Long-term Exposure to Black Carbon and Carotid Intima-Media Thickness: The Normative Aging Study

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BACKGROUND: Evidence suggests that air pollution is associated with atherosclerosis and that traffic-related particles are a particularly important contributor to the association.

OBJECTIVES: We investigated the association between long-term exposure to black carbon, a correlate of traffic particles, and intima-media thickness of the common carotid artery (CIMT) in elderly men residing in the greater Boston, Massachusetts, area.

METHODS: We estimated 1-year average exposures to black carbon at the home addresses of Normative Aging Study participants before their first CIMT measurement. The association between estimated black carbon levels and CIMT was estimated using mixed effects models to account for repeated outcome measures. In secondary analyses, we examined whether living close to a major road or average daily traffic within 100 m of residence was associated with CIMT.

RESULTS: There were 380 participants (97% self-reported white race) with an initial visit between 2004 and 2008. Two or three follow-up CIMT measurements 1.5 years apart were available for 340 (89%) and 260 (68%) men, respectively. At first examination, the average ± SD age was 76 ± 6.4 years and the mean ± SD CIMT was 0.99 ± 0.18 mm. A one-interquartile range increase in 1-year average black carbon (0.26 µg/m³) was associated with a 1.1% higher CIMT (95% CI: 0.4, 1.7%) based on a fully adjusted model.

CONCLUSIONS: Annual mean black carbon concentration based on spatially resolved exposure estimates was associated with CIMT in a population of elderly men. These findings support an association between long-term air pollution exposure and atherosclerosis.


Introduction

Exposure to particulate air pollution has been associated with cardiovascular morbidity and mortality in numerous epidemiologic studies (Brook 2004; Brook et al. 2010; Dockery et al. 1993; Pope and Dockery 2006). Evidence suggests that local traffic is a major source of within-city heterogeneity in air pollution exposures (Brugge et al. 2007; Clougherty et al. 2008) and that mobile sources of pollution may be an important contributor to adverse health effects (Künzli et al. 2000; Laden 2000; Peters et al. 2004). Several studies focusing specifically on the traffic-related constituents of pollution have reported short-term associations with indicators of cardiovascular health (Delfino et al. 2010a, 2010b; Madrigano et al. 2010; Mordukhovich et al. 2009). Evidence for long-term effects of chronic exposure to traffic-related air pollution has come largely from animal studies, which have demonstrated proatherosclerotic effects of diesel exhaust particles and concentrated ambient urban particles (Chen and Nadziejko 2005; Quan et al. 2010; Sun 2005). Recently, a growing number of epidemiologic studies have also observed associations between subclinical atherosclerosis and estimated fine particulate matter (particulate matter ≤ 2.5 µm in aerodynamic diameter: PM2.5) or distance to major roadway (Bauer et al. 2010; Diez Roux et al. 2008; Hoffmann et al. 2007; Künzli et al. 2005).

Black carbon is a correlate of traffic-related combustion products, and a common surrogate for traffic particles in general, weighted toward diesel particles. We have developed a nonlinear land use regression model to estimate black carbon exposures and have applied it within the greater Boston, Massachusetts, metropolitan area (Gryparis et al. 2007). In the present study making use of up to three repeated carotid intima-media thickness (CIMT) measures in a cohort of elderly men, we hypothesized that the estimated annual average concentration of black carbon at participants’ homes in the year before the first study visit would be associated with CIMT, a reliable measure of subclinical atherosclerosis (Kanters et al. 1997; O’Leary and Bots 2010) that predicts cardiovascular outcomes (Nambi et al. 2012; O’Leary et al. 1999). In secondary descriptive analyses, we also estimated associations with residential proximity to a major roadway [defined as U.S. Census feature Class Code A1 (Primary Highway with Limited Access) or A2 (Primary Highway Without Limited Access)] and with average daily traffic within 100 m of residence.

Methods

Study population. The Normative Aging Study is a cohort of community-dwelling men from the greater Boston area recruited in the early 1960s. CIMT was measured in a subsample of participants beginning in 2004, after participants had been followed for four decades. Participants in the CIMT substudy were followed for up to three time points scheduled 1.5 years apart. Our analysis included 380 participants with complete information regarding black carbon concentrations and all covariates at baseline (i.e., the time of the first CIMT measurement). Baseline visits occurred between 2004 and 2008.

