (95% CI 1.4–6.8) and for each 40 ppb NO<sub>x</sub> coronary calcium progressed by 4.8 Agatston units per year (0.9–8.7). Pollutant exposures were not associated with intima-media thickness change. The estimate for the effect of a 5 µg/m<sup>3</sup> higher long-term exposure to PM<sub>2.5</sub> in intima-media thickness was –0.9 µm per year (95% CI –3.0 to 1.3). For 40 ppb higher NO<sub>x</sub>, the estimate was 0.2 µm per year (–1.9 to 2.4).

**Interpretation** Increased concentrations of PM<sub>2.5</sub> and traffic-related air pollution within metropolitan areas, in ranges commonly encountered worldwide, are associated with progression in coronary calcification, consistent with acceleration of atherosclerosis. This study supports the case for global efforts of pollution reduction in prevention of cardiovascular diseases.

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## Introduction

Particulate air pollution and traffic-related air pollutants are associated with overall mortality, cardiovascular mortality, and cardiovascular disease events. In particular, long-term exposure to high concentrations of air pollutants has been associated with risk of myocardial infarction and stroke.<sup>1</sup> However, previous studies of cardiovascular disease and air pollution have had short follow-up duration, have often been limited by between-city exposure contrasts without precisely accounting for

within-city variation, and have comprised secondary analyses of existing datasets collected to test other hypotheses. Furthermore, the underlying pathological process has not been well established, leaving the biological plausibility of these findings open to question.

To reduce uncertainties in the understanding of the potential health effects of ambient air pollutants, the US Environmental Protection Agency (EPA) supported an unprecedented effort to characterise pollutant exposures in participants of the National Heart,

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## Research in context

### Evidence before this study

At study launch, there was no literature on progression of atherosclerosis in relation to long-term exposure to air pollution; the study was in response to the US Environmental Protection Agency's Request For Applications for a prospective observational study of cardiovascular disease initiation and progression associated with long-term exposure to ambient particulate matter and other air pollutants in a population-based sample. Although previous research has been considered to be consistent with a causal relationship between particulate matter air pollution and ischaemic heart disease events and mortality, these studies had substantial limitations and biological plausibility has continued to be questioned. Previous studies have had short follow-up durations, little attention to fine-scale variation in pollutant exposure, and comprised secondary analyses of existing datasets collected to test other hypotheses.

### Added value of this study

This study provides important new information about the underlying biological processes of long-term exposure to air

pollutant concentrations and their association with cardiovascular disease, through repeated assessment of coronary artery calcification by CT (a surrogate of atherosclerosis extent) in a cohort and with an unprecedented effort to characterise air pollutant exposures. The study was specifically designed to address the hypothesis that air pollutants would be associated with progression in subclinical atherosclerosis.

Exposures assessed in this study are low and relevant for understanding the health effects of ambient environments occurring nowadays in high-income, low-income, and rapidly industrialising countries.

### Implications of all the available evidence

Together with accumulating observational evidence of the relationship between ambient pollutants and cardiovascular disease events, this study substantially advances the case for global efforts to reduce exposures to ambient air pollutants.

Lung, and Blood Institute's Multi-Ethnic Study of Atherosclerosis (MESA).<sup>2</sup> The resultant study (the Multi-Ethnic Study of Atherosclerosis and Air Pollution, [MESA Air])<sup>3</sup> tested a priori the associations of air pollution concentrations, specifically particulate matter of less than 2.5 µm in diameter (PM<sub>2.5</sub>), nitrogen oxides (NO<sub>x</sub>), and black carbon, with progression of subclinical arteriosclerosis. We report the association between long-term exposure to ambient air pollution and progression of coronary artery calcium and common carotid artery intima-media thickness.

## Methods

### Study design and participants

The designs of the MESA<sup>2</sup> and MESA Air<sup>3</sup> studies have been described previously. Briefly, MESA recruited a cohort of 6814 participants with no history of clinical cardiovascular disease from four ethnic groups (Hispanic, black, white, and Chinese), with sex balance and uniform age distribution (range 45–84 years at recruitment) in six areas of the USA: Baltimore, MD; Chicago, IL; Los Angeles County, CA; New York City, NY; St Paul, MN; and Winston-Salem, NC. Community-based strategies that varied by clinical centre were used to recruit participants. Recruitment and baseline examinations were done between July 17, 2000, and Aug 29, 2002. Between Feb 22, 2005, and May 9, 2007, MESA Air recruited 257 additional participants in Rockland County, NY (grouped as being from the same area as New York City, NY participants); Riverside County, CA (grouped as being from the same area as Los Angeles County, CA participants); and a coastal area of Los Angeles County, CA, to add heterogeneity in air

pollution exposures. The study protocol was approved by the institutional review board at each of the six study centres, and participants provided written informed consent upon their arrival at the study clinic.

