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## Long- and Short-term Air Pollution Exposure and Measures of Arterial Stiffness in the Framingham Heart Study

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### Abstract

**Background:** Studies of air pollution exposure and arterial stiffness have reported inconsistent results and large studies employing the reference standard of arterial stiffness, carotid-femoral pulse-wave velocity (CFPWV), have not been conducted.

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Declarations of interest:

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**Aim:** To study long-term exposure to ambient fine particles (PM<sub>2.5</sub>), proximity to roadway, and short-term air pollution exposures in relation to multiple measures of arterial stiffness in the Framingham Heart Study.

**Methods:** We assessed central arterial stiffness using CFPWV, forward pressure wave amplitude, mean arterial pressure and augmentation index. We investigated long-and short-term air pollution exposure associations with arterial stiffness with linear regressions using long-term residential PM<sub>2.5</sub> (2003 average from a spatiotemporal model using satellite data) and proximity to roadway in addition to short-term averages of PM<sub>2.5</sub>, black carbon, particle number, sulfate, nitrogen oxides, and ozone from stationary monitors.

**Results:** We examined 5,842 participants (mean age 51 ± 16, 54 % women). Living closer to a major roadway was associated with higher arterial stiffness (0.11 m/s higher CFPWV [95 % CI: 0.01, 0.22] living < 50 m vs 400–1000 m). We did not observe association between arterial stiffness measures and long-term PM<sub>2.5</sub> or short-term levels of PM<sub>2.5</sub>, particle number, sulfate or ozone. Higher levels of black carbon and nitrogen oxides in the previous days were unexpectedly associated with lower arterial stiffness.

**Conclusions:** Long-term exposure to PM<sub>2.5</sub> was not associated with arterial stiffness but positive associations with living close to a major road may suggest that pollutant mixtures very nearby major roads, rather than PM<sub>2.5</sub>, may affect arterial stiffness. Furthermore, short-term air pollution exposures were not associated with higher arterial stiffness.

## Keywords

Arterial stiffness; air pollution; applanation tonometry; epidemiology

## Introduction

Exposure to air pollution has been associated with cardiovascular morbidity and mortality in many studies (1). Atherosclerosis and vascular dysfunction contribute to the development of cardiovascular events and may represent a pathway by which air pollution may exert effects both as a result of short- and long-term exposure (2). Long-term exposure to particulate matter pollution over months to years has been associated with vascular risk factors and subclinical disease including high blood pressure (3), carotid intima media thickness (4, 5) and increased calcification of arteries (6), although associations were not consistent for these measures in all studies (7, 8).

Increased central arterial stiffness, another measure of vascular dysfunction, is a risk factor for the development of cardiovascular events and may be a precursor to hypertension (9, 10). To date, studies of long-term air pollution exposure and arterial stiffness have reported inconsistent results (11–17) but only one study measured carotid femoral pulse wave velocity (CFPWV), considered the reference standard measure of arterial stiffness (15). Instead most studies used measures such as augmentation index, that with age becomes a less sensitive marker for arterial stiffness and future CVD risk (10).

Short-term exposures to air pollution on the order of days, including both gaseous and particulate components, also have been associated with measures of vascular function

including changes in blood pressure (18), peripheral vascular function (19–22), and coronary ischemia (23). Changes in arterial stiffness also have been studied in relation to short-term air pollution exposure in previous studies but with varying results and a lack of large-scale studies using CFPWV (24–28).

Whereas it is generally perceived that air pollution has an adverse effect on vascular function, resulting in increased risk of cardiovascular events in the short- and long-term, previous studies have yielded inconsistent results, possibly because the approach to measuring arterial stiffness has been problematic. Variation in study populations and constituents of air pollution mixtures may also explain inconsistencies across studies. In addition, none of the previous studies have assessed both long- and short-term air pollution exposure. We hypothesized that living close to a major road and at addresses with higher long-term averages of particulate matter is associated with higher arterial stiffness. We also hypothesized that higher short-term averages of particulate air pollution are associated with higher arterial stiffness. Therefore, we evaluated both long- and short-term exposure to air pollutants and traffic to the reference standard measure of arterial stiffness (and also several complementary measures) in a well-characterized large community-based cohort.

## Methods

### Study participants

Participants in the Framingham Heart Study Offspring and Third Generation cohorts were eligible based on having performed valid examinations of arterial stiffness in examination rounds 8 and 1 respectively and having a primary address in the Northeastern US corresponding to the catchment area of the spatially resolved fine particulate matter (PM<sub>2.5</sub>) satellite model, resulting in 5,842 participants. These cohorts have been described in detail previously (29, 30). Ethical approval was obtained from the Institutional Review Boards of the Beth Israel Deaconess Medical Center and Boston University Medical Center. Written informed consent was obtained from all participants.

Individual-level covariates were collected through physician interview, blood draws, and physical examination. Neighborhood-level data concerning socio-economic characteristics were collected through the U.S. Census 2000 based on the primary residential address of each participant. These included median household income and median value of owner-occupied housing units, at the census tract level.