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of land use (e.g., cumulative traffic density within 100 m, population density, distance to nearest major roadway, percent urbanization) at a given location. Weather data were obtained from the Boston airport weather station, and planetary boundary layer data from the National Oceanic and Atmospheric Administration’s national reanalysis data set (http://www.esrl.noaa.gov/psd/data/gridded/data.narr.html).

Measurements from continuous ambient monitors and specific monitoring campaigns were used to develop model predictions. We obtained hourly outdoor black carbon concentrations from a total of 15 ambient monitors from 1999 to 2004: 12 of these monitors were included in a study of spatial variability in traffic-related pollutant concentrations conducted by the Northeast States for Coordinated Air Use Management (NESCAUM), two sites were operated by the Massachusetts Department of Environmental Protection, and one site was located on the roof of Harvard School of Public Health (HSPH) and operated by the HSPH Department of Environmental Health. Measurements from specific monitoring campaigns came from two sources. First, beginning in 1999, hourly outdoor and indoor black carbon concentrations were measured inside and outside of 30 residential homes, using aethelometers over 48-hr intervals as part of a National Institute of Environmental Health Sciences (NIEHS)-funded study of air pollution and heart rate variability (APAHRV) conducted at HSPH (Zanobetti et al. 2010). Second, 24-hr average outdoor elemental carbon concentrations measured over 7-day periods in 23 locations during the winter and summer of 2000 were obtained from a U.S. Environmental Protection Agency (EPA)-funded multi-pollutant exposures study of sensitive individuals (Brown et al. 2008). We have also incorporated interactions between temporal predictors, such as mixing height and wind speed, and source-based geographic variables, such as traffic density. We used regression
splines to allow nonlinear relations between predictors and exposure levels and thin-plate splines (a two-dimensional extension of regression splines) to model spatial variability that was not accounted for by the spatial predictors in the model. Separate models were fit for warm and cold seasons. The prediction equation also used central monitor concentrations as an independent variable to reflect average concentration levels for a given day. In essence, the central monitor concentrations serve as direct estimates of the daily time effect. Latent variable models were used to integrate measures of outdoor black carbon, indoor black carbon, and elemental carbon from the monitoring campaigns. The resulting multipollutant model is fit using a Bayesian Markov Chain Monte Carlo approach. The adjusted $R^2$ for the model was 0.83 and the average correlation between predicted and measured BC concentrations in four out-of-sample validation samples was 0.59. This model has been previously used to examine the associations between black carbon and a variety of health outcomes including mortality (Maynard et al. 2007), cognitive function in children (Suglia et al. 2008) and adults (Power et al. 2011), birth weight (Gryparis et al. 2009), lung function (Franco Suglia et al. 2008), and biomarkers of endothelial function (Alexeeff et al. 2011).

GIS (geographic information system) analyses were performed using ArcMap, version 10.1 (ESRI, Redlands CA, USA). All addresses of Normative Aging Study participants have been geocoded and assigned daily predicted black carbon concentrations. For this analysis, we calculated annual average concentrations during the year before the first CIMT measurement for participants for ≥ 9 months of contiguous daily black carbon data during that year. Available data were used as a proxy for a 1-year average for participants who were missing 1–3 months of data. The primary reason that individuals did not have complete black carbon data was moving to a new home or having a second home outside the study region. If an individual had multiple addresses during the year before their first CIMT measurement and black carbon data were available for all addresses, a composite individual-level annual mean measure of black carbon was calculated using data from the time the individual spent at each address.

Distance to roadway measures and average daily traffic within 100 m. We also examined associations with distance to a major roadway and traffic density within a 100-m buffer of residence during the year before the first CIMT measurement in descriptive analyses. Major roadway classifications were provided by Census TIGER files (U.S. Census Bureau 2013). Distance to the nearest major roadway (Class Code A1 or A2) was computed using the near tool in ArcGIS. We classified residential distance to major roadways as 0 to ≤ 100 m, 100 to ≤ 200 m, 200 to ≤ 1,000 m, and > 1,000 m based on prior studies showing that living within 100 m of a major road is associated with cardiovascular events (Tonne et al. 2007), all-cause mortality among myocardial infarction survivors (Rosenbloom et al. 2012), and atherosclerotic progression (Künzli et al. 2010). In addition, living ≤ 200 m of a major road has been associated with coronary artery calcification, another measure of atherosclerotic burden (Hoffmann et al. 2007). Average daily traffic was determined by summing the product of road segment length and estimated annual average daily traffic within a 100-m buffer of the subject’s residence using the MassHighway 2002 Road Inventory database (Massachusetts Department of Transportation 2013). The measures of annual average daily traffic are based on actual traffic counts for major roadways and estimated according to regional traffic for more local roads.

