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Relation of Long-term Exposure to Air Pollution to Brachial Artery Flow-Mediated Dilation and Reactive Hyperemia

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Abstract

Long-term exposure to ambient air pollution has been associated with cardiovascular morbidity and mortality. Impaired vascular responses may in part explain these findings, but the association of such long-term exposure with measures of both conduit artery and microvascular function have not been widely reported. We evaluated the association between residential proximity to a major roadway (primary or secondary highway) and spatially resolved average fine particulate matter (PM_{2.5}) and baseline brachial artery diameter and mean flow velocity, flow mediated dilation % and hyperemic flow velocity, in the Framingham Offspring and Third Generation Cohorts. We examined 5,112 participants (2,731 (53%) women, mean age 49±14 years). Spatially resolved average PM_{2.5} was associated with lower flow mediated dilation% and hyperemic flow velocity. An interquartile range difference in PM_{2.5} (1.99 µg/m³) was associated with −0.16% (95%CI:

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–0.27%, –0.05%) lower FMD% and –0.72 (95%CI: –1.38, –0.06) cm/s lower hyperemic flow velocity %. Residential proximity to a major roadway was negatively associated with flow mediated dilation %. Compared to living 400 m away, living <50 m from a major roadway was associated with 0.32% lower flow mediated dilation (95% confidence interval (CI): –0.58%, –0.06%), but results for hyperemic flow velocity had wide confidence intervals –0.68 cm/s (95%CI: –2.29, 0.93). In conclusion, residential proximity to a major roadway and higher levels of spatially resolved estimates of PM_{2.5} at participant residences are associated with impaired conduit artery and microvascular function in this large community-based cohort of middle-aged and elderly adults.

Keywords

Air Pollution; Brachial Artery; Microvessels; Endothelium; Vascular

INTRODUCTION

Flow-mediated dilation (FMD) of the brachial artery is a noninvasive measure of large conduit artery function that is a predictor of cardiovascular events.^{1,2} Literature describing the effects of ambient pollutants on FMD is limited, but a few small studies, in controlled settings or in susceptible populations, have examined short-term exposure to air pollution and have observed mixed results.^{3–6} A recent study reported an association between long-term exposures to ambient PM_{2.5} and impaired conduit artery function as indicated by lower brachial artery FMD%.⁷ Evidence also suggests that long-term exposure to higher levels of PM_{2.5} may be associated with damage to the microvasculature, including reduced retinal vessel diameter.⁸ However, studies of the long-term implications of residential exposure to ambient pollution on vascular measures remain limited, particularly at lower levels of PM_{2.5} and little is known about associations with microvessel vasodilator function. We hypothesized that residential proximity to major roadways and long-term exposure to spatially resolved average PM_{2.5} in an urban and suburban region with relatively low levels that are in compliance with contemporary regulatory limits would be associated with impaired conduit artery and microvascular function. We examined associations between residential proximity to major roadways and spatially resolved average PM_{2.5} at the home address of participants in the Framingham Offspring and Third Generation cohorts who underwent measures of brachial function and hyperemic flow velocity.

METHODS

The design of the Framingham Offspring Study and Third Generation Studies has been described in detail elsewhere.^{9,10} Participants who attended Examination 7 of the Offspring Study (1998–2001) or Examination 1 of the Third Generation study (2002–2005) and also completed the brachial examination were eligible for inclusion in this analysis. All participants provided written informed consent for the Framingham Heart Study examinations, and both the Committee on Clinical Investigation at Beth Israel Deaconess Medical Center and the Institutional review board at the Boston Medical Center approved the study protocol. There were 5,719 participants for whom residential proximity to roadway

and PM_{2.5} data were available. We then excluded 37 addresses identified as zip-code centroid or street midpoint and 570 participants who smoked within six hours of the examination, leaving a total of 5,112 eligible participants, 2,828 of whom were participants in the Third Generation study (55%). Participant primary addresses were geocoded using ArcGIS 10 (ESRI, Redlands, CA).

Neighborhood-level socioeconomic characteristics, including median household income was assigned at the census tract level from US Census 2000 data. Distance to nearest major road was determined by residential proximity to the nearest A1, A2, or A3 road (US Census Features Class) at the time of the brachial examination (Offspring Examination 7, Third Generation Examination 1). Based on previous work showing that particle levels diminish to background levels 100 to 300 meters from major roads¹¹ we first examined associations using categories of distance: <50 m, 50 to <100 m, 100 to <200 m, 200 to <400 m, and 400 to <1000 m. These categories were selected a priori to reflect the decay function of traffic pollution and noise as proximity to roadway decreases to background levels. We also tested the natural logarithm of the proximity to a major roadway and brachial function because it is associated linearly with mortality.¹² Participants living further than 1,000 m from a major road in rural areas beyond background were excluded from the roadway analyses (530 participants, 10%).