### Measures of arterial stiffness

Offspring cohort examination round 8 was conducted between 2005 and 2008 and Third Generation cohort examination round 1 was conducted between 2002 and 2005. The methodology of arterial stiffness measures in the Framingham cohorts has been described in detail elsewhere (31, 32). Briefly, using a custom transducer, electrocardiogram, and body-surface measurements, tonometric measurements were obtained from the carotid and femoral sites to calculate CFPWV. Left ventricular outflow tract diameter was measured with 2-dimensional echocardiography and Doppler flow velocity was multiplied by outflow tract area to obtain aortic volume flow. Wave separation analysis was used to determine the

forward pressure wave amplitude (FWA) and carotid pressure waveform analysis was used to assesses augmentation index. Mean arterial pressure was calculated from the brachial pressure wave form based on tonometry or oscillometric cuff waveform.

Of the several methods used to quantify arterial stiffness CFPWV is considered the reference standard. CFPWV is primarily a measure of aortic wall stiffness. FWA is a function of the peak systolic blood flow and aortic impedance and increases with greater aortic wall stiffness or in the presence of mismatch between aortic diameter and flow. Mean arterial pressure provides a measure of steady-flow load and is influenced by cardiac output and peripheral vascular resistance. Augmentation index is based on pulse wave analysis in the carotid artery and is used to measure relative wave reflection.

### Exposure assessment

**Long-term PM<sub>2.5</sub>**—We assessed annual averages of PM<sub>2.5</sub> exposure at the primary residential address of each participant recorded at the examination round using modeled estimates of daily PM<sub>2.5</sub> with a 1×1 km resolution. The basis of the model used satellite-derived aerosol optical depth (AOD), a quantitative measure of particle abundance in a column of air, to predict a PM<sub>2.5</sub> concentration for a 1 × 1 km grid (33). These estimates were calibrated using 161 ground monitoring stations within 1 km of an AOD value and adjusted for meteorological parameters (temperature, daily visibility, sea land pressure, relative humidity, and wind speed) and local land-use regression parameters (distance to point source emissions, population density, percentage of land use, total area-source emissions, elevation, and traffic density). We then predicted daily PM<sub>2.5</sub> concentrations in grid cells without monitors but with available AOD using the model fit from the preceding model. Finally, for grid cells without AOD measurements on a given day, we used region-specific associations between grid-cell AOD and PM<sub>2.5</sub> levels using neighboring cells to calculate daily levels. The difference between ground-level PM<sub>2.5</sub> data and model predictions were regressed against temporal and spatial predictors of monitored PM<sub>2.5</sub> at a 200 × 200 m resolution including the following factors: distance to major roads, traffic density, percent urban, elevation, distance to point source emissions, population density, height of planetary boundary layer, and visibility. Our model predictions demonstrated an out-of-sample 10-fold cross-validated R<sup>2</sup> of 0.88 (0.82–0.90 between 2003 and 2011). We summed daily grid predictions and localized residual PM<sub>2.5</sub> predictions for each address and averaged them over a year.

We expected temporal trends for PM<sub>2.5</sub> levels over the years in which arterial measurements were collected (2002–2008) as well as lower arterial stiffness in the generally healthier and younger Third Generation cohort examined between 2002–2005 compared to higher arterial stiffness in the older Offspring cohort examined later between 2005–2008. In an effort to avoid introducing the bias of these temporal trends we used a similar strategy employed in previous studies (34, 35), of assigning the annual PM<sub>2.5</sub> concentration of a fixed year (2003) as a measure of recent, longer-term PM<sub>2.5</sub> exposure. We used the address recorded at the time of their Framingham exam (Third Generation cohort Examination Round 1, 2002–2005 and Offspring cohort Examination Round 8, 2005–2008) and assigned the PM<sub>2.5</sub> 2003 annual average for these addresses for all participants. In this way we aimed to contrast the

geographical differences in levels of exposure in our study sample while controlling for temporal trends. We picked 2003, a year preceding most exams, assuming that the rank-ordering of exposure would be reasonably well-preserved between 2002–2008.

**Distance to a major roadway**—We calculated the distance between geocoded primary residential addresses and the nearest major roadway classified as A1, A2 or A3 according to the U.S. Census Features Class. We examined proximity to roadways both as a natural logarithm as well as in categories of proximity <50 m, 50 to <100 m, 100 to <200 m, 200 to <400 m, and 400 to 1,000 m because previous studies have demonstrated log-linear associations between proximity to roadway and health outcomes (36) and a return to background ultrafine and PM<sub>2.5</sub> levels within 100–300 m and 100–400 m respectively from major roadways (37). Residential addresses further than 1,000 m from a major roadway are likely to reflect different exposures compared to those addresses in urban or suburban areas. We, therefore, excluded these addresses (> 1,000 m, 635 observations or 11%) in analyses of proximity to roadway and arterial stiffness as distance to roadway for these addresses is not likely an indicator of traffic-related exposure resulting in 5,207 participants for these analyses.

**Short-term averages of air pollutant exposure**—In line with other studies of short-term air pollution exposure we made use of continuous measurements from fixed monitoring stations strategically situated to capture temporal variations in levels from day to day. Hourly levels of PM<sub>2.5</sub>, black carbon, particle number, sulfate, nitrogen oxides, and ozone retrieved from fixed site monitors were used to construct daily 9 AM to 9 AM means. We used PM<sub>2.5</sub>, black carbon, particle number and sulfate measurements from the Harvard Air Pollution Monitoring Supersite situated on the rooftop of the Francis A. Countway Library of Medicine, 5 stories above ground level and 50 m from the nearest street. We used a tapered-element oscillating microbalance (Model 1400A, Rupprecht & Patashnick Co. Inc., Albany, New York) to measure PM<sub>2.5</sub>, an Aethalometer (Model AE-16, Magee Scientific Corp., Berkeley, California) to measure black carbon on the basis of optical transmittance at a single wavelength ( $\lambda = 880\text{nm}$ ), and a condensation particle counter (Model 3011A, TSI, Inc., Shoreview, Minnesota) to measure number of particles per cm<sup>3</sup>. Sulfate concentration was calculated from an elemental sulfur measured by x-ray fluorescence analysis of PM<sub>2.5</sub> filter samples and on days when sulfur measurements were not available, by using a sulfate analyzer (Model 5020, Thermo Electron Corp., Franklin, Massachusetts). Nitrogen oxides and ozone were measured by local state monitors within the Greater Boston area and averaged from the available sites. We modeled separate 1-, 3-, 7-, and 14-day averages for each single pollutant model and restricted analyses of short-term air pollution exposure to arterial stiffness measures in participants living within 50 km of the Harvard Supersite monitor.

**Meteorology**—We calculated daily averages from hourly measurements of temperature and relative humidity from the Logan International Airport (Boston, Massachusetts) weather station, 12 km from the air pollution monitoring site.

## Statistical methods

We fit multivariable linear regression models for all analyses using the same covariate model for both long and short-term analyses. We selected covariates *a priori* based on biological plausibility and consistency with our previous publications of air pollution and vascular function in this cohort (38, 39). All models were adjusted for age at examination (age, age<sup>2</sup>), sex, cohort, body mass index (BMI), triglycerides, ratio of total cholesterol/high density lipoprotein, heart rate at examination, diabetes status, smoking status (never, former or current), pack-years of smoking, individual-level education (high school or less, some college, college graduate), median census-tract household income in 2000, median census-tract value of owner-occupied housing in 2000, day of week, season (as sine and cosine functions of the exam date), time-trend (as a linear term for date), temperature and relative humidity of the day prior to outcome measurement as well as a multiplicative interaction term of temperature and relative humidity. We calculated means with standard deviations and counts with percent for continuous and categorical variables respectively. Spearman correlations were calculated for daily averages of air pollutants measured at the central monitoring site.

We explored effect modification for proximity to roadway analyses by including multiplicative terms of log proximity and categories of BMI (categorized <30 and ≥30 kg/m<sup>2</sup>), median age (<64 and ≥64 years) and sex.

We also performed several sensitivity analyses. In an attempt to investigate associations between long-term exposure and arterial stiffness independent of short-term variations in particulate pollution we performed analyses adjusting for PM<sub>2.5</sub> levels obtained from the central site monitor for the day preceding tonometry examinations. We also relaxed our exclusion of participants living >1,000m from a major roadway for proximity to roadway analyses. Similarly, we performed sensitivity analyses using the same population for all analyses by restricting to individuals living within 50 km to the central site monitors in long-term exposure analyses. Previous literature has highlighted the dependence of pulse wave velocity on blood pressure (40), however, we did not include hypertension as a covariate in our main model since it may be an intermediate on the pathway of the association. Instead, we performed sensitivity analyses by including hypertension therapy in all models and in another separate analyses we included mean arterial blood pressure in models of CFPWV. We further explored possible over-adjustment of regression models by excluding heart rate in CFPWV models and in all long-term exposure models by excluding covariates predominately targeting short-term confounders (such as day of week, time-trend, season, ambient temperature, relative humidity, and season) in all long-term exposure models. Finally, we conducted cohort-specific analyses to assess the consistency of results across cohorts.

Long-term PM<sub>2.5</sub> exposure at residential address was modeled for the index year 2003 scaled to the interquartile range (1.46 µg/m<sup>3</sup>). Proximity to roadway was modeled both as a continuous log-linear independent variable scaled to the difference between living at the 75<sup>th</sup> (405 m) vs the 25<sup>th</sup> (61 m) percentile rounded off to 400 m vs 50 m from a major road as well as a categorical variable (<50 m, 50 to <100 m, 100 to <200 m, 200 to <400 m, and 400 to ≥1,000 m). Short-term associations were scaled to 5 µg/m<sup>3</sup> PM<sub>2.5</sub>, 0.4 µg/m<sup>3</sup> black

carbon, 15,000 particles/cm<sup>3</sup>, 2 µg/m<sup>3</sup> sulfate, and 0.01ppm nitrogen oxides and ozone. Consistent with previous publications of CFPWV in the Framingham Heart Study we inverse-transformed CFPWV to reduce heteroscedasticity and multiplied by -1000 to restore effect direction and convert units to milliseconds per meter(9). Results were interpreted focusing on describing and highlighting consistent association patterns across air pollution exposures and measures of arterial stiffness.

## Results

### Participant characteristics and measures of arterial stiffness

Participant characteristics are summarized in Table 1. Our study cohorts were almost exclusively white (99%) and consisted of a middle to older aged group of individuals with similar numbers of men and women. Few were current smokers and almost half had never smoked. Nearly half of participants completed college, and on average participants lived in census tracts with median household incomes that were above the US median in 2003 (\$43,318)(41). Distributions for measures of arterial stiffness as well as the transformed CFPWV are provided in Table 2.