Statistical methods. CIMT was natural log (ln) transformed to improve the normality of the dependent variable distribution. We fit general additive models based on penalized splines using both ln-transformed and untransformed annual average black carbon concentrations to assess the functional form of the outcome–exposure association. These models strongly supported a linear association between CIMT and ln-transformed black carbon exposure, whereas the spline on the natural scale is reported in the Supplemental Material, Figure S1, and showed a nonlinear association. Specifically, there was a positive association between black carbon and CIMT at lower levels of black carbon, where most of the observations occurred, and a negative association with wide confidence intervals (CIs) at high levels, where there were few observations. Therefore, our primary analyses were based on ln-transformed black carbon exposures. We estimated the association between ln-transformed CIMT and average annual ln-transformed daily black carbon concentrations at each participant’s home address during the year before their first CIMT measurement using linear mixed effects with subject-specific random intercepts in SAS PROC MIXED (SAS, version 9.1; SAS Institute Inc., Cary, NC, USA) to account for repeated measures of the outcome in a subset of participants.

We fit our models in stages, first adjusting for a limited set of covariates including age at baseline, BMI, smoking status, and time since beginning of the study to capture long-term time trends. In the second stage, we added information on health status, medication use, and socioeconomic position, any of which could be potential confounders or mediators of the association between black carbon exposure and atherosclerosis. Covariates included in the second stage model were pack-years smoked, years of education (< 12, 12–16, and ≥ 16 years), alcohol intake (≥ 2 servings/day), categories of physical activity (0 to < 12, 12 to < 30, ≥ 30 METs/week), median income of the 2000 U.S. Census tract of residence, total cholesterol, lipid-lowering medication (statins), systolic blood pressure, blood pressure medications, and diabetes diagnosis. Time-varying covariates (all but education, baseline exposure, and median income at the U.S. Census tract at baseline) were updated at each visit. We also examined effect modification by using cross-product terms to estimate associations between black carbon and CIMT stratified on age (≤ 75, > 75 years of age), education (≤ 12, > 12 years of education), statin use (yes or no), diabetes (yes or no), and obesity (BMI < 30, ≥ 30) at baseline.

We conducted a separate analysis of CIMT progression (specifically, the change in CIMT from baseline to 3 years after baseline) in association with ln-transformed black carbon at baseline among the 260 participants with a measure of CIMT after 3 years of follow up, adjusting for the baseline values of covariates included in the fully adjusted model.

We also conducted several sensitivity analyses. We examined whether removal of potential confounders and mediators (i.e., statin medication use, total cholesterol, blood pressure medication use, diabetes diagnosis) altered the findings, and we also removed age at baseline from our model because some studies have observed that age is an important confounder and potential effect modifier (Rivera et al. 2013). Next, we explored the exposure–response relationship in fully adjusted models using generalized additive models with penalized splines in R (version 2.13; R Foundation for Statistical Computing, Vienna, Austria). We also estimated the cross-sectional association between black carbon during the year before the first CIMT measurement, and CIMT at the first measurement, with model covariates as defined at baseline. We then restricted analyses to participants whose location of residence did not change during the study and examined associations with a 1-year average exposure to black carbon in 2003 as a surrogate for long-term exposure among this population. The year 2003 was chosen because it is the year before the earliest possible baseline visits. In addition, we estimated the association between black carbon and CIMT after excluding participants who resided outside of the eastern Massachusetts region [approximately within the boundaries of Interstate 495 (I-495); Figure 1] where the original exposure model was developed and tested.
Table 1. Population characteristics [mean ± SD or n (%)] at study center visits (2004–2008) when CIMT was measured.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Visit 1 (n = 260)</th>
<th>Visit 2 (n = 240)</th>
<th>Visit 3 (n = 340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>75.9 ± 6.4</td>
<td>77.1 ± 6.2</td>
<td>78.0 ± 6.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.1 ± 4.1</td>
<td>28.2 ± 4.2</td>
<td>28.1 ± 4.2</td>
</tr>
<tr>
<td>Median income (US$)</td>
<td>63,334 ± 20,196</td>
<td>63,360 ± 20,353</td>
<td>64,286 ± 20,858</td>
</tr>
<tr>
<td>Pack-years</td>
<td>17.8 ± 22.7</td>
<td>18.3 ± 22.5</td>
<td>15.9 ± 19.9</td>
</tr>
<tr>
<td>METs (hr/week) &lt; 12</td>
<td>247 (65)</td>
<td>215 (63)</td>
<td>163 (63)</td>
</tr>
<tr>
<td>&gt; 12–30</td>
<td>81 (21)</td>
<td>74 (22)</td>
<td>52 (20)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>50 (13)</td>
<td>50 (15)</td>
<td>45 (17)</td>
</tr>
<tr>
<td>Education (years) &lt; 12</td>
<td>6 (2)</td>
<td>5 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>12–16</td>
<td>215 (57)</td>
<td>190 (56)</td>
<td>149 (57)</td>
</tr>
<tr>
<td>&gt; 16</td>
<td>159 (42)</td>
<td>145 (43)</td>
<td>110 (42)</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>174 (37)</td>
<td>173 (37)</td>
<td>170 (34)</td>
</tr>
<tr>
<td>Statin use</td>
<td>208 (55)</td>
<td>202 (59)</td>
<td>162 (62)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>74 (20)</td>
<td>72 (21)</td>
<td>59 (23)</td>
</tr>
<tr>
<td>≥ 2 Servings of alcohol per day</td>
<td>67 (18)</td>
<td>60 (18)</td>
<td>46 (18)</td>
</tr>
<tr>
<td>CIMT (mm)</td>
<td>0.99 ± 0.18</td>
<td>1.00 ± 0.18</td>
<td>1.01 ± 0.18</td>
</tr>
<tr>
<td>Years since baseline</td>
<td>0</td>
<td>1.6 ± 0.4</td>
<td>3.0 ± 2.2</td>
</tr>
<tr>
<td>Progression since baseline (mm)</td>
<td>0</td>
<td>0.02 ± 0.08</td>
<td>0.04 ± 0.09</td>
</tr>
</tbody>
</table>

Table 2. CIMT percent difference associated with a 1-IQR increase (0.26 µg/m³) in average exposure to black carbon during the year before the first CIMT measurement.

<table>
<thead>
<tr>
<th>Modeling approach</th>
<th>Percent difference (95% CI)</th>
<th>No. of observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model Parsimonious model (model 1)²</td>
<td>0.9 (0.2, 1.5)</td>
<td>380 977</td>
</tr>
<tr>
<td>Fully adjusted model (model 2)³</td>
<td>1.1 (0.4, 1.7)</td>
<td>378 988</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age + other potential mediators removed²</td>
<td>1.2 (0.5, 1.9)</td>
<td>390 976</td>
</tr>
<tr>
<td>Medications and health covariates only²</td>
<td>0.8 (0.1, 1.5)</td>
<td>380 971</td>
</tr>
<tr>
<td>Cross-sectional model³</td>
<td>1.0 (0.3, 1.7)</td>
<td>378 378</td>
</tr>
<tr>
<td>Stable residential address only³</td>
<td>1.0 (0.3, 1.7)</td>
<td>320 624</td>
</tr>
<tr>
<td>Stable residential address for entire study²</td>
<td>0.8 (0.2, 1.5)</td>
<td>315 316</td>
</tr>
<tr>
<td>Restriction to region where model was originally built and validated for whole population²</td>
<td>1.4 (−1.3, 4.2)</td>
<td>295 750</td>
</tr>
<tr>
<td>Restriction to region where model was originally built and validated stable residential address for entire study²</td>
<td>1.9 (−1.0, 4.9)</td>
<td>254 646</td>
</tr>
<tr>
<td>Random effect for ZIP code³</td>
<td>1.1 (0.4, 1.8)</td>
<td>378 988</td>
</tr>
</tbody>
</table>

*Adjusted for age at baseline, BMI, smoking status (never, current, former), time since baseline (days). *Adjusted for model 1 covariates + statin medication use, total cholesterol, systolic blood pressure, blood pressure medication use, and diabetes diagnosis, adjusted exam date, systolic blood pressure, and total cholesterol. *Adjusted for age at baseline, BMI, pack-years smoked, statin use (yes/no), blood pressure meds (yes/no), smoking status (never, current, former), education status (< 12 years, 12–16, > 16 years), ≥ 2 servings of alcohol per day, median income at the census tract level, diabetes (yes/no), time since study inception, systolic blood pressure, cholesterol. *Adjusted for model 2 covariates.