Our approach utilizes Moderate Resolution Imaging Spectroradiometer (MODIS) satellite-derived Aerosol Optical Density (AOD) measurements to predict daily PM_{2.5} concentration levels at a 10 × 10 km spatial resolution across New England. Starting in 2000, AOD was calibrated daily using ground PM_{2.5} measurements from 78 monitoring stations, land use regression and meteorological variables (temperature, wind speed, visibility, elevation, distance to major roads, percent of open space, point emissions and area emissions). To estimate PM_{2.5} daily concentrations in each grid cell, we first calibrated the AOD – PM_{2.5} relationship with data from grid cells including both monitor and AOD values by using mixed models with random slopes for day and nested regions. Next, we estimated exposures on days when AOD measures were not available (due to cloud coverage or snow, for example). A model was fit with a smooth function of latitude and longitude and a random intercept for each cell that takes advantage of associations between grid cell AOD values and PM_{2.5} data from monitors located elsewhere and associations with available AOD values in neighboring grid cells. We averaged each daily concentration for the year 2001 in the 10×10 km grid cell for each home address. The year 2001 was selected because it falls between the Offspring Cycle 7 (1998-2001) and Third Generation Examination 1 (2002-2005) data collection and complete data were available. The first model calibrations resulted in high out-of-sample 10-fold cross-validated R² (mean out-of-sample R²= 0.83). Even with days without any AOD data, our model presented extremely high fits (R²=0.81). We also evaluated the spatial and temporal components of the model separately, which also resulted in very high fits (R² of spatial component=0.78 and temporal component=0.84). We then used local land use terms (distance to primary highways, distance to point source emissions, population density, percent open spaces, elevation, and traffic density) to model the difference between the 10×10 km grid cell predictions and monitored values. We regressed the residuals for each monitor against local land use characteristics for each monitor and a smooth function of traffic density. The sum of the grid cell predictions and

residuals from the land use model represents a measure of total PM_{2.5} at a specific location within a 50×50 m grid. This further increased the overall model R² by 1.9%.

Fasting brachial artery tracings were measured by one of three experienced sonographers following rigorous standardized protocols¹³ and were acquired for participants in Framingham Offspring Examination 7 and Third Generation Examination 1. Baseline diameter, FMD % (percent change in diameter from baseline), baseline mean flow velocity and mean hyperemic flow velocity were determined as the outcomes of interest. Hyperemic flow velocity was assessed using mid-artery pulse Doppler signal. FMD % and reactive hyperemia as measured by hyperemic flow velocity may reflect, in part, decreased endothelial-dependent vasodilation mediated by NO in the conduit and forearm microvessels respectively.¹⁴

Investigators measured brachial artery diameter at baseline and one minute after reactive hyperemia induced by 5-minute forearm cuff occlusion using commercially available software (Brachial Analyzer v. 3.2.3, Medical Imaging Applications). Doppler flow was assessed at baseline and during reactive hyperemia. Mean baseline and hyperemic flow velocities were analyzed from digitized audio data with semi-automated signal averaging (Cardiovascular Engineering). Reproducibility of the approach is extremely high and has been described elsewhere.^{13,15} Flow measurements were available for a subset of participants because measures began after the Offspring 7th Examination cycle had started. Of the 5,112 eligible participants, there were 498 Offspring participants (22%) in whom flow was not measured and 79 (3%) missing flow data in the Third Generation cohort.

History of cardiovascular disease (coronary heart disease, intermittent leg claudication, heart failure or stroke or transient ischemic attack) was determined by a panel of 3 investigators using previously published criteria.¹⁶ At Examination 7, participants were asked about anti-hypertension and lipid-lowering medication, and post-menopausal hormone use. In the Third Generation Examination 1, participants brought their medications and these were coded according to their World Health Organization anatomical therapeutic chemical (ATC) codes. We used the ATC codes to classify anti-hypertensive, lipid-lowering drugs and post-menopausal hormone use. Prevalent diabetes was defined as having a fasting glucose ≥126 mg/dL or oral hypoglycemic or insulin use at an examination or any previous history of diabetes (excluding gestational diabetes). Systolic and diastolic seated blood pressures were calculated as the mean of 2 measurements taken by the physician administering the clinical exam.

Linear regression was used to evaluate associations between ambient pollutants (near roadway measures and PM_{2.5}) and brachial measures (baseline brachial diameter (mm), FMD (%), baseline mean flow velocity (cm/s) and hyperemic flow velocity (cm/s)). Associations were first modeled using a parsimonious approach (Model 1) adjusting for age, age², sex, body mass index, individual level education (No high school diploma, high school degree, some college, technical school or associate's degree and bachelor's degree or higher), date of examination, median household income from 2000 census tract (quartiles), cohort (Offspring or Third Generation), smoking status and seasonality (sine and cosine of day of year). We next adjusted for additional covariates that have been associated with

brachial measures in previous studies of this sample.^{13,17} Model 2 covariates added to those included in Model 1 were: walk test administered before brachial examination, history of diabetes, lipid-lowering medications, anti-hypertensive medications, current post-menopausal hormone use, a history of cardiovascular disease, systolic blood pressure, diastolic blood pressure, heart rate, triglycerides and total cholesterol/HDL ratio. We then evaluated the linearity of exposure response relationships for the log of distance to roadway and PM_{2.5} measures using restricted cubic splines with knots at the 5, 27.5, 50, 72.5 and 95 percentiles of the distribution.

We hypothesized that associations between exposure to ambient air pollution and vascular function may differ by factors related to sex, history of diabetes, current smoking status, and age > 65 years (n=776) and median household income at the census tract level below the first quartile (\$48,973). We therefore, tested for statistical interaction using cross-product terms and determined statistical significance from the p-value from the Wald test of the cross-product. We also hypothesized that regular use of vasoactive medication would alter the association between long-term exposure to ambient air pollution and vascular response; therefore, we evaluated stratification by use of anti-hypertensive and statin drug use.

We performed several sensitivity analyses. Two outliers were identified in the distribution of PM_{2.5} exposures ($> 19 \mu\text{g}/\text{m}^3$) and analyses were conducted excluding these observations. We also analyzed the associations with PM_{2.5} among participants who lived within 1000m of a major road. Previous studies have used different approaches to account for the fact that FMD is calculated as a ratio, and the denominator (baseline brachial artery diameter) may be associated with air pollution exposure.^{3,7} We therefore adjusted our FMD % results first by hyperemic flow velocity and then by 1/baseline diameter. To account for potential clustering of the observed brachial outcomes by neighborhood-level characteristics, analyses were also conducted using generalized estimating equations with exchangeable covariance structure to examine the associations after accounting for census tract.

For models in which we examined residential proximity to roadway in five categories, tests for linear trends were performed by assigning each exposure category the natural log of the median distance within each category and including the term as a continuous variable in the regression model. The p-value obtained represents the log-linear component of trend (p-trend). We present the results of log-linear residential proximity to major roadway analyses by contrasting participants who live 50 m from the nearest major roadway to those living 400 m away from the nearest major road to reflect the mean adjusted difference in brachial measures between participants likely to have high levels of exposure to traffic-related pollution versus those exposed to near-background levels. This calculation was performed by scaling the beta coefficient such that $\ln(400 \text{ m}) * \beta - \ln(50 \text{ m}) * \beta = \ln(400/50) * \beta$, where β denotes the beta coefficient from the linear regression model treating log of distance to roadway as a linear continuous variable. Results for models of PM_{2.5} are scaled to an interquartile range (IQR) for the observed distribution in our data. All analyses were conducted in Stata v.12 (Statacorp, College Station, TX) and R 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria, MGCv, 1.7-22). Plots were created using the POSTRCSPLINE package in Stata.¹⁸ All statistical tests were two-sided and p<0.05 was considered statistically significant.

RESULTS

Participant characteristics are described in Table 1. Among participants who reported their race (n=4,790), there were 17 participants who reported a race other than white (<1%). When compared to other participants, participants who in whom hyperemic flow was not measured did not differ by age, blood pressure, prevalence of diabetes mellitus, baseline diameter or FMD %. The exposure distribution is summarized in Table 2. Analyses examining residential proximity to a major roadway as the exposure of interest excluded participants living greater than 1,000 m from a major road (530 participants, 10%).

Neither residential proximity to a major roadway nor PM_{2.5} was associated with baseline brachial diameter or mean flow velocity. Associations with categories of distance to roadway showed no consