Residential Proximity to Major Roads, Exposure to Fine Particulate Matter, and Coronary Artery Calcium

The Framingham Heart Study

Kirsten S. Dorans, Elissa H. Wilker, Wenyuan Li, Mary B. Rice, Petter L. Ljungman, Joel Schwartz, Brent A. Coull, Itai Kloog, Petros Koutrakis, Ralph B. D’Agostino Sr, Joseph M. Massaro, Udo Hoffmann, Christopher J. O’Donnell, Murray A. Mittleman

Objective—Long-term exposure to traffic and particulate matter air pollution is associated with a higher risk of cardiovascular disease, potentially via atherosclerosis promotion. Prior research on associations of traffic and particulate matter with coronary artery calcium Agatston score (CAC), an atherosclerosis correlate, has yielded inconsistent findings. Given this background, we assessed whether residential proximity to major roadway or fine particulate matter were associated with CAC in a Northeastern US study.

Approach and Results—We measured CAC ≤ twice from 2002 to 2005 and 2008 to 2011 among Framingham Offspring or Third-Generation Cohort participants. We assessed associations of residential distance to major roadway and residential fine particulate matter (2003 average; spatiotemporal model) with detectable CAC, using generalized estimating equation regression. We used linear mixed effects models to assess associations with loge(CAC). We also assessed associations with CAC progression. Models were adjusted for demographic variables, socioeconomic position markers, and time. Among 3399 participants, 51% had CAC measured twice. CAC was detectable in 47% of observations. At first scan, mean age was 52.2 years (standard deviation 11.7); 51% male. There were no consistent associations with detectable CAC, continuous CAC, or CAC progression. We observed heterogeneous associations of distance to major roadway with odds of detectable CAC by hypertensive status; interpretation of these findings is questionable.

Conclusions—Our findings add to prior work and support evidence against strong associations of traffic or fine particulate matter with the presence, extent, or progression of CAC in a region with relatively low levels of and little variation in fine particulate matter. (Arterioscler Thromb Vasc Biol. 2016;36:1679-1685. DOI: 10.1161/ATVBAHA.116.307141.)

Key Words: air pollution ▪ atherosclerosis ▪ coronary artery calcium ▪ epidemiology ▪ multidetector computed tomography

Long-term exposure to particulate matter air pollution is associated with a higher risk of cardiovascular disease (CVD) morbidity and mortality. Long-term exposure to traffic and particulate matter air pollution is associated with a higher risk of cardiovascular disease (CVD) morbidity and mortality. One pathway through which this could occur is by atherosclerosis promotion, with potential mechanisms including a systemic inflammatory and oxidative stress response, autonomic nervous system imbalance, and possibly, the transport of particulate matter or its constituents directly into arterial blood circulation. Studies in susceptible animal models have found that particulate matter exposure leads to atherosclerosis progression.

Epidemiological studies have also provided evidence of positive associations between ambient particles and traffic with atherosclerosis markers. Positive associations between fine particulate matter (PM$_{2.5}$) and cardiovascular or all-cause mortality have been observed in regions with relatively low PM$_{2.5}$ levels, including New England. Studies in Massachusetts have found positive associations between traffic exposure and adverse cardiovascular outcomes and between PM$_{2.5}$ and acute myocardial infarction. In a multicity US study, traffic...
exposure was associated with left ventricular mass and microvascular abnormalities. PM$_{2.5}$ or traffic have been associated with impaired conduit artery and microvascular function among Framingham Heart Study participants living in the Northeastern United States. In a Boston area study, black carbon, a correlate of traffic, was associated with carotid intima–media thickness (CIMT), a marker of subclinical atherosclerosis. However, prior US and German studies of residential proximity to a major roadway and particulate matter exposure with coronary artery calcium Agatston score (CAC), a marker of a later stage in the atherosclerotic disease process than CIMT, have yielded inconsistent results. Given this background, we aimed to assess whether there were associations of these exposures with CAC among participants from the Framingham Heart Study living in the Northeastern United States, a region with relatively low PM$_{2.5}$ levels. CAC provides a quantitative estimate of total coronary atheroma (both calcified and noncalcified plaque). An independent predictor of coronary heart disease (CHD) and CVD, CAC has been used as a CVD prognostic tool. In Framingham Heart Study participants, CAC improved discrimination and risk reclassification for major CHD beyond traditional risk factors. We assessed associations of CAC measured ≤2 times during the periods 2002 to 2005 and 2008 to 2011, with residential distance to a major roadway and with exposure to spatially resolved PM$_{2.5}$ at home address in the Framingham Offspring and Third Generation Cohorts. Residential distance to a major roadway, here defined as A1, A2, or A3 road (US Census Features Class), is a surrogate of exposure to local traffic emissions. PM$_{2.5}$ is emitted by both local and regional pollution sources.

**Materials and Methods**

Materials and Methods are available in the online-only Data Supplement.

**Results**

**Study Participants**

Table 1 describes participant characteristics of the 5118 observations from 3399 participants. Average age of participants was 52.2 years and 59.0 years during the first and second rounds of multidetector computed tomography (MDCT) scans, respectively. Overall, women contributed to 51% of observations, and college graduates contributed to 45% of observations. Participants from the second round of MDCT scans were less likely than those from the first round to be current smokers (7% versus 13%) and more likely to report being on hypertension medication (35% versus 19%) or lipid medication (38% versus 14%).

**Exposure Distributions**

Table 2 summarizes the distributions of exposures. The median distance to the nearest major roadway, defined as A1, A2, or A3 road (US Census Features Class), was 201 m, and 23% of observations came from participants who lived within 50 m of a major roadway. Among 1937 residential locations within 150 m of a major roadway, the largest roadway within 150 m was an A1 for 73, an A2 for 209, and an A3 for 1655 locations. Median PM$_{2.5}$ in 2003 was 10.7 μg/m$^3$, which is lower than the current US Environmental Protection Agency annual PM$_{2.5}$ National Air Quality Standard of 12 μg/m$^3$.

**Associations With Odds of Detectable CAC and Average CAC**

We found no associations of residential proximity to a major roadway or average residential PM$_{2.5}$ (2003 or 2003–2009) exposure with the odds of detectable CAC (Table 3). We also observed no associations of these exposures with average natural log-transformed CAC among those with detectable CAC (Table 3). Some point estimates were in the opposite direction than expected. For instance, compared with living 400 to <1000 m from a major roadway, living <50 m from a major roadway was associated with a 5.8% lower CAC, though confidence intervals were wide.

**Associations With Odds of Detectable CAC Progression and Average Annual Change in CAC**

Among 1719 participants with CAC measured during MDCT round 1 and round 2, 41% had detectable CAC progression. We observed no association between residential distance to a major roadway or PM$_{2.5}$ and the odds of detectable CAC progression (Table 4). We observed a weak association of residential proximity to a major roadway with average annual change in CAC: living further from a roadway was associated with a higher average annual change in CAC (Table 4). There was no association of PM$_{2.5}$ with average annual change in CAC (Table 4).

**Sensitivity Analyses**

We found evidence of nonlinearity for the associations of PM$_{2.5}$ (2003 and 2003–2009) with natural log-transformed CAC—there was a suggested positive association at lower PM$_{2.5}$ levels and suggested negative association at higher PM$_{2.5}$ levels, though confidence intervals were wide (Figure I in the online-only Data Supplement).

When we only adjusted for age and sex, results were similar. In the main analyses, we adjusted for age and age$^2$ at scan, sex, body mass index, smoking status, pack-years, individual-level education, median census-tract value of owner-occupied housing units, cohort, and time. We did not observe materially different results when we further adjusted for physical activity index, alcohol intake, menopausal status, diabetes mellitus, antihypertensive medication, systolic blood pressure, diastolic blood pressure, lipid-lowering medication, total cholesterol, high-density lipoprotein cholesterol, and triglycerides. Results were also similar when we adjusted for year of computed tomography scan as a categorical variable.
Table 1. Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean±SD or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at MDCT Scan, y</td>
<td>52.2±11.7</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>1443 (51)</td>
</tr>
<tr>
<td>Offspring, %</td>
<td>1123 (39)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>915 (32)</td>
</tr>
<tr>
<td>College graduate</td>
<td>1277 (45)</td>
</tr>
<tr>
<td>Median census value of owner-occupied housing</td>
<td>222,497±101,214</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>370 (13)</td>
</tr>
<tr>
<td>Former smokers, %</td>
<td>1060 (37)</td>
</tr>
<tr>
<td>Pack-years</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>29.8±13.7</td>
</tr>
<tr>
<td>Former smokers</td>
<td>16.9±17.7</td>
</tr>
<tr>
<td>Alcohol (average drinks/week)</td>
<td>4.9±7.3</td>
</tr>
<tr>
<td>Physical activity index (dimensionless)</td>
<td>37.6±7.4</td>
</tr>
<tr>
<td>Menstrual periods stopped,* %</td>
<td>738 (52)</td>
</tr>
<tr>
<td>Diabetes mellitus history, %</td>
<td>146 (5)</td>
</tr>
<tr>
<td>Clinically apparent CVD at MDCT scan, %</td>
<td>154 (5)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.8±5.3</td>
</tr>
<tr>
<td>Hypertension medications, %</td>
<td>535 (19)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>122±16</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>76±9</td>
</tr>
<tr>
<td>Lipid medications, %</td>
<td>389 (14)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>127±89</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>197.0±34.9</td>
</tr>
<tr>
<td>High-density cholesterol</td>
<td>53.7±16.6</td>
</tr>
<tr>
<td>10-year predicted risk of CVD†, %</td>
<td>0.05±0.07</td>
</tr>
<tr>
<td>MDCT scan results</td>
<td></td>
</tr>
<tr>
<td>CAC&gt;0, %</td>
<td>1284 (45)</td>
</tr>
<tr>
<td>CAC, among those with CAC&gt;0†</td>
<td>70.5 (278.5)</td>
</tr>
</tbody>
</table>

Data calculated from 5118 observations, from 3399 participants with at least one CAC measurement. CAC indicates coronary artery calcium Agatston score; CT, computed tomography; CVD, cardiovascular disease; and MDCT, multidetector computed tomography.

*Among women.
†American College of Cardiology/American Heart Association 2013 10-year predicted risk of atherosclerotic CVD; Median, interquartile range.
‡Median, interquartile range.

Results were similar when we restricted to those free of CVD. We found no consistent pattern of heterogeneity of associations with the presence or extent of CAC by age, sex, cohort, 10-year risk of atherosclerotic CVD, or smoking status (Table I in the online-only Data Supplement). We observed heterogeneity of the association of distance to a major roadway with odds of detectable CAC by hypertensive status or use of antihypertensive medications. Living closer to a major roadway was associated with higher odds of detectable CAC among those who had hypertension or used antihypertensive medications and lower odds of detectable CAC among those without hypertension or who did not use antihypertensive medications. However, we did not observe such patterns of association with the extent of CAC, nor with associations of PM2.5 with CAC. Given the lack of consistent heterogeneity by hypertension or antihypertensive treatment, interpretation of these findings is questionable.

Results were similar when we assessed associations of living close to a major roadway (<150 m) with CAC. We did not observe an association of distance to nearest A1 or A2 road with the presence, extent, detectable progression, or annual change of CAC. Results were similar when we ran analyses separately for MDCT round 1 and MDCT round 2.

Carrying out the CAC>0 analyses with a mixed logistic model yielded similar results, though with wider confidence intervals. We observed no strong associations of distance to a major roadway or PM2.5 with log(CAC+1) or with CAC greater than the 75th or 90th age- and sex-specific healthy referent cut points.

Discussion

In this study in a region with relatively low levels of and variation in PM2.5, we found no consistent associations between residential distance to a major roadway or PM2.5 with the presence or extent of CAC or with CAC progression. Sensitivity analyses yielded generally robust findings.

Prior studies of associations of these exposures with CAC have yielded somewhat inconsistent results. In the Heinz Nixdorf Recall Study, based in an industrial region of Germany, residential distance to a major road was associated with elevated CAC and higher continuous CAC.9 PM2.5 was associated with CAC only among individuals who had not recently worked full time. In the US-based Multi-Ethnic Study of Atherosclerosis (MESA), cross-sectional associations of PM2.5 and thoracic particles (<10 μm) with CAC were weak (not statistically significant) or inconsistent.10 However, more recently, MESA has found that PM2.5 and nitrogen oxides, a marker of traffic-related air pollution, were positively associated with CAC progression.11

Our results add to prior research assessing associations of PM2.5 and distance to a major roadway with coronary atherosclerosis. We performed thorough analyses and did not find evidence of strong associations of these exposures with CAC. Unlike the Heinz Nixdorf Recall Study, we did not find that living closer to a major road was associated with more extensive CAC. These findings may be because of regional differences in pollution and population characteristics. Average PM2.5 levels in our study region were generally much lower than in the Heinz Nixdorf Recall Study region.9 Diesel cars are more common in Germany than in the United States, and diesel exhaust may be more harmful than gasoline exhaust. Additionally, compared with our study, participants in the
Heinz Nixdorf Recall Study were older (mean age 60.2 years).9 On the contrary, our findings were more consistent with the cross-sectional results from MESA than with those from the Heinz Nixdorf Recall Study. Participants were also, on average, older in the cross-sectional analysis of MESA (mean 62.0 years)10 than in our study. Additionally, average PM2.5 levels in the MESA cross-sectional study were generally higher than in our study region. At the different MESA sites,10 mean annual 2001 PM2.5 averages (in \( \mu g/m^3 \)) ranged from 12.82 (Minnesota) to 24.10 (California).

With repeated measures of CAC, we were able to assess for evidence of associations between distance to a major roadway and PM2.5 exposures with CAC progression. In contrast to MESA,16 we did not find evidence of strong positive associations of PM2.5 with CAC progression. Of note, there was a relatively short time between the first and second MDCT scans (average 6.1 years) in our study.

Studies have also assessed the associations of PM2.5 or residential distance to a major roadway with other atherosclerosis surrogates. For instance, the Heinz Nixdorf Recall Study and MESA examined associations with calcification in the thoracic and abdominal aorta, respectively, which both predict incident CVD.29,30 In the Heinz Nixdorf Recall Study, PM2.5 was associated with more extensive thoracic aortic calcium.13 In MESA, there was a weak association of PM2.5 with the presence but not extent of abdominal aortic calcium.31 Many studies have found associations between particulate air pollution and CIMT.11,14,15 Particulate air pollution has been somewhat more consistently associated with CIMT than with CAC. This may be due in part to different ranges and composition of ambient particulate air pollution in various study regions. Additionally, CAC and CIMT are correlates of different aspects of subclinical atherosclerosis32; CIMT represents an earlier stage in vascular injury. Relatively recent exposures may contribute more to earlier stages of disease than

### Table 2. Distributions of Proximity to a Major Roadway, PM2.5

<table>
<thead>
<tr>
<th>Exposure to a major roadway,* m</th>
<th>Median (IQR) or n [%]</th>
<th>Range (min, max)</th>
<th>Range (5th–95th)</th>
<th>Range (25th–75th)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximity to a major roadway,* m</td>
<td>201 (359)</td>
<td>0.01–999.7</td>
<td>6.9–815.1</td>
<td>57.5–416.9</td>
</tr>
<tr>
<td>Total PM2.5, ( \mu g/m^3 ), 2003†</td>
<td>10.7 (1.4)</td>
<td>2.9–26.7</td>
<td>8.2–12.6</td>
<td>9.9–11.4</td>
</tr>
<tr>
<td>Total PM2.5, ( \mu g/m^3 ), 2003–2009‡</td>
<td>9.8 (1.1)</td>
<td>2.6–17.2</td>
<td>7.2–11.1</td>
<td>9.2–10.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Residential proximity in categories*</th>
<th>Median (IQR) or n [%]</th>
<th>Range (min, max)</th>
<th>Range (5th–95th)</th>
<th>Range (25th–75th)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 m</td>
<td>1063 [23%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 to &lt;200 m</td>
<td>1212 [27%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 to &lt;400 m</td>
<td>1071 [23%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 to &lt;1000 m</td>
<td>1218 [27%]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; and PM2.5, fine particulate matter.
*Proximity to a major roadway analyses restricted to individuals living <1000 m from a major road; 4564 observations (554 observations, 11% lived ≥1000 m).
†PM2.5 2003 data calculated from 5118 observations.
‡PM2.5 2003–2009 calculated from 5116 observations.

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### Table 3. Adjusted Associations of Proximity to Major Roadway and PM2.5 With CAC*

<table>
<thead>
<tr>
<th>CAC&gt;0†</th>
<th>Linear Mixed Effects (Among Those With CAC&gt;0)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>&lt;50 m</td>
<td>0.95</td>
</tr>
<tr>
<td>50 to &lt;200 m</td>
<td>0.94</td>
</tr>
<tr>
<td>200 to &lt;400 m</td>
<td>0.90</td>
</tr>
<tr>
<td>400 to &lt;1000 m</td>
<td>1.00</td>
</tr>
<tr>
<td>Log of Distance to a Major Road§</td>
<td>1.03</td>
</tr>
<tr>
<td>2003 PM2.5, ( \mu g/m^3 )‖</td>
<td>0.98</td>
</tr>
<tr>
<td>2003–2009 PM2.5, ( \mu g/m^3 )‖</td>
<td>0.98</td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcium Agatston score; CI, confidence interval; and PM2.5, fine particulate matter.
†Adjusted for covariates described in the online-only Data Supplement.
‡For binary outcome, distance to roadway, 4564 observations (2205 CAC>0); PM2.5 2003, 5118 observations (2427 CAC>0); PM2.5 2003–2009, 5116 observations (2426 CAC>0).
§Model loge(CAC) among those with CAC>0. Distance to roadway, 2205 observations; PM2.5 2003, 2427 observations; PM2.5 2003–2009, 2426 observations. Percentile bootstrapped CIs (n=1000 clustered bootstrap samples).
‖Scaled to the difference between 75th (416.9 m) vs the 25th (57.5 m) percentile from a major road.
‖Scaled to the 2003 PM2.5 IQR (1.4 \( \mu g/m^3 \)).
to progression to arterial calcification. It would be of interest to study the association of particulate air pollution with soft plaques in the coronary arteries.

Importantly, the lack of associations of residential proximity to a major road or residential estimates of PM$_{2.5}$ exposure with CAC in our study population does not mean that ambient air pollution does not cause atherosclerosis among people living in the Northeastern US. For example, our group has previously reported associations between traffic-related air pollution and CIMT in a Boston area study. There are several pathways through which particulate matter exposure could lead to atherosclerosis. First, particulate matter inhalation can lead to a pulmonary inflammatory and oxidative stress response, which can spill-over, yielding systemic oxidative stress and inflammation. This may lead to atherosclerosis progression through vascular inflammation and impaired vascular function. Second, particulate matter inhalation can activate the sympathetic nervous system, which may yield vasoconstriction, plaque instability, and endothelial dysfunction. Third, there is some evidence that particulate matter or its constituents can directly transport into systemic circulation, yielding downstream effects, such as coagulation, platelet function, vascular inflammation, and atherosclerosis.

This study has several limitations. Because the analyses are observational, there is potential for residual or unmeasured confounding. However, we have adjusted for many potential confounders, including both individual- and area-level socioeconomic position markers. Estimates of distance to a major roadway and PM$_{2.5}$ are subject to unavoidable measurement error. However, we do not expect this error to be related to the presence or extent of CAC. Additionally, we aimed to calculate distance to roadway from the actual house, which should be a better correlate of exposure at a person’s residence than would distance to the edge of the property. Importantly, the goal of our exposure assessment is to use residential location to correctly rank an individual’s exposure, not to assign correct absolute levels to each individual. In the main analyses, we assessed distance to nearest A1, A2, or A3 roadway and did not differentiate between types of major roadway (few participants lived close to an A1 or A2 roadway). We expect that traffic volume is, on average, generally highest on A1 roads (primary highways with limited access) and lowest on A3 roads (secondary and connecting roads) and could potentially range, on average, from <10000 to >150000 vehicles per day. In analyses looking at distance to A1 or A2 roadway only, results were similar. The association of categories of distance to a major roadway with log-transformed CAC may be difficult to interpret, so we also assessed associations of living close to a major roadway (<150 m versus ≥150 m). We also did not consider year-to-year variability in exposures, though adjusting for year of computed tomography scan (as a categorical variable) did not change results. Additionally, using PM$_{2.5}$ from 2003 to 2009 instead of from 2003 yielded similar findings, suggesting that results were not sensitive to PM$_{2.5}$ index period. As we do not have detailed long-term residential history, we were unable to study a long-term exposure window (eg, 20 years). For a chronic disease process like atherosclerosis, exposure over a period of many years might have a greater impact on the disease process than relatively recent exposure.

Measuring CAC is only one of the many approaches aimed at quantifying atherosclerosis. Additionally, the ability of CAC to predict future CHD may be most informative when combined with other risk factors. However, prior work has shown a consistent association between CAC and risk of incident CHD and CVD. A meta-analysis found that compared with individuals with a CAC of 0, those with CAC>400 had 10x the odds of incident CHD (95% confidence interval 3.1–34). In the Framingham Heart Study, many cardiovascular risk factors, including age, sex, and Framingham risk score, have been associated with CAC and CAC is associated with incident CHD and CVD in this cohort. Because the participants in this study are predominantly white and of middle to upper middle class, these results might not be generalizable to populations with other characteristics.

The study also has several strengths. We used spatially resolved PM$_{2.5}$ exposures that benefit from spatial resolution of land use regression and spatiotemporal resolution of satellite data. We used 2 different measures of exposure to air pollution: distance to a major roadway and PM$_{2.5}$. Although distance to a major roadway is correlated with exposure to local traffic-related exposures, PM$_{2.5}$ captures both local and regional sources of air pollution. Additionally, measuring CAC twice among some participants enabled us to conduct analyses assessing the associations of distance to a major roadway and PM$_{2.5}$ with CAC progression.

<table>
<thead>
<tr>
<th>Detectable CAC Progression*</th>
<th>OR 95% CI</th>
<th>Associations With Change in CAC*</th>
<th>Mean CAC change/y</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 m</td>
<td>0.92</td>
<td>0.66, 1.29</td>
<td>−3.6</td>
<td>−9.3, 1.9</td>
</tr>
<tr>
<td>50 to &lt;200 m</td>
<td>0.78</td>
<td>0.56, 1.08</td>
<td>−2.0</td>
<td>−8.3, 3.3</td>
</tr>
<tr>
<td>200 to &lt;400 m</td>
<td>0.90</td>
<td>0.65, 1.25</td>
<td>−1.1</td>
<td>−7.6, 4.4</td>
</tr>
<tr>
<td>400 to &lt;1000 m</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log distance to road†</td>
<td>1.06</td>
<td>0.91, 1.22</td>
<td>2.2</td>
<td>0.1, 4.3</td>
</tr>
<tr>
<td>2003 PM$_{2.5}$, µg/m³‡</td>
<td>1.02</td>
<td>0.91, 1.14</td>
<td>−0.8</td>
<td>−2.3, 0.6</td>
</tr>
<tr>
<td>2003–2009 PM$_{2.5}$, µg/m³‡</td>
<td>1.06</td>
<td>0.93, 1.20</td>
<td>−0.8</td>
<td>−2.4, 0.8</td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcium Agatston score; CI, confidence interval; IQR, interquartile range; and PM$_{2.5}$, fine particulate matter.

*Adjusted for covariates described in the online-only Data analyses. Percentile bootstrapped CIs (n=1000 clustered bootstrap samples) for change in CAC analyses.

†Scaled to the difference between 75th (416.9 m) vs 25th (57.5 m) percentile from a major road. Detectable CAC progression: 1356 observations (647 detectable progression). Change in CAC: 4564 observations (1536 two CAC measurements).

‡Scaled to 2003 PM$_{2.5}$ IQR (1.4 µg/m³). 2003 PM$_{2.5}$ detectable CAC progression: 1719 observations (711 detectable progression). 2003–2009 PM$_{2.5}$ detectable CAC progression: 1718 observations (711 detectable progression). 2003 PM$_{2.5}$ change in CAC: 5118 observations (1718 two CAC measurements). 2003–2009 PM$_{2.5}$ change in CAC: 5116 observations (1718 two CAC measurements).
In conclusion, we observed no evidence that residing closer to a major roadway or having higher ambient residential PM_{2.5} exposure was strongly associated with the presence, extent, or progression of CAC among individuals residing in a region with relatively low levels of and little variation in PM_{2.5} levels. These findings add to the total evidence of the association of traffic and PM_{2.5} exposure and coronary atherosclerosis in humans.

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Disclosures

None.

References


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**Highlights**

- Long-term exposure to particulate air pollution and traffic are associated with a higher risk of cardiovascular disease, possibly via promotion of atherosclerosis.
- Studies assessing associations of particulate air pollution and traffic with coronary artery calcium Agatston score, a correlate of subclinical atherosclerosis, have had inconsistent findings.
- We found no strong associations between residential proximity to a major roadway or fine particulate matter air pollution exposure and coronary artery calcium Agatston score among Framingham Heart Study participants living in the Northeastern US, a region with low levels of and low variability in fine particulate matter.
Residential Proximity to Major Roads, Exposure to Fine Particulate Matter, and Coronary Artery Calcium: The Framingham Heart Study

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MATERIALS AND METHODS

Study Participants

The study population consists of individuals from the Framingham Offspring and Third Generation Cohorts; these cohorts have been previously described in detail.\(^1\,\,^2\) From 2002 to 2005, a subset of participants from the Offspring and Third Generation Cohorts underwent multidetector computed tomography (MDCT) scans.\(^3\) For inclusion in this substudy, men were ≥35 years old and women were ≥40 years old and not pregnant. Due to scanner specifications, participants weighed less than 350 pounds. From 2008 to 2011, some of the participants who were scanned in the first round and additional Framingham participants underwent an MDCT scan. Overall, 3,421 participants (Offspring: 1,329; Third Generation: 2,092) had coronary artery calcium Agatston scores (CAC) measured from 2002–2005, and 2,613 participants (Offspring: 1,204; Third Generation: 1,409) had CAC measured from 2008–2011. For these analyses, we included participants who received at least one MDCT scan and lived in the Northeastern region of the U.S. For scans carried out during the first round, we included participants who attended either Offspring Examination 7 (1998–2001) or Third Generation Examination 1 (2002–2005). For scans carried out during the second round, we included participants who attended either Offspring Examination 8 (2005–2008) or Third Generation Examination 2 (2008–2011). The study was approved by the Institutional Review Boards of the Boston University Medical Center, Beth Israel Deaconess Medical Center and the Massachusetts General Hospital. All participants provided written consent for the Framingham Heart Study examinations and the MDCT scans.

Participant Characteristics

At visits, participants underwent a clinic exam consisting of a physician interview, physical examination and laboratory tests, as previously described.\(^2\,\,^4\) Details on measurement of blood pressure, definitions of diabetes and antihypertensive and lipid-lowering medication use have previously been described.\(^5\) A panel of three investigators determined the prior occurrence of clinically apparent cardiovascular disease (coronary heart disease, intermittent leg claudication, heart failure or stroke or transient ischemic attack) based on published FHS criteria.\(^2\,\,^4\) Using primary address reported at Examination 1 or Examination 7, we used U.S. Census 2000 data to assign area-level socioeconomic characteristics, including median value of owner-occupied housing units, at the census tract level.

Exposure Assessment

Distance to Roadway. The primary addresses of participants were geocoded with ArcGIS 10 (ESRI, Redlands, CA). Using address reported at Examination 7 (Offspring) or Examination 1 (Third Generation), we evaluated distance to nearest major roadway, defined as A1, A2 or A3 road (U.S. Census Features Class). Where possible, proximity to roadway was measured from the actual house location on the property, by using RoofTop coordinates. Prior work has shown that ultrafine particle counts return to background levels within 100 to 300 m from major roadways and that particulate matter mass concentration returns within approximately 100 to 400 m.\(^6\) Similar to our prior analyses, we categorized distance to major
roadway as <50 m, 50 to <200 m, 200 to <400 m, and 400 to <1,000 m, in an effort to reflect the
decay of traffic-related pollution and noise to background levels. We also examined the natural
logarithm of distance to roadway as an exposure, because in previous work we have identified
log-linear associations between distance to roadway and cardiovascular health outcomes.\(^7,8\) We
present results contrasting participants who reside 416.9 m to those living 57.5 m from the
nearest major roadway (the interquartile range (IQR) of distance to a major roadway).
Individuals living in exurb areas 1,000 m or further from a major roadway are likely to have
different exposures than people living in urban and suburban areas. In such locations, it is
unlikely that residential distance to roadway is an indicator of traffic-related pollution exposure.
We therefore excluded observations from participants living ≥1,000 m from a major road (554
observations, 11%) in all analyses of distance to roadway.

Spatially Resolved Average Fine Particulate Matter (PM\(_{2.5}\)). We used modeled estimates
daily PM\(_{2.5}\) levels at residential address to calculate annual averages of exposure for each
participant. Our data on PM\(_{2.5}\) exposure concentration is based on models using satellite-derived
measurements of aerosol optical depth, a quantitative measure of particle abundance in the
atmospheric column.\(^9\) Kloog et al. developed a model that uses aerosol optical depth, PM\(_{2.5}\)
measurements from monitoring stations and meteorological and land-use regression terms to
predict daily PM\(_{2.5}\) at a scale of 1 × 1 km across the northeastern U.S. (New England, New York
and New Jersey).\(^9\) Among 1 × 1 km grid cells that had a PM\(_{2.5}\) monitor, there was excellent out-
of-sample 10-fold cross-validated \(R^2\) (mean out of sample \(R^2\)=0.88; year-to-year variation 0.82–
0.90) and a slope of observed versus predicted PM\(_{2.5}\) concentrations of 0.99 (year-to-year
variation 0.98–1.01) for the cross-validated results.\(^9\) For each PM\(_{2.5}\) monitoring site, residuals
(difference between daily predicted and measured PM\(_{2.5}\)) were regressed against local spatial
and temporal variables. The fit of this model was used to estimate daily localized predictions for
each residential address, which represent deviations from grid predictions. To estimate annual
average PM\(_{2.5}\), we first summed the daily grid prediction and localized residual PM\(_{2.5}\) prediction
corresponding to each address. We averaged these daily total PM\(_{2.5}\) predictions over the year.
Similar to prior work,\(^5,10–12\) we used the same index year for all participants. This preserves the
spatial variation of PM\(_{2.5}\) among residential locations, while minimizing the influence of PM\(_{2.5}\)
secular trends. We chose the year 2003. For models including PM\(_{2.5}\), we scaled the results to
the IQR of 2003 PM\(_{2.5}\) (1.4 µg/m\(^3\)).

Coronary Artery Calcium

An eight-slice MDCT scan of the chest (LightSpeed Ultra, General Electric, Milwaukee,
WI) was performed during the first round of MDCT scans on each participant,\(^9\) and a 64-slice
MDCT scan (General Electric Discovery VCT 64-slice PET/CT scanner, GE Healthcare), for
participants in the second round of MDCT scans. Prospective electrographic triggering during a
single breath hold with sequential data acquisition was used. Forty-eight 2.5-mm slices were
acquired from the carina to the diaphragm (120 kVp, 500-ms gantry rotation time, tube current
320/400 mA (< and ≥ 100 kg of body weight, respectively).\(^13\) A calcified lesion was defined as
an area of ≥3 connected pixels with an attenuation >130 Hounsfield units.\(^3,14\) To calculate a
modified Agatston score, the area of each lesion was multiplied with a weighted attenuation
score based on the maximal lesion attenuation.\(^3,14\) Correlation of CAC between two separate
scans was high (Spearman correlation coefficient of 0.96; based on four experienced observers
calculating CAC in a subset of 161 participants).\(^15\) For scans carried out from 2002–2005, each
subject has two measures of CAC (two sequential scans); we used the average of the two CAC
scores.
**Statistical Analyses**

We first used a two-stage modeling approach to assess the associations of each exposure with any detectable CAC and with the amount of CAC among participants with CAC>0. For the binary outcome of any detectable CAC, we used generalized estimating equation regression with a logit link, robust standard errors and an unstructured correlation structure assumption to account for the fact that 51% of participants contributed two measurements (one from 2002-2005 and one from 2008-2011). We used linear mixed effects models to assess associations with the amount of CAC among participants with detectable CAC. Due to its skewed distribution, we modeled log-transformed CAC and estimated 95% confidence intervals (CIs) by block bootstrapping 1,000 samples and reporting percentile CIs. We used bootstrapped CIs, as we did not expect the residuals to be normally distributed.

We also assessed associations with detectable progression of CAC and annual change in CAC between the first and second round of scans, as CAC progression has been shown to be a risk factor for coronary heart disease events. Thresholds for detectable CAC progression were based on within-person measurement variability of repeated CAC measurements taken during the first round of MDCT scans and defined as follows: CAC=0, threshold change in score of 3.4; 0<CAC≤100, change of 15.9; 100<CAC≤300, change of 46.7; 300<CAC≤1,000, change of 73.7; CAC>1,000, change of 325. Prior work in the Framingham Heart Study has shown that CVD risk factors were associated with detectable CAC progression. First, we used logistic regression to model odds of detectable CAC progression from the first to second MDCT scan. Second, we used a linear mixed effects modeling approach that assessed associations of exposures with both CAC at a participant's first MDCT scan and annual change in CAC per year (the latter assessed by including interaction terms between exposure and time between scans). For this second approach, we used all observations, including participants scanned at one or both rounds of MDCT scans (block bootstrapped CIs).

In our primary models, we adjusted for covariates chosen *a priori* to be potential confounders of the relationship between air pollution and atherosclerosis. In all models, we adjust for age and age^2 at scan, sex, body mass index, smoking status (current, former, never), pack-years, individual-level education (high school or less, some college, college graduate), median census-tract value of owner-occupied housing units (quartiles), cohort (Offspring or Third Generation), date of scan and number of days between scan and examination at which individual-level covariates reported.

For the repeated measures analyses, we also adjusted for scan (first or second round). For the detectable CAC progression analyses, we adjusted for age at MDCT1 (age, age^2), covariates reported at Offspring Examination 7 or Generation 3 Examination 1, and time between MDCT scans. For the annual change in CAC analyses, we adjusted for age at 1st scan (age, age^2) and time since first scan and included the following interaction terms with time since first scan: age at first scan (age, age^2), sex and cohort.

As this is a descriptive study, we focused on the overall pattern of results, rather than results of specific hypothesis tests. We present 95% CIs with all point estimates. We carried out analyses in SAS 9.3 (SAS Institute Inc., Cary, NC) and Stata v.12 (Statacorp, College Station, TX).
Sensitivity Analyses

We ran several sensitivity analyses. As we may not have captured all confounders of the exposure-response relationships, we adjusted for additional covariates. We first also adjusted for variables that are potential confounders or predictors of CAC: physical activity ( tertiles of physical activity index\textsuperscript{22}), alcohol intake (0, 0 to 7, \geq7 drinks per week) and menopausal status in women (whether periods stopped for at least one year before examination). We then extended the model further, also adjusting for covariates that could be confounders, outcome predictors or mediators: diabetes, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, triglycerides, anti-hypertensive medication and lipid-lowering medication.

We assessed whether associations between distance to a major roadway and PM\textsubscript{2.5} with CAC (defined as CAC>0 and as log\textsubscript{e}(CAC)) were similar when we included interactions with age (\leq65, >65), sex, cohort (Offspring, Third Generation), 10-year cardiovascular disease risk ( tertiles: 0.1–1.6%, 1.6–5.2%, 5.2–81.3%) as defined by the American College of Cardiology/American Heart Association in 2013\textsuperscript{23}, smoking status (never, former, current), use of anti-hypertensive medication (yes, no), and hypertension (yes, no). We also ran analyses restricted to those without clinically apparent cardiovascular disease (4,848 observations, 95%).

We additionally assessed whether there were associations of living close to a major roadway (<150 m \textit{versus} \geq150 m) and CAC. As A1 and A2 roads are larger than A3 roads, we assessed whether residential distance to nearest A1 or A2 road ( rather than nearest A1, A2 or A3 road) was associated with CAC. In an effort to adjust for long-term exposures, we adjusted for year of CT scan as a categorical variable. We also assessed sensitivity of the main PM\textsubscript{2.5} results to the choice of index year; we ran analyses using PM\textsubscript{2.5} averaged from 2003–2009. To assess whether results differed by scanning period, we ran the main analyses separately for the 1\textsuperscript{st} and 2\textsuperscript{nd} rounds of CT scans.