We also considered clustering by socioeconomic status by including an additional random effect for ZIP code. In secondary descriptive analyses, we estimated associations between CIMT and residential proximity to a major roadway (0 to ≤ 100 m, > 100 to ≤ 200 m, > 200 to ≤ 1,000 m, > 1,000 m) and between CIMT and average daily traffic within 100 m of the participant’s residence (categorized according to quartiles).

**Results**

A total of 380 participants completed a baseline visit between 2004 and 2008, including 340 (89%) who completed at least two follow-up visits and 260 (68%) who completed three follow-up visits through 2010 (Table 1). At baseline (the time of first CIMT measure), the mean (± SD) age and BMI of participants were 75.9 ± 6.4 years and 28.1 ± 4.1 kg/m², respectively, and 355 (93%) were retired or semi-retired. The mean CIMT at baseline was 0.99 ± 0.18 mm, which was higher than levels observed in younger, population-based cohorts. Participants were 61 to 96 years of age at baseline and CIMT ranged from 0.63 to 2.10. Median predicted black carbon concentrations at baseline for each subject was 0.29 µg/m³, with the interquartile range (IQR) equivalent to 0.26 µg/m³ (25th to 75th quartile, 0.16–0.42 µg/m³).

Based on our fully adjusted model, an IQR increase in average annual black carbon during the year before baseline was associated with a 1.1% (95% CI: 0.4, 1.7%) higher CIMT, consistent with a 0.01-mm increase from the mean CIMT of 0.99 mm at baseline (Table 2), which was similar to the mean rate of progression per year in this population (i.e., 0.01 mm). This association was stronger than estimated by the parsimonious model (0.9% higher; 95% CI: 0.2, 1.5%) adjusted for age, BMI, smoking, and time since baseline only.

*p-Values for cross-product terms indicated a statistically significant interaction (p < 0.05) for BMI only (Table 3). Specifically, the association between an IQR increase in black carbon and CIMT was stronger among men who were not obese at baseline (1.4%; 95% CI: 0.7, 2.2%; n = 284) than among men who were obese (0.6%; 95% CI: −0.6, 1.8%; n = 96;Interaction = 0.04). No other significant interactions were observed. CIMT progression among the 260 men with CIMT measured 3 years apart was not significantly associated with an IQR increase in annual average black carbon at baseline (−0.0002 mm decrease from baseline on average; 95% CI: −0.002, 0.001 mm; p = 0.79).

In our sensitivity analyses (Table 2), point estimates did not change when we removed additional potential mediators associated with health status. Results from our cross-sectional
Intima-media thickness and black carbon

3 and PM studies from cross-sectional analyses of CIMT one which can show considerable spatial het
marker for traffic particles than PM study is the use of modeled black carbon at
address during the year before baseline and
Discussion
CIMT, respectively.

Inclusion of the random effect for ZIP code
did not materially change the results from the
full model [1.1% higher CIMT (95% CI:
0.4, 1.8%)].

In descriptive analyses, we estimated associa-
tions between residential proximity to an A1 or A2 roadway and average daily traffic
within 100 m of home address at baseline.
Because there were only 10 participants liv-
ing < 100 m from a major road, we collapsed
the ≤ 100-m and 100- ≤ 200-m categories.
In comparison to living > 1,000 m from a
major road, living < 200 m or 200–1,000 m
away was associated with –1.4% (95% CI:
–7.11, 4.6%) or –2.2% lower CIMT (95% CI:
–5.7, 1.5%), respectively. For the average
daily traffic, we estimated associations by
quartiles of exposure (7,795–212,923; 212,
924–416,029; 416,030–1,251,886; and 1,251,
887–9,861,107 vehicles/day).
Compared with living in a location in the low-
est quartile of exposure, living in a location
with average daily traffic in the second, third,
or fourth quartile of exposure was associated
with 4.6% higher (95% CI: –0.3, 9.6%),
4.3% higher (95% CI: –0.5, 9.3%), or
2.7% (95% CI: –2.0, 7.6%) higher
CIMT, respectively.

Discussion
We observed a positive association between
average black carbon exposure at the home
address during the year before baseline and
subsequent subclinical atherosclerosis mea-
sured by CIMT. A major feature of this
study is the use of modeled black carbon at
home address; black carbon is a more specific
marker for traffic particles than PM2.5 and one which can show considerable spatial het-
ergy within distances of a few hundred
meters. Our findings are consistent with prior
studies from cross-sectional analyses of CIMT
and PM2.5 exposures among participants in
Los Angeles, California (Künzli et al. 2005);
the Multi-Ethnic Study of Atherosclerosis
(MESA) (Diez Roux et al. 2008), which used
20-year estimates of modeled exposure; and
1-year averaged modeled exposure from the
Heinz-Nixdorf Recall study in Germany
(Bauer et al. 2010) in addition to a recent
study that reported associations with NO2
(nitrogen dioxide), which is also a marker of
traffic particles (Rivera et al. 2013).

Previous studies have reported that CIMT
is a strong predictor of future vascular events.
A meta-analysis reported that age- and sex-
adjusted relative risks of myocardial infarction
and stroke per 0.10 mm CIMT difference
were 1.15% (95% CI: 1.12, 1.17%) and
1.18% (95% CI: 1.16, 1.21%), respectively;
and although the relationship between CIMT
and risk was not linear, linear models fit well
for moderate-to-high CIMT levels. The levels
of CIMT at baseline observed for men who
participated in our study were higher than
those reported in populations that included
younger, healthier populations of both men
and women (Chambless et al. 1997; Lim
et al. 2008) and were more similar to those
reported in a study of patients with arterial
disease and cardiovascular risk factors (Dijk
et al. 2006). In the Atherosclerosis Risk in
Communities (ARIC) study, a cutoff of 1 mm
was used to evaluate risk of coronary heart
disease, and the hazard ratio for coronary heart
disease comparing men with CIMT measures
≥ 1 mm versus < 1 mm was 1.85 (95% CI:
1.28, 2.69), which would suggest that the
levels of CIMT observed in our study popula-
tion might be associated with elevated risk of
cardiovascular disease.

A few recent studies have begun to exam-
ine associations between ambient air pollu-
tion exposure and atherosclerotic progression
as measured by CIMT. In one recent study,
both PM2.5 and residential distance from
highway were examined in a population of
participants pooled from five double-blind
randomized trials that estimated the effects
of interventions on the progression of CIMT
in the Los Angeles area (Künzli et al. 2010).
Künzli et al. (2010) observed a rate of pro-
gression of 5.46 µm (95% CI: 0.13, 10.79)
per year associated with living within 100 m
of major road and that a 10-µg/m3 increase
in PM2.5 was associated with a slightly smaller
change of 2.53 (95% CI: –0.31, 5.38) µm per
year. More recently, similar results have been
reported in MESA, where Adar et al. (2013)
observed that 2.5-µg/m3 increase in PM2.5
(95% CI: 3.6, 7.4 µg/m3/year) greater IMT progressions
among persons in the same metropolitan
area. We did not observe a significant asso-
ciation with progression over 3 years; given
the relatively short period of follow-up on
only 260 participants, we had limited power
to test this association in the present study.

In addition, men who survived long enough
to participate in the present study may have
had a low likelihood of CIMT progression,
and healthier participants within the cohort
may have been more likely to have completed
follow-up than men with increasing CIMT.
The annual rate of CIMT progression in our
study population (approximately 0.01 mm, or
10 µm/year) was similar to rates reported in
MESA and other cohort studies including the
ARIC study (Ranjit et al. 2006) and in older
men and women in the Whitehall II study
(Halcox et al. 2009).

We observed significant associations with
the corrected daily predictions of black carbon at participant residence. In
our secondary, exploratory analyses, we exam-
ined associations with measures of residen-
tial proximity to major roadways as well as
traffic density. In the present study, contrary
to our expectation, mean CIMT was greatest
in men living farthest from a major road at
baseline, although associations were not
statistically significant and only a small num-
ber of participants (n = 32) lived ≤ 200 m
from a major road at baseline. A study by
Allen et al. (2009) reported no association
between roadway proximity and abdominal
aortic artery calcification, another measure
of atherosclerotic burden. As these authors
have pointed out, the roadway classification
system describes a type of road and not the
traffic volume and traffic pollution, more
directly, which may in part explain these dif-
fering results. In the present study, CIMT
was higher in participants exposed to traffic
counts higher than the first quartile, but
estimates were relatively imprecise and not
statistically significant.

Of the potential susceptibility factors that
we examined, the only statistically significant
interaction was observed for stratification
by obesity: We observed higher associations
with black carbon among non-obese indi-
viduals. We hypothesized that this finding
was due to the strong association between
BMI and CIMT in this study, such that
obesity and other related factors likely have
a larger effect on a measure of subclinical
atherosclerosis than black carbon and the
association between black carbon and intima-
media thickness is observed only in the
non-obese individuals. In addition, Freedman
et al. (2004) have noted that CIMT may be
more difficult to measure in obese individu-
als and may be assessed with less precision.
The association between black carbon and
CIMT was also somewhat stronger in men
without diabetes than in men with diabe-
tes, although estimates were imprecise. These
results contrast those of other studies that
have reported evidence to suggest that per-
sions with diabetes are particularly susceptible
to the effects of traffic pollution (Baja et al.

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To attempt to address this, we also analyzed black carbon concentrations estimated for long-term time trends because they were not fully account for long-term time trends. These results that we observed may differ from those observed in previous studies because of differences in exposure characterization, age range, and other population characteristics. We also cannot rule out the possibility that our findings of a significant association for BMI may be due to chance.

Our estimates of long-term black carbon exposure were model based, rather than direct measures from monitors. Use of exposure estimates based on residential address may misclassify personal exposure levels. However, because we are examining relatively recent long-term exposures and only 16% of the population changed residence over the course of follow-up, the lack of substantial occupational or commuting exposure to traffic-related air pollution in this largely retired cohort (93% completely retired or semi-retired at baseline) suggests that residence-based exposure estimates may serve as a good proxy for personal exposure. In addition, our exposure is modeled on the log scale, which limits the influence of very high estimates of black carbon levels. On the other hand, this approach does not address the influence of very low exposure values. Whereas our model diagnostics suggested that the association was linear on the log scale, results from analyses examining the association on the natural scale suggested a nonlinear dose response and a negative slope at high levels, although these results were imprecise and the CIs were wide. Our black carbon model predicts lower levels of exposure outside the region within I-495, in which it was originally developed. Although we had considerably less power to detect an association in analyses restricted to within I-495 only (77% of participants), in these analyses we estimated stronger associations between black carbon levels and CIMT, but results were no longer statistically significant. It is possible, however, that the estimates we report in the full population underestimate the true association because of exposure misclassification, although we had considerably less power to detect an association in analyses restricted to within I-495 only. In addition, our analysis of annual black carbon concentrations may not fully account for long-term time trends because they were based on associations with annual average black carbon concentrations estimated for the year prior to baseline, which occurred between 2004 and 2008 and, therefore, may not fully account for long-term time trends.

To attempt to address this, we also analyzed the associations assigning everyone black carbon exposure based on 2003 data for their addresses and the results were similar to those observed in our final model. Future work will be necessary to elucidate this association.

Because our study participants were elderly male residents of the Boston area, 97% of whom reported their race as white, these results may not be generalizable to other populations of environmentally exposed men and women. This particular analysis was also limited to a subset of Normative Aging Study participants who continued to be followed during the study period, many of whom consented to return on an additional day for CIMT testing. Our study participants were elderly men ranging in age from 61 to 96 years of age at first visit, who, on average, had already developed a considerable degree of atherosclerotic burden at baseline. Furthermore, the mean CIMT reported at baseline was higher than has been reported in other community-based samples, which generally have younger participants (Adar et al. 2013; Gupta et al. 2015). There may be some degree of measurement error in CIMT, but this would likely be nondifferential with respect to exposure. In addition, we also cannot rule out the role of residual confounding by socioeconomic position or other factors. Although there was some attrition over time, two or more measurements were obtained for 89% of individuals.

Conclusions

We observed that low levels of ambient exposure to estimated black carbon were associated with CIMT in a population of elderly men continuing to participate in a long-term prospective cohort study. Given the growing interest in the relationship between air pollution and atherosclerosis (Künzli et al. 2011) and the limited body of human studies examining repeated measurement of indicators of atherosclerotic burden, future studies are needed to substantiate the association between specific sources of pollution and atherosclerotic progression in order to clarify the underlying mechanisms.

References


Wilker et al.