### Procedures

All participants received CT scans at baseline to measure coronary artery calcium as previously described.<sup>4</sup> Repeated scans were done for nearly all participants between 2002 and 2005, for a subset of participants between 2005 and 2007, and for half of all participants between 2010 and 2012. CT technology differed between clinical centres and over time.<sup>5</sup> A four-density calibration phantom was imaged with each scan to enhance comparability of images between scanners and to scale the voxels in each composite scan before the calculation of coronary artery calcium scores. Scans were scored in the Harbor-UCLA Los Angeles Biomedical Research Institute by the Agatston method.<sup>4</sup>

To measure the common carotid artery intima-media thickness, one ultrasound and transducer model (Logiq 700, M12L, GE Medical Systems, Waukesha, WI, USA) were used at all sites in all examinations.<sup>6</sup> Images were read by the University of Wisconsin Carotid Ultrasound Reading Center. Baseline images were read only for participants with images from the 2010–12 examination.<sup>6</sup>

### Exposure assessment

The MESA Air pollution measurement and modelling methods have been described previously.<sup>3,7,8</sup> MESA Air measured ambient PM<sub>2.5</sub>, NO<sub>x</sub>, nitrogen dioxide (NO<sub>2</sub>), and black carbon (assessed by light absorption) at 27 long-term sites, 771 community snapshot locations (simultaneous

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2-week measurements collected on three occasions), and outside 697 participants' homes between 2005 and 2009 to supplement measurements from Environmental Protection Agency Air Quality System monitoring locations.

Participants reported all residential addresses from 1980 to 2012. Community-specific spatio-temporal models were developed to predict pollutant concentrations at participants' residences for each fortnight from 1999 to 2012, with statistical methods to accommodate irregular monitoring data and incorporate

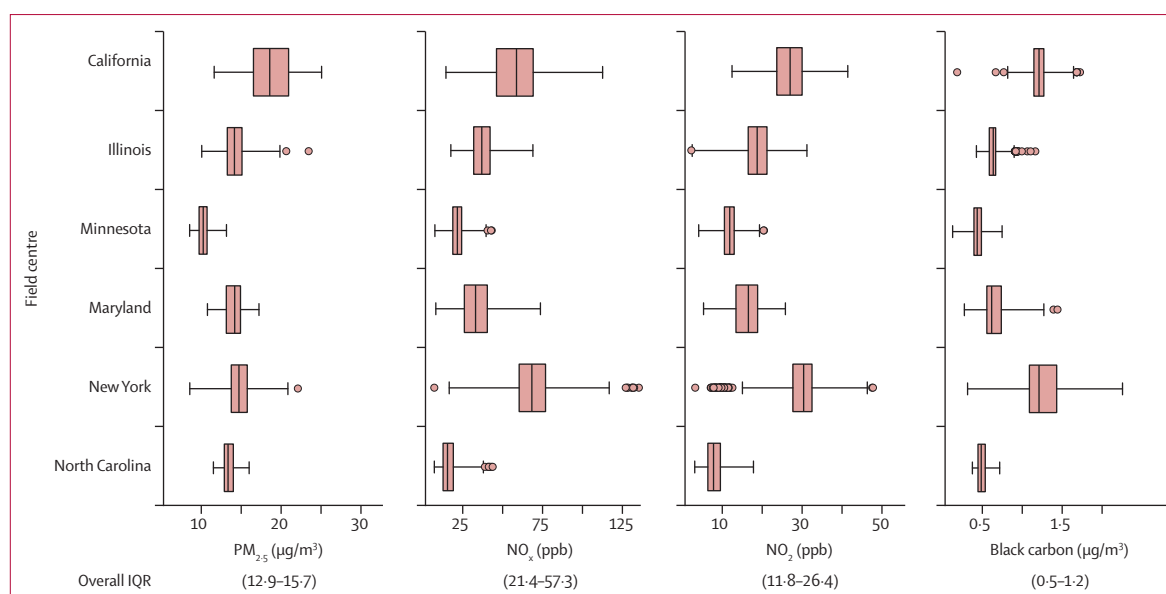
all monitoring results. These models explained 90–97% of the variation (model-fit  $R^2$ ) in measurements at participant homes. The cross-validated  $R^2$  values (assessing out-of-sample validation) for predictions from the area-specific models at residence locations varied by site. Median (range)  $R^2$  values for these models were 0·79 (0·54–0·85) for  $PM_{2.5}$ , 0·78 (0·45–0·90) for  $NO_2$ , 0·72 (0·50–0·92) for  $NO_x$ , and 0·67 (0·51–0·78) for black carbon. These  $R^2$  values at participants' homes leverage temporal as well as spatial variability.  $R^2$  values from the