### Distributions of exposure

Distributions of measures of long-term exposures as well as short-term averages of pollutants are summarized in Table 3. The median level of PM<sub>2.5</sub> at residential address in 2003 was 10.7 µg/m<sup>3</sup> and 23 % lived within 50 m of a major roadway. Mean levels of long-term and short-term air pollutants were generally low. PM<sub>2.5</sub>, black carbon, and sulfates were moderately to highly correlated with each other (Spearman correlation coefficients >0.7, Table 4). Black carbon and NO<sub>x</sub> were moderately positively correlated and both were negatively correlated to ozone.

### Long-term air pollution, proximity to major roadway and measures of arterial stiffness

**Associations between PM<sub>2.5</sub> and measures of arterial stiffness.**—We did not observe associations among the 5,842 participants between higher residential PM<sub>2.5</sub> levels and CFPWV, FWA or mean arterial pressure (Figure 1). The estimate for augmentation index gave some indication of lower augmentation index in association with higher PM<sub>2.5</sub>; however, the confidence intervals included the null.

**Associations between proximity to major roadway and measures of arterial stiffness.**—In 5,207 participants with home addresses > 1,000 m of a major road, living closer to major roadways was associated with higher CFPWV both when proximity was modeled as a continuous or categorical variable (Figure 1). Similar results were observed for mean arterial pressure and augmentation index although confidence interval estimates included the null (Figure 1). No association was observed between proximity to roadway and FWA.

**Effect modification**—There was no apparent difference in associations between proximity to roadway (continuous) and CFPWV by BMI (categorized <30 and ≥ 30 kg/m<sup>2</sup>),

age (categorized <64 and ≥64 years), or sex (all p-values for interaction terms >0.05; Online Supplemental Figure E1).

**Sensitivity analyses**—Adjusting for PM<sub>2.5</sub> levels obtained from the central site monitor for the day preceding tonometry examinations did not affect estimates (Online Supplemental Figure E2). Proximity to roadway associations were similar in models not excluding observations from addresses >1,000m from a major roadway (Online Supplemental Figure E3). Likewise, results from long-term analyses conducted using only the same individuals as in the short-term analyses (living within 50km from the central site monitor), including hypertension therapy in the covariate model, or excluding day of week, season, temperature, relative humidity and time-trend were very similar (Online Supplemental Figures E4, E5, and E6.). We observed consistent results in regression models assessing long-term exposure and CFPWV excluding adjustment for heart rate. Adjusting for mean arterial pressure in models of long-term exposure and CFPWV attenuated results, possibly reflecting an intermediate pathway of effect through blood pressure (Online Supplemental Figures E7).

Conducting separate exploratory analyses by cohort demonstrated consistent results for CFPWV across cohorts. Results for FWA did not show a clear pattern of association with PM<sub>2.5</sub> or proximity to roadway in either cohort and we observed positive associations of proximity to roadway with augmentation index and mean arterial pressure only in the older Offspring cohort in comparison to the Third Generation cohort (Online Supplemental Figure E8).

### Short-term air pollution and measures of arterial stiffness

We examined short-term exposures to air pollution in 3,927 participants living within 50 km of the Harvard Supersite monitor. We did not observe consistent evidence to support associations between higher particulate air pollutants such as PM<sub>2.5</sub> mass, particle number, and sulfate and measures of arterial stiffness (Figure 2). Higher short-term ozone levels were associated with higher estimates for mean arterial pressure and to a lesser degree CFPWV. Higher short-term levels of black carbon and NO<sub>x</sub> demonstrated a tendency of lower CFPWV and mean arterial pressure (Figure 2).

**Sensitivity analyses**—Models including mean arterial pressure as a covariate for estimating the association of short-term air pollution on CFPWV demonstrated very similar results, however, the negative associations (indicating protective effects) of black carbon and NO<sub>x</sub> became weaker and confidence intervals spanned the null. A similar but less pronounced pattern was observed for NO<sub>x</sub> in models excluding heart rate as a covariate (Online Supplemental Figure E9). Including hypertension therapy as a covariate for all models of arterial stiffness did not change results (Online Supplemental Figure E10). Similar to analyses of the overall participants, the cohort-specific analyses of short-term air pollution exposure and measures of arterial stiffness demonstrated large heterogeneity with wider confidence intervals and without any clear pattern of association (Online Supplemental Figure E11). In the Offspring cohort the negative associations between black carbon and CFPWV were slightly more pronounced and positive associations with wide confidence intervals were observed between several moving averages of particle number and



augmentation index. In the Third Generation cohort we observed some associations between moving averages of ozone with higher FWA and mean arterial pressure, the latter largely concordant with the Offspring cohort.

## Discussion

In our community-based sample in the Northeastern US, we observed higher levels of arterial stiffness among participants living closer to major roadways, but not among those exposed to higher levels of PM<sub>2.5</sub>. Short-term exposure to pollutants in the preceding days was not associated with arterial stiffness, and for some pollutants, there was unexpectedly lower stiffness measures following exposure. Taken together, these results add some evidence to suggest that long-term exposure to local near-roadway traffic-related exposures may be associated with higher arterial stiffness, but did not find evidence to support associations between short-term air pollution exposure and higher arterial stiffness.