To assess the linearity of the exposure-outcome relationships for log distance to roadway and PM\textsubscript{2.5} in our main repeated measures and detectable CAC progression models, we used restricted cubic splines, with knots at the 5, 27.5, 50, 72.5 and 95 percentiles of exposure distribution.\textsuperscript{24} We use plots of the splines to assess departure from linearity, using the POSTRCSPHLINE package in Stata.\textsuperscript{25}

To evaluate the robustness of our primary analyses, we re-ran the binary CAC>0 repeated measures analyses using mixed effects logistic regression, instead of generalized estimating equation regression. For comparability with prior work\textsuperscript{26}, we used mixed effects linear regression models to assess associations with log\textsubscript{e}(CAC+1) and used generalized estimating equation regression (logit link, unstructured covariance) to assess associations with CAC greater than the 75\textsuperscript{th} and 90\textsuperscript{th} age- and sex-specific percentiles among a healthy referent subpopulation.\textsuperscript{3}
REFERENCES


Supplemental Figure I: Non-linear Association of 2003 PM$_{2.5}$ and Natural Log-transformed CAC

Adjusted results for association between 2003 PM$_{2.5}$ (restricted cubic spline; 5 knots) and log$_e$(CAC) among participants with detectable CAC. There was a suggested positive association at lower PM$_{2.5}$ levels and negative association at higher PM$_{2.5}$ levels, though CIs were very wide.
Supplemental Table I: Associations of Proximity to Major Roadway and PM$_{2.5}$ with CAC: Subgroups*

<table>
<thead>
<tr>
<th>CAC&gt;0†</th>
<th>Linear Mixed Effects (among those with CAC&gt;0)‡</th>
<th>2003 PM$_{2.5}$($\mu$g/m$^3$)§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>≤65 years</td>
<td>1.04 (0.92, 1.17)</td>
<td>10.8 (-1.8, 23.7)</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>1.01 (0.80, 1.27)</td>
<td>2.2 (-9.2, 13.9)</td>
</tr>
<tr>
<td>p-interaction</td>
<td>0.80</td>
<td>0.30</td>
</tr>
<tr>
<td>Men</td>
<td>1.03 (0.88, 1.21)</td>
<td>3.3 (-7.7, 15.4)</td>
</tr>
<tr>
<td>Women</td>
<td>1.04 (0.89, 1.21)</td>
<td>13.1 (-3.4, 29.2)</td>
</tr>
<tr>
<td>p-interaction</td>
<td>0.95</td>
<td>0.31</td>
</tr>
<tr>
<td>Offspring</td>
<td>1.04 (0.87, 1.24)</td>
<td>4.9 (-6.0, 16.7)</td>
</tr>
<tr>
<td>Third Generation</td>
<td>1.03 (0.89, 1.19)</td>
<td>11.2 (-5.2, 27.4)</td>
</tr>
<tr>
<td>p-interaction</td>
<td>0.92</td>
<td>0.53</td>
</tr>
<tr>
<td>10-year risk of atherosclerotic CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1–1.6%</td>
<td>0.95 (0.78, 1.16)</td>
<td>-5.4 (-26.7, 27.7)</td>
</tr>
<tr>
<td>1.6–5.2%</td>
<td>1.04 (0.88, 1.22)</td>
<td>15.0 (-5.2, 31.2)</td>
</tr>
<tr>
<td>5.2–81.3%</td>
<td>1.04 (0.86, 1.27)</td>
<td>12.5 (1.1, 28.6)</td>
</tr>
<tr>
<td>p-interaction</td>
<td>0.75</td>
<td>0.42</td>
</tr>
<tr>
<td>Never smokers</td>
<td>0.99 (0.85, 1.15)</td>
<td>2.1 (-13.0, 15.1)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>1.08 (0.91, 1.29)</td>
<td>15.0 (-0.8, 32.3)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>1.10 (0.84, 1.44)</td>
<td>1.1 (-19.6, 27.0)</td>
</tr>
<tr>
<td>p-interaction</td>
<td>0.67</td>
<td>0.38</td>
</tr>
<tr>
<td>Anti-hypertensive medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.13 (1.00, 1.28)</td>
<td>7.9 (-2.4, 21.2)</td>
</tr>
<tr>
<td>p-interaction</td>
<td>0.003</td>
<td>0.96</td>
</tr>
<tr>
<td>Yes</td>
<td>0.80 (0.65, 0.98)</td>
<td>7.5 (-7.6, 16.2)</td>
</tr>
<tr>
<td>p-interaction</td>
<td>0.003</td>
<td>0.96</td>
</tr>
</tbody>
</table>

* Adjusted for age at scan (age, age$^2$), body mass index, sex, cohort, scan (first or second round), smoking status (current, former, never), pack-years, individual-level education (high school or less, some college, college graduate), median census-tract value of

1 2 3
owner-occupied housing (quartiles), date of scan, number of days between scan and examination at which individual-level covariates reported.

†For binary outcome, distance to roadway includes 4,564 observations (2,205 with CAC>0). PM$_{2.5}$ 2003 includes 5,118 observations (2,427 with CAC>0).

‡For linear mixed effects regression, model log$_e$(CAC) among those with detectable CAC. Distance to roadway includes 2,205 observations, PM$_{2.5}$ 2003 includes 2,427 observations. Percentile bootstrapped CIs (n=1,000 clustered bootstrap samples).

§Natural Log of proximity to a major road scaled to the difference between living at the 75$^{th}$ (416.9 m) vs the 25$^{th}$ (57.5 m) percentile from a major road.

‖PM$_{2.5}$ scaled to the IQR for the 2003 average (1.4 µg/m$^3$).
No Associations of Distance to Major Road, PM$_{2.5}$ with CAC$>0$ or Detectable CAC Progression

Distance to road scaled to living at 75$^{th}$ (416.9 m) vs 25$^{th}$ (57.5 m) percentile from a major roadway; PM$_{2.5}$ scaled to 1.4 µg/m$^3$ (IQR). Adjusted for demographic markers, socioeconomic position, time.