	Winston-Salem, NC	New York City, NY	Baltimore, MD	St Paul, MN	Chicago, IL	Los Angeles County, CA
Year 2000–10 $PM_{2.5}$ ( $\mu g/m^3$ )*	13·5 (0·4)	14·5 (1·9)	13·7 (0·8)	10·6 (0·6)	14·1 (1·0)	17·7 (1·3)
n						
Baseline	1008	1166	1005	1027	1143	1446
Follow-up	897	1007	847	898	1004	1182
Follow-up time (years)	6·4 (3·5)	6·6 (3·4)	5·6 (3·6)	6·5 (3·4)	6·6 (3·5)	5·5 (3·4)
Coronary artery calcium						
Baseline (Agatston score)	143 (403)	131 (413)	186 (462)	172 (474)	121 (312)	129 (374)
Progression (Agatston per year)†	26 (61)	22 (60)	26 (63)	26 (60)	22 (47)	21 (52)
Demographics						
Age (years)	62 (10)	62 (10)	63 (10)	60 (10)	62 (10)	63 (10)
Male	471 (47%)	521 (45%)	471 (47%)	507 (49%)	537 (47%)	695 (48%)
Ethnicity						
White	547 (54%)	281 (24%)	498 (50%)	590 (57%)	542 (47%)	220 (15%)
Chinese	..	2 (0%)	..	..	303 (27%)	490 (34%)
Black	458 (45%)	395 (34%)	507 (50%)	..	298 (26%)	166 (11%)
Hispanic	3 (0%)	488 (42%)	..	437 (43%)	..	570 (39%)
Education level						
Less than high school	76 (8%)	271 (23%)	112 (11%)	194 (19%)	84 (7%)	472 (33%)
High school	211 (21%)	222 (19%)	202 (20%)	224 (22%)	89 (8%)	261 (18%)
Some college or technical	314 (31%)	322 (28%)	303 (30%)	359 (35%)	278 (24%)	375 (26%)
University or graduate	407 (40%)	351 (30%)	388 (39%)	250 (24%)	692 (61%)	338 (23%)
Smoking status						
Never	412 (41%)	564 (48%)	432 (43%)	430 (42%)	543 (48%)	872 (60%)
Former	435 (43%)	429 (37%)	423 (42%)	405 (39%)	451 (39%)	422 (29%)
Present	161 (16%)	173 (15%)	150 (15%)	192 (19%)	149 (13%)	152 (11%)
General health characteristics						
Body-mass index ( $kg/m^2$ )	29 (5)	29 (5)	29 (6)	29 (5)	27 (5)	27 (5)
Systolic blood pressure (mm Hg)	133 (22)	124 (20)	128 (21)	122 (20)	124 (21)	127 (23)
HDL cholesterol (mmol/L)	1·32 (0·39)	1·37 (0·39)	1·32 (0·39)	1·27 (0·36)	1·40 (0·41)	1·27 (0·36)
Total cholesterol (mmol/L)	4·89 (0·88)	4·99 (0·91)	4·97 (0·93)	5·17 (0·93)	5·04 (0·93)	5·07 (0·96)
LDL cholesterol (mmol/L)	2·95 (0·78)	3·03 (0·83)	3·03 (0·80)	3·10 (0·80)	3·03 (0·80)	3·05 (0·85)
Hypertension	553 (55%)	538 (46%)	515 (51%)	357 (35%)	435 (38%)	626 (43%)
Statin use	164 (16%)	197 (17%)	193 (19%)	126 (12%)	165 (14%)	196 (14%)
Diabetes						
Normal	769 (76%)	831 (71%)	721 (72%)	776 (76%)	908 (79%)	964 (67%)
Impaired fasting glucose	120 (12%)	169 (14%)	155 (15%)	133 (13%)	136 (12%)	242 (17%)
Diabetic	119 (12%)	165 (14%)	126 (13%)	118 (11%)	98 (9%)	240 (17%)

Data are mean (SD) or n (%). All percentages are calculated using the baseline as the denominator.  $PM_{2.5}$ =fine particulate matter less than 2·5  $\mu m$  in diameter.

HDL=high density lipoprotein. LDL=low density lipoprotein. \*Average of 2-week predictions from January, 2000, to December, 2010, generated at each participant's baseline address. †Based on individually-derived slopes.

**Table:** Participant characteristics at baseline and unadjusted longitudinal outcomes by field centre, for participants included in the analysis of coronary artery calcification



**Figure 1: Long-term outdoor air pollutant concentrations by area**

Pollutant concentrations are averaged over the time between the first and last CT scan, rounded to the nearest full year. Boxes cover the 25–75th percentile (IQR) with a centre line for the median concentration. Whiskers extend to the highest observation within 3 IQR of the box, with more extreme observations shown as points. Black carbon was measured by light absorption coefficient, where  $0.5 \times 10^{-5} \text{ m}^{-1}$  was approximately equivalent to  $0.5 \text{ µg/m}^3$  of elemental carbon. PM<sub>2.5</sub>=fine particulate matter less than 2.5 µm in diameter. NO<sub>x</sub>=nitrogen oxides. NO<sub>2</sub>=nitrogen dioxide. ppb=parts per billion.

cross-validation of the measured long-term fixed sites were similar.<sup>8</sup>

MESA Air participants completed detailed questionnaires at recruitment and after life changes, including moving homes. Examples of items queried included heating choices, air conditioner use, and window opening, and time spent indoors and outdoors, during summer and winter.<sup>9</sup> Responses, meteorology, and an outdoor PM<sub>2.5</sub> tracer (particulate sulphur assessed in concurrent samples inside and outside selected homes) were used to predict the fraction of ambient PM<sub>2.5</sub> infiltrating homes.<sup>10</sup> Indoor PM<sub>2.5</sub> exposures were calculated as the predicted fortnight's outdoor PM<sub>2.5</sub> concentration multiplied by the weather-specific and residence-specific infiltration fraction. An individually-weighted exposure to ambient-derived PM<sub>2.5</sub> (PM<sub>2.5(amb)</sub>) for each fortnight was calculated by time-weighting the outdoor concentration by time spent outdoors, and indoor exposure by time spent indoors.