Arterial stiffness increases with advancing age and is associated with the risk of hypertension (9) and cardiovascular events (10, 42). Increased inflammatory markers (43) and conditions of inflammation such as rheumatoid arthritis (44) have been associated with increased arterial stiffness and concordantly a reduction of inflammation has been associated with reduced central arterial stiffness (45). This implies both chronic structural changes, amenable for studies exploring effects of long-term air pollution exposure, and dynamic functional components, amenable to studies exploring effects of short-term air pollution exposure.

### Long-term exposures and arterial stiffness

In our study, the long-term estimate of PM<sub>2.5</sub> exposure was not associated with the reference standard measure of arterial stiffness CFPWV, nor any of our other measures including FWA, augmentation index, or mean arterial pressure. These results are in line with findings from the Multi-Ethnic Study of Atherosclerosis (MESA), perhaps the most comparable to our study sample, including almost 4,000 participants from 6 US cities in which no associations were observed between estimated 20-year exposure to PM<sub>10</sub> or PM<sub>2.5</sub> and carotid stiffness, assessed by Young's modulus measure of elasticity, or stiffness assessed using radial artery applanation tonometry (16). Similarly, long-term PM<sub>2.5</sub> was not associated with radial artery derived pulse wave velocity (PWV) or augmentation index in a study of 745 young adults in a Dutch study (15). In contrast, other studies have demonstrated associations between higher long-term PM<sub>2.5</sub> or PM<sub>10</sub> and measures of arterial stiffness such as brachial-ankle PWV or carotid stiffness using Young's modulus, distensibility and stiffness index but in relation to prenatal exposure (11), or in specific subpopulations such as physically inactive older adults (12) or patient undergoing hemodialysis (17).

In contrast to results for PM<sub>2.5</sub> exposure, we observed positive associations between living close to a major roadway and higher CFPWV and a similar pattern of association for mean arterial pressure and augmentation index, results that were more pronounced in the older Offspring cohort. These findings are largely consistent with several other studies of arterial stiffness using distance to major roadway as a proxy for long-term air pollution exposure. In

371 adults from an urban community in Shanghai, living within 50 m of a major road was associated with higher augmentation index (14) and in 52 children in southern Italy, living within 300 m from a major road was associated with higher carotid stiffness compared to living 330–730 m and 780–1,450 m (13).

The difference between associations observed for long-term  $PM_{2.5}$  and proximity to roadway in relation to arterial stiffness may reflect an estimation of different exposures. Proximity to roadway may better capture exposure to particle number than fine particle mass and include gaseous mixtures. Indeed, two large studies in the Netherlands and Switzerland observed positive associations between long-term exposure to  $NO_2$  and PWV (12, 15) and previous studies have demonstrated that particle number is highest near roadways and rapidly dissipates with increasing distance (36). In addition to being a proxy for air pollution exposure, proximity to roadway may also reflect noise exposure, a proposed risk factor for cardiovascular outcomes (46, 47), or socioeconomic status. Indeed, the apparent absence of association between long-term exposure to  $PM_{2.5}$  and arterial stiffness in our study coupled with the associations observed for proximity to roadway strengthen the argument of proximity to roadway as a proxy for noise pollution in this study. Unfortunately, we did not have noise pollution data to test this hypothesis.

### Short-term exposures and arterial stiffness

In order to study short-term exposures and arterial stiffness, we limited our analyses to participants living within a 50 km radius from the monitoring facility. While reducing our sample size from 5,842 to 3,927 individuals this was an effort to maintain a reasonable assessment of day-to-day variation in pollution exposure using the central monitor. We found no strong evidence in our results to support an association between exposures to elevated short-term levels from 1 to 14 days and higher arterial stiffness. Results for black carbon and  $NO_x$  suggested lower CFPWV and mean arterial pressure in association with higher pollutant levels and we observed largely reciprocal associations between ozone and these measures possibly reflecting to some extent the degree of negative correlations between these pollutants. In sensitivity analyses, the negative associations for black carbon and  $NO_x$  were, however, attenuated in models including mean arterial pressure or excluding heart rate suggesting some sensitivity to model specification.

Our results are based on the largest cohort yet to consider short-term air pollution exposure and arterial stiffness and are in line with some, but not all previous studies. A study from Athens including 1,222 hypertension patients did not observe associations between 5-day or 24-hour  $PM_{10}$  levels and augmentation pressure or index in the full sample, consistent with our results, but reported higher augmentation pressure in men following higher 5-day  $PM_{10}$  levels (24). Other small studies using personal samplers for black carbon,  $NO_2$  or  $PM_{2.5}$  did not observe any associations between daily levels of these pollutants and higher PWV or augmentation index in patients with metabolic syndrome, in rural mothers, or healthy workers in China (48–50).

In contrast, several studies have reported positive associations between short-term air pollution levels and arterial stiffness in various populations. Particle number levels and to a lesser extent  $PM_{2.5}$  was associated with higher augmentation index and pressure for

exposure periods ranging from 1-day to 14-day averages among 370 older men in the New England area, where our study was also conducted (28). Same day black carbon, PM<sub>2.5</sub> and NO<sub>2</sub> levels were associated with higher PWV and measures of carotid artery stiffness in small studies including 54 healthy Belgian nurses (51) or 89 healthy Taiwanese bankers (52). In addition, welding and exposure to high levels of PM<sub>2.5</sub> was associated with higher augmentation index on the day of exposure but a decrease subsequent day (53) suggesting that this rapid change in pulse-wave reflection may indicate a change in ventricular preload or peripheral vascular tone rather than structural changes in arterial stiffness.

In addition to panel studies, a few studies of controlled short-term exposure to diesel exhaust and wood-smoke with a randomized double-blind crossover approach have been conducted, with inconsistent results. In two of the diesel chamber studies, CFPWV was examined with null associations in one study (27) and higher PWV in another when participants were infused with nitric oxide synthase inhibition, possibly suggesting pathways dependent on NO bioavailability (26). Similarly, diesel exposure demonstrated conflicting associations with augmentation index and pressure with positive associations reported immediately following diesel exposure in one study but lower augmentation index (indicating lower arterial stiffness) in another study. Conflicting results are also reported in chamber studies of wood-smoke exposure for both PWV and augmentation index measures of arterial stiffness (25, 54). Thus, studies of short-term studies of air pollution, including controlled exposure studies, have not consistently demonstrated associations with arterial stiffness.

### Limitations

We only assessed arterial stiffness at a single visit for each participant and therefore we were not able to analyze air pollution exposure in relation to a longitudinal change in arterial stiffness. We based assessment of long-term exposure on residential address as a proxy for average exposure and could not account for time spent away from home. In order to preserve the rank-ordering of long-term pollution exposure regardless of the downward trends of air pollution exposure over time, we assigned exposure at the home address recorded when tonometry measures were performed according to that address' annual level in 2003. These approximations of long-term exposure will contribute to some exposure misclassification but minimize the potential bias based on cohort and temporal air pollution trends and are unlikely to introduce major bias in relation to stiffness measures. For short-term exposure, we used a central monitoring site to capture day-to-day variations in pollution levels in a region within 50 km. This disregards the spatial variation in exposure. However, within this 50 km radius, this variation is likely lower than the temporal variability within short-term exposure periods of up to 14 days.

### Strengths

We applied a multitude of sensitivity analyses with consistent results. We benefitted from a very large community sample of a well-characterized middle aged to older adults living in a region of the US where air pollution levels are mostly below air quality standards. Arterial stiffness was measured using multiple methods following a rigorous protocol. In addition, we studied the associations of both short-term and long-term air pollution exposures in the

same sample, allowing us to study both functional and structural changes in arterial stiffness in the same population.

## Conclusions

In conclusion, we observed that living closer to a major roadway was associated with higher arterial stiffness, indicating possible harmful effects of traffic-related exposure on vascular function in this generally healthy cohort of adults. However, the lack of associations between long-term exposure to PM<sub>2.5</sub> and arterial stiffness suggest the associations may be driven by the mixture of pollutants in close proximity to major roads, rather than PM<sub>2.5</sub>, or possibly by unmeasured effects from traffic-noise. Furthermore, in contrast to some previous studies, we did not observe higher arterial stiffness in association with short-term exposures to air pollution.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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GFM is owner and of Cardiovascular Engineering Inc., a company that develops and manufactures devices to measure vascular stiffness, and serves as a consultant to and receives honoraria from Merck and Novartis.

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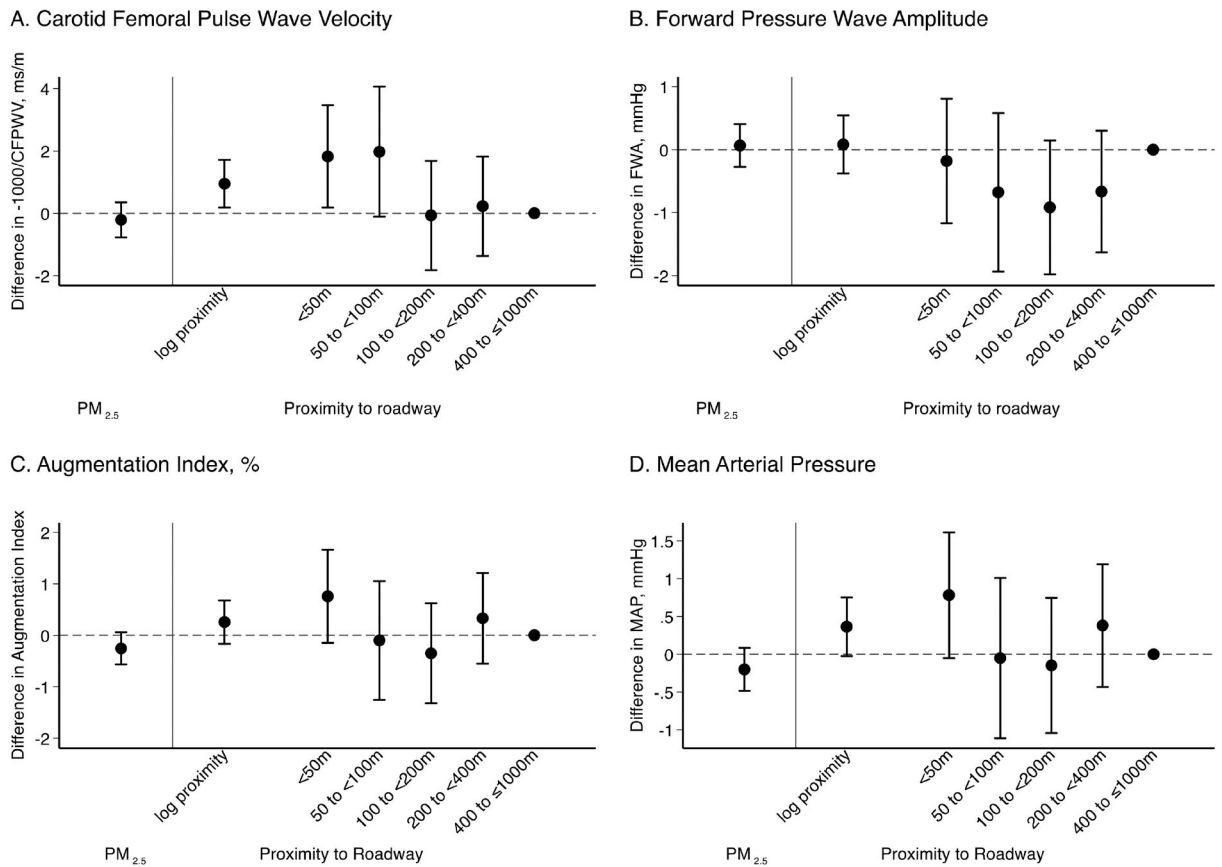
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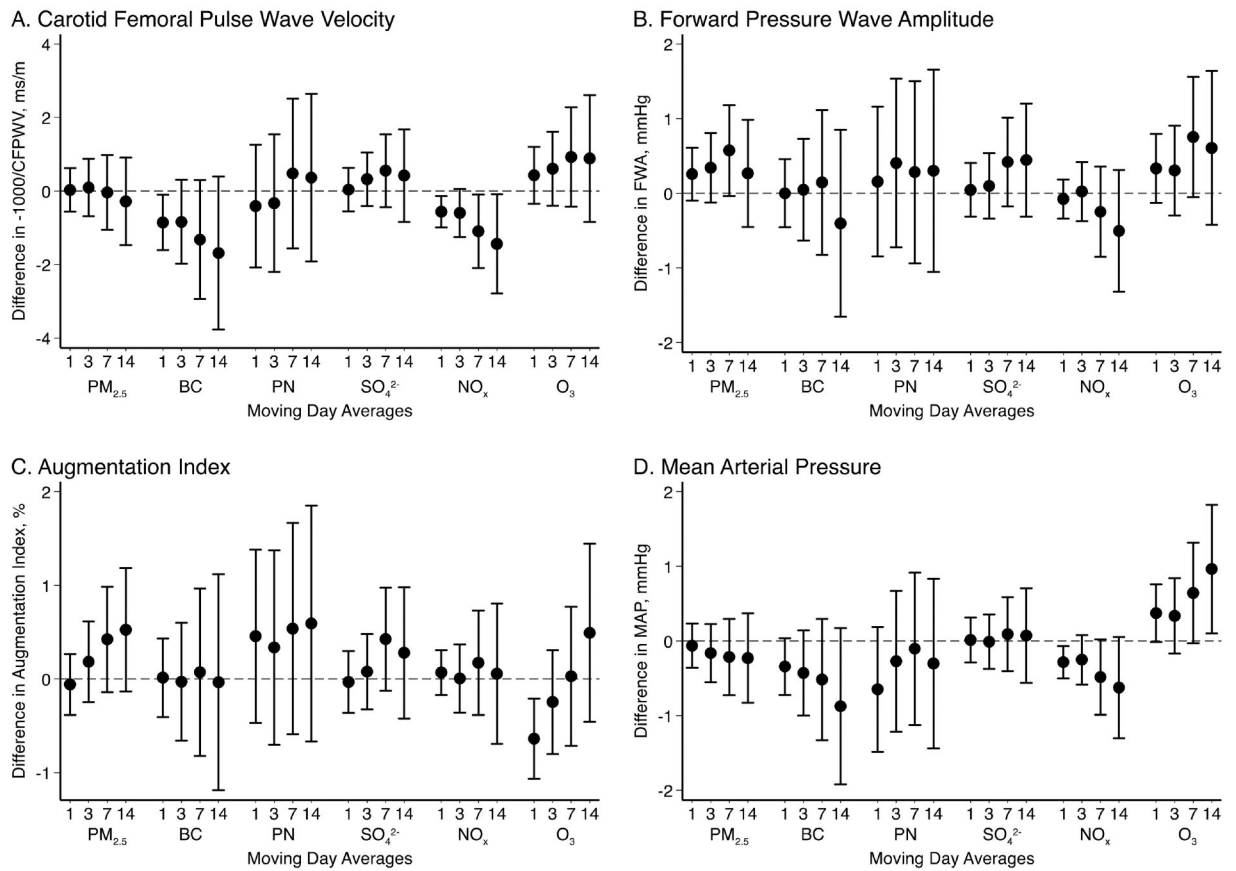
### Highlights

- Living nearby a major road was associated with higher arterial stiffness
- Particle matter measured by satellite was not associated with arterial stiffness
- No associations were observed for short-term exposure to air pollution



**Figure 1.**

Long-term PM<sub>2.5</sub> exposure at residential address in 2003 and residential proximity to major roadway and measures of arterial stiffness. Associations with arterial stiffness measures were scaled to the interquartile range in 2003 (1.46  $\mu\text{g}/\text{m}^3$ ) of PM<sub>2.5</sub>, 75<sup>th</sup> (400 m) to the 25<sup>th</sup> (50 m) centile of the log-transformed residential proximity to a major roadway and as categorical variable for residential proximity to major roadway using the residences between 400 m and less than or equal to 1000 m as the reference category.

**Figure 2.**

Short-term exposures to air pollution and measures of arterial stiffness. Associations expressed as a change in unit of outcome per  $5 \mu\text{g}/\text{m}^3$  PM<sub>2.5</sub>,  $0.4 \mu\text{g}/\text{m}^3$  black carbon (BC),  $15000 \text{ particles}/\text{cm}^3$  (PN),  $2 \mu\text{g}/\text{m}^3$  sulfate (SO<sub>4</sub><sup>2-</sup>)  $0.01$  parts per million nitrogen oxides (NO<sub>x</sub>), and  $0.01$  parts per million ozone (O<sub>3</sub>).

**Table 1.**

Characteristics of Study Participants, N=5,842

	Mean or N		SD or (%)
Age at exam, years	51	±	16
Women, %	3,170		54
Offspring Cohort, %	2,424		41
Body Mass Index, kg/m <sup>2</sup>	28	±	6
Triglycerides, mg/dl	117		82
Total cholesterol/HDL ratio	3.7	±	1.3
Heart rate, beats/min	62	±	10
Diabetes Mellitus, %	490		8
Current smokers, %	830		14
Former Smokers, %	2,164		37
Pack-years of smoking			
Current Smokers	28	±	17
Former Smokers	18	±	19
Education			
Some College, %	1,883		32
College Graduate, %	2,608		45
Census-tract Median Household income, USD	64,534	±	20,769
Census-tract Median Value of Owner-Occupied Housing units, USD	220,221	±	101,841

**Table 2.**

Distributions of measures of arterial stiffness

Measure of arterial stiffness	N	Mean	Median	Standard deviation	Interquartile Range
CFPWV*, m/s	5,598	8.5	7.6	3.2	2.9
-1000/CFPW, ms/m	5,598	-129.7	-131.6	34.7	47.5
Augmentation index, %	5,842	10.7	11.7	14.3	16.2
Forward Pulse Pressure	5,761	50.0	46.9	15.1	18.0
Amplitude, mmHg	5,842	93.3	92.0	12.3	17.0
Mean Arterial Pressure, mmHg					

\* CFPWV, Carotid Femoral Pulse Wave Velocity

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**Table 3.**Distributions of PM<sub>2.5</sub> and Proximity to a Major Roadway

	Median (IQR) or n [%]	Range (min, max)	Range (5 <sup>th</sup> to 95 <sup>th</sup> )
2003 Annual average PM <sub>2.5</sub> , µg/m <sup>3</sup>	10.7 (1.5)	2.9–26.7	8.3–12.7
Proximity to Major Roadway, m	195.4 (342.8)	0.01–999.7	7.1–804.9
Residential Proximity in Categories, m			
<50	1186 [23]		
50 to <100	541 [10]		
100 to <200	912 [18]		
200 to <400	1252 [24]		
400 to 1000	1316 [25]		
Preceding Day PM <sub>2.5</sub> , µg/m <sup>3</sup> * (n=3,921)	8.3 (6.2)	0.9–75.9	3.5–21.1
Preceding Day Black Carbon, µg/m <sup>3</sup> * (n=3,923)	0.6 (0.5)	0.1–4.2	0.3–1.5
Preceding Day Particle Number, particles/cm <sup>3</sup> * (n=3,499)	19,234 (15,000)	3,791–63,866	7,983–40,771
Preceding Day Sulfate, µg/m <sup>3</sup> * (n=3,589)	2.4 (2.5)	0.002–27.9	0.9–8.6
Preceding Day NOx, ppm * (n=3,927)	0.03 (0.02)	0.006–0.17	0.02–0.07
Preceding Day Ozone, ppm * (n=3,927)	0.02 (0.02)	0.001–0.09	0.01–0.05
Preceding Day Temperature, °C	10.5 (15.2)	–18.3–31.0	–5.1–25.0
Preceding Day Relative Humidity, %	66 (26)	21–99	40–92

\* For subpopulation living within 50 km from the central site monitor with non-missing pollutant data for days preceding examination cycle.

**Table 4.**

Daily Spearman's Rank Correlation Coefficients for Pollutants

Pollutant	PM <sub>2.5</sub>	Black Carbon	Particle Number	Sulfate	Nitrogen oxides	Ozone
PM <sub>2.5</sub>	1.00					
Black Carbon	0.71	1.00				
Particle Number	-0.19	0.18	1.00			
Sulfate	0.85	0.59	-0.17	1.00		
Nitrogen Oxides	0.37	0.48	0.41	0.27	1.00	
Ozone	0.06	-0.19	-0.29	0.16	-0.57	1.00

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