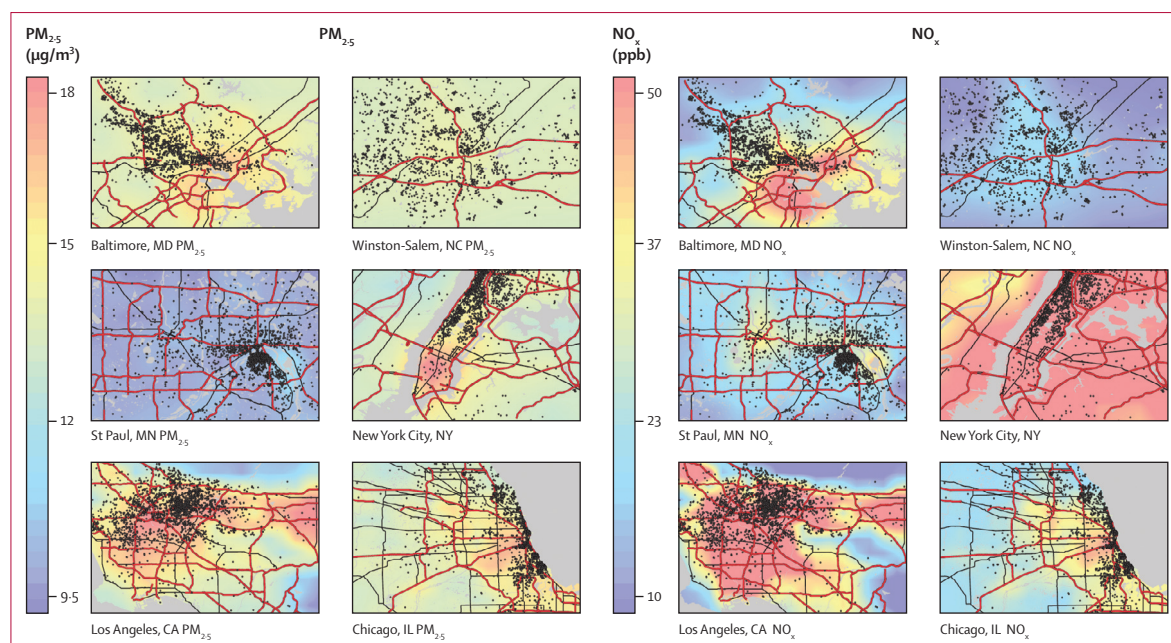
Long-term exposures were the average of fortnightly residence-specific predictions from recruitment to follow-up for each examination. Year 2000 concentrations at the baseline address were used to model baseline cross-sectional relationships. Outdoor concentrations of black carbon were generated only for the years 2006–08 because comparable air quality system data were not available at other times (EPA's measurement method for black carbon was not comparable to the study-specific measurement method). Long-term black carbon averages were calculated by weighting the residence-specific 2006–08 means by the amount of time participants lived at each location between their examinations.

### Statistical analysis

The study was designed to be adequately powered to detect air pollutant effects of 2 Agatston units per year or 7 µm per year intima-media thickness per 10 µg per m<sup>3</sup> PM<sub>2.5</sub>, based on pollution contrasts observed between MESA communities before 2003.

The associations of progression of coronary artery calcium and mean intima-media thickness with long-term average outdoor pollutant concentrations (PM<sub>2.5</sub>, NO<sub>x</sub>, and black carbon) were the primary interests, with NO<sub>2</sub> and ambient-derived PM<sub>2.5</sub> assessed as secondary. The primary adjustment model included baseline age, sex, ethnicity, site, CT scanner type (in the coronary artery calcium analysis), body-mass index (BMI), physical activity, smoking and second-hand smoke exposure (both time-varying), employment outside the home, total cholesterol, high density lipoprotein (HDL), triglycerides, statin use (time-varying), neighbourhood socioeconomic index, level of education, income, and the interactions between these variables and study time. Participants were censored at the time of coronary revascularisation procedures for analysis of coronary artery calcium. Additional models incorporated information on blood pressure and diabetes.

A mixed model jointly analysed both the cross-sectional association between air pollution and the outcomes at baseline examination and the relationship between air pollution and the rate of progression.<sup>11</sup> Repeated measurements were modelled as a function of study time, with time-varying exposures modelled as an interaction with time to obtain a rate. Participant-specific



**Figure 2: Maps of predicted  $PM_{2.5}$  and  $NO_x$  concentrations for 2005 in the MESA Air communities, by the city of the clinical site**

Contrasts are smoothed in these figures, which might attenuate the visibility of fine-scale variation. Participant residential locations are shown by black dots, jittered to protect their privacy.  $PM_{2.5}$ =fine particulate matter less than 2.5  $\mu m$  in diameter.  $NO_x$ =nitrogen oxides. ppb=parts per billion.

random intercepts and slopes were included, along with random intercepts for neighbourhood clusters. We investigated potential effect modification by sex, ethnicity, obesity (BMI <30 kg/m<sup>2</sup> vs BMI  $\geq$ 30 kg/m<sup>2</sup>), age category (10-year intervals), smoking status, hypertensive status, diabetes status, HDL cholesterol concentration (HDL cholesterol <1.03 mmol/L vs HDL cholesterol  $\geq$ 1.04 mmol/L), total cholesterol (total <5.17 mmol/L, total 5.17–6.21 mmol/L, or total >6.21 mmol/L), and LDL cholesterol concentration (LDL cholesterol <2.59 mmol/L, LDL cholesterol 2.59–3.36 mmol/L, LDL cholesterol 3.36–4.14 mmol/L, or LDL cholesterol >4.14 mmol/L). Evidence for effect modification was assessed by including three-way interaction terms between study time, the effect modifier, and air pollution concentration. A concentration-response curve was generated using a thin plate regression spline with five degrees of freedom for long-term average  $PM_{2.5}$  concentrations.

We also examined the relationship between pollutants and relative progression of coronary artery calcium, using a  $\ln(\text{Agatston score} + 25)$  transformation of the outcome.

#### Role of the funding source

This study was overseen by a Steering Committee and an External Scientific Advisory Committee (ESAC). The primary funder of MESA Air, the US Environmental Protection Agency, had ex-officio representation on the ESAC. The funder had no role in data collection, analysis, interpretation, or writing of the study reports. All authors

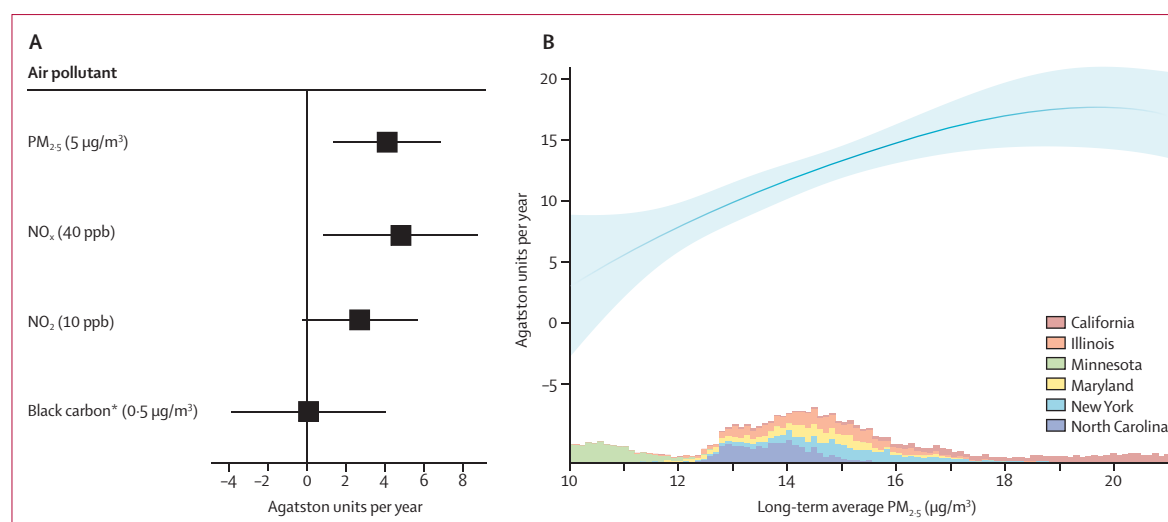
were provided complete access to the data and all authors share responsibility for the decision to submit the manuscript.

#### Results

Of the 7060 participants initially enrolled, 5834 underwent at least two examinations and had sufficient data to be included longitudinally in the analysis of coronary artery calcium. 961 participants were included only at baseline. The mean age of the cohort at baseline was 62 years (SD 10), and 3593 (53%) of the 6795 participants assessed were women. Overall, the cohort included 2678 (39%) white, 795 (12%) Chinese, 1824 (27%) black, and 1498 (22%) Hispanic participants (table). The differences in population characteristics between sites, notably in ethnicity and level of education, reflect purposefully implemented sampling strategies; differences in smoking rates reflect community differences. Mean follow-up time for participants with at least two coronary artery calcium measurements was 6.2 years (SD 3.5) and for those with intima-media thickness measurements from at least two timepoints was 9.2 years (1.8).

Figure 1 shows summary statistics of air pollutant concentrations in the year 2000 and over follow-up. Long-term average levels of pollution were lower than levels of pollution in 2000. Mean concentrations also varied between sites by pollutant, with  $PM_{2.5}$  concentrations being highest in Los Angeles County and lowest in St Paul, and  $NO_x$  and  $NO_2$  being highest in New York City and lowest in Winston-Salem (figure 1). Figure 2





**Figure 3: Long-term average air pollutant concentrations and coronary artery calcium progression**

(A) The linear longitudinal association of fine particulate matter (PM<sub>2.5</sub>), nitrogen oxides (NO<sub>x</sub>), nitrogen dioxide (NO<sub>2</sub>), and black carbon, with coronary artery calcium progression (Agatston units per year), from linear mixed models adjusted for age, sex, ethnicity, city, income, employment outside the home, smoking status, second-hand smoke exposure, physical activity, adiposity, cholesterol, statin use, neighbourhood socioeconomic index, income, education and scanner type. (B) The concentration-response curve with 95% CIs for the overall change in and coronary artery calcium (progression rate associated with long-term average PM<sub>2.5</sub> concentrations). The curve is based on a mixed model that includes a thin plate regression spline with five degrees of freedom to more flexibly assess the potentially non-linear association. The relationship at the extremes is less certain and might rely on concentrations that are recorded only in one geographical region; the highest and lowest 5% of overall concentrations have been trimmed for visualisation. The histogram at the bottom of the right panel shows the relative overall distribution of long-term PM<sub>2.5</sub> concentrations in the cohort, with different colours representing each clinic location. \*Black carbon as measured by light absorption coefficient, where  $0.5 \times 10^{-5} \text{ m}^{-1}$  is approximately equivalent to  $0.5 \mu\text{g}/\text{m}^3$ .

shows between-city and within-city exposure contrasts of concentrations of PM<sub>2.5</sub> and NO<sub>x</sub> in 2005 (appendix p 11).

The mean progression rate over follow-up for coronary artery calcium was 24 Agatston units per year (SD 58) and for intima-media thickness was 12 µm per year (10); at baseline, coronary artery calcium scores were 145 Agatston units (407). Because the intima-media thickness analysis was restricted to participants who returned for ultrasound scans during the last examination, participants with intima-media thickness data were on average 2 years younger, more educated, and less likely to have diabetes than were those included in the coronary artery calcium analysis (appendix p 15).

In the primary analysis adjusted for potential confounders, a 5 µg/m<sup>3</sup> higher PM<sub>2.5</sub> concentration was associated with 4.1 Agatston units per year (95% CI 1.4–6.8) increased rate of coronary artery calcium progression (figure 3). A 40 parts per billion (ppb) higher NO<sub>x</sub> concentration was associated with a 4.8 Agatston units per year (0.9–8.7) increased rate of coronary artery calcium progression, and a 10 ppb higher NO<sub>2</sub> concentration was associated with 2.7 Agatston units per year (–0.3 to 5.7) increased rate of coronary artery calcium progression. Neither black carbon nor ambient-derived PM<sub>2.5</sub> were associated with coronary artery calcium progression (0.1 Agatston units per year for a 0.5 µg/m<sup>3</sup> higher black carbon concentration [–3.8 to 4.1] and 1.0 Agatston units per year for a 5 µg/m<sup>3</sup> higher ambient-derived PM<sub>2.5</sub> exposure [–1.9 to 3.9]). Results were similar in models incorporating blood pressure and diabetes status.

Pollutant exposures were not associated with intima-media thickness change. The estimate for the effect of a 5 µg/m<sup>3</sup> higher long-term exposure to PM<sub>2.5</sub> in intima-media thickness was –0.9 µm per year (95% CI –3.0 to 1.3). For 40 ppb higher NO<sub>x</sub>, the estimate was 0.2 µm per year (–1.9 to 2.4).

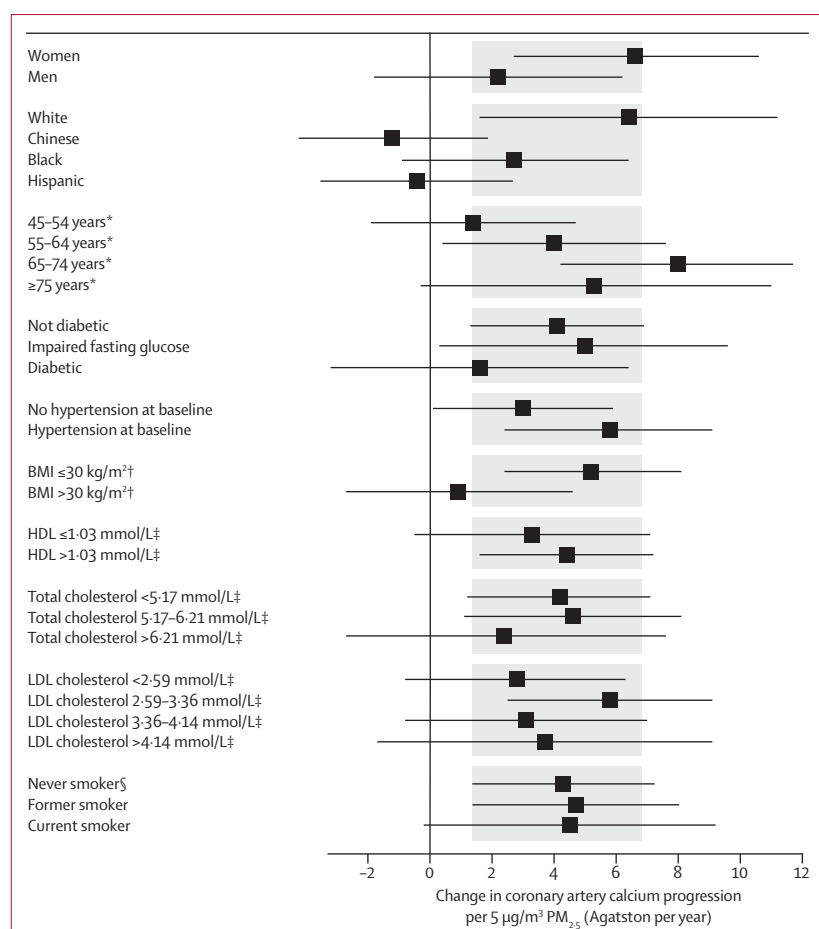
Results for both outcomes were consistent in sensitivity analyses. The associations of PM<sub>2.5</sub> and NO<sub>x</sub> with coronary artery calcium progression were attenuated with widened confidence intervals if one was adjusted for the other. Exposure to outdoor PM<sub>2.5</sub>, NO<sub>x</sub>, NO<sub>2</sub>, and ambient-derived PM<sub>2.5</sub> were all positively associated with relative coronary artery calcium progression (appendix p 13).

The concentration-response function between outdoor PM<sub>2.5</sub> and coronary artery calcium progression concentration suggests attenuation of the association at higher concentrations (figure 3). Evidence for effect modification by several factors was weak and inconsistent between PM<sub>2.5</sub> and NO<sub>x</sub>, although it suggested that the effects of exposures to these pollutants might be greater in older, non-obese, and hypertensive individuals (figure 4).

## Discussion

In this multi-ethnic prospectively studied population, ambient concentrations of PM<sub>2.5</sub> and NO<sub>x</sub> were strongly associated with accelerated atherosclerosis, as shown by assessment of coronary artery calcium over a 10-year period. Air pollution was not associated with progression of intima-media thickness. This study benefited from

See Online for appendix



**Figure 4: Association between pollutant concentrations and coronary artery calcium progression, by baseline participant characteristics**

The shaded region indicates the 95% confidence interval for the overall association per 5 µg/m³ of PM<sub>2.5</sub>.

\*Linear adjustments for age were replaced with categories. †Linear adjustments for adiposity were replaced with indicator for body-mass index >30 kg/m². ‡Linear adjustments for cholesterol were replaced with categories.

§Not adjusted for pack-years or second-hand smoke.

state-of-the-art exposure estimation at the time and location of each residence during follow-up and incorporated high-quality information about potential confounding factors, including time-varying covariates such as statin use. The cohort-focused air quality monitoring effort and spatio-temporal modelling methods enabled us to generate individually resolved exposures and examine relationships between atherosclerosis progression and air pollution over time, using within-city contrasts with an unprecedented level of accuracy. These results provide important evidence that long-term exposure to these ambient air pollutants is associated with atherosclerosis progression in the coronary arteries and can explain previous findings that pollutants are associated with cardiovascular events and mortality.

Exposures during follow-up of this cohort were low by historical and international standards. The present US National Ambient Air Quality Standards<sup>12</sup> permit

annual average PM<sub>2.5</sub> concentrations of 12 µg/m³ and the European Union Air Quality Standards<sup>13</sup> permit 25 µg/m³, whereas the mean ambient PM<sub>2.5</sub> concentration that participants in our study were exposed to over 2000–10 was 14.2 µg/m³ (range 9.2–22.6). The concentrations in rapidly industrialising countries are substantially higher.<sup>14</sup>

Calcified plaques in the coronary arteries have been consistently associated with cardiovascular disease in both clinical trials and observational research.<sup>15</sup> Coronary artery calcium is a very strong risk marker of future ischaemic vascular events. Although most often studied as a one-time measure of atherosclerotic extent and plaque burden,<sup>16</sup> change in coronary artery calcium also predicts subsequent ischaemic events.<sup>2</sup> Risk factors that accelerate coronary artery calcium progression (including age, male sex, adiposity, systolic blood pressure, smoking, and diabetes) are also strong predictors of subsequent ischaemic events.<sup>17</sup> Coronary artery calcium measurements might represent more mature atherosclerotic lesions than forming or vulnerable plaques.<sup>18</sup>

The association between coronary artery calcium progression and air pollution has not been reported, although the plausibility of a causal relationship between air pollution and atherosclerosis is suggested through several mechanisms.<sup>19</sup> In a cross-sectional analysis in the Heinz-Nixdorf Recall study,<sup>20</sup> coronary artery calcium was higher in individuals living near roads than in those who did not live near major roads. Our findings provide evidence that exposure to air pollution is associated with coronary artery calcium progression.

Although coronary artery calcium progression was associated with PM<sub>2.5</sub> and NO<sub>x</sub>, it was not associated with black carbon. Unlike the other pollutants, for which exposures were estimated between 1999 and 2012, black carbon exposures were limited to only spatial contrasts in 2006–08; hence, analyses could not capture the decreasing trends in pollutant concentrations recorded during follow-up.<sup>21</sup> Additionally, coronary artery calcium progression was not as strongly associated with NO<sub>2</sub> as it was with total NO<sub>x</sub>. The total NO<sub>x</sub> is highest in the most near-road environments (measured in previous research as proximity to a major roadway or time in traffic),<sup>22</sup> and might better represent the group of primarily emitted traffic-related air pollutants present in these locations. Therefore, characterisation of NO<sub>x</sub> exposure might be a better way to capture the effects of the near-road environment on health.

We noted a somewhat stronger association between PM<sub>2.5</sub> and coronary artery calcium progression in hypertensive, in non-obese, and in individuals older than 65 years. The findings with age and hypertension suggest a synergistic association between air pollutants and these two strong risk factors for progression of atherosclerosis, though this association was not found for other strong risk factors such as diabetes or elevated cholesterol levels. The finding that pollutant associations with coronary

artery calcium progression appeared stronger in non-obese participants is not what would be expected because inflammatory and metabolic consequences of obesity are thought to share mechanistic pathways with those of air pollutants.<sup>19</sup> Although this study's sample size and precision provided adequate statistical power for the primary comparisons, analyses of effect modification were less well powered.

Our findings for the effect of pollutants on coronary artery calcium progression were robust to a variety of sensitivity analyses and did not differ depending on stages of control of potential confounding variables. This result strengthens our confidence in these associations. In addition, air pollutant relationships were recorded whether the outcome was measured as an absolute or relative change in calcification. Although absolute change in the extent of calcifications was our a-priori outcome choice, assessment of the outcome as a relative change did suggest additional associations with NO<sub>2</sub> and ambient-derived PM<sub>2.5</sub> that were not observed with the absolute change outcome.

An association between air pollution and progression of carotid wall thickness has been noted in some, but not all, previous studies.<sup>23,24</sup> An interim analysis<sup>25</sup> in MESA showed that exposure to a 2.5 µg/m<sup>3</sup> higher PM<sub>2.5</sub> concentration was associated with a 5 µm per year increase in intima-media thickness progression; the interim study used a different approach to image analysis, a less-developed approach to exposure estimation, and a much shorter period of follow-up. An observational study<sup>26</sup> within clinical trial data showed associations between PM<sub>2.5</sub> and intima-media thickness progression in some subgroups. Carotid wall thickness is a challenging outcome for observational studies because the change in intima-media thickness over time is small relative to the measurement error at each timepoint. The mechanism by which air pollution might accelerate atherosclerosis might also be unrelated to intima-media thickness, which is a marker of arterial injury rather than atherosclerosis per se.<sup>27</sup> Unlike coronary artery calcium, change over time in intima-media thickness is not predictive of subsequent cardiovascular disease events in observational studies, although it is a commonly used outcome in pharmaceutical studies.<sup>28,29</sup> In MESA participants, coronary artery calcium has been a much stronger predictor of subsequent coronary heart disease events than intima-media thickness.<sup>30</sup>

The MESA cohort provides an extraordinarily well characterised population in terms of potential confounders of the relationship between air pollution and cardiovascular disease. Nevertheless, residual confounding by unmeasured factors remains a possibility. Additionally, though we chose a-priori exposures and outcomes of interest, the presence of more than one exposure and outcome in our analyses could be criticised for including multiple comparisons.

This study focused on the health effects of ambient-derived air pollutants on cardiovascular health. Our

primary exposure metrics focused on concentrations of pollutants outside homes, although individuals spend time in specific micro-environments, including indoors. We developed the ambient-derived PM<sub>2.5</sub> measure specifically to address this issue, to better characterise actual exposure to ambient PM<sub>2.5</sub> by adjusting outdoor concentrations by time spent indoors and infiltration of particles into the home. Because these predictions represent the product of two different modifiers of outdoor concentration (each imperfectly assessed and not available for all study participants) we believe that the additional error in exposure estimation was the primary driver for the weak associations reported for ambient-derived PM<sub>2.5</sub>. Full characterisation of time–location patterns and indoor exposures is notoriously difficult. Ascertainment of highly resolved, individualised micro-environmental exposure estimates over several years of follow-up is elusive, hence our primary exposure estimation approach relies on outdoor concentrations.

In conclusion, evidence from this study provides strong biological support for the observation that long-term exposures to outdoor particulate matter and traffic-related air pollution, specifically PM<sub>2.5</sub> and NO<sub>x</sub>, are related to the development of atherosclerotic cardiovascular disease.

#### Contributors

All authors contributed substantially to the conception or design of the manuscript or the acquisition, analysis, or interpretation of data for the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. All authors approved the final version submitted. JDK directed the MESA Air investigator team and the remaining investigators are listed alphabetically.

#### Declaration of interests

We declare no competing interests.

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For a full list of participating MESA investigators and institutions see <http://www.mesa-nhlbi.org>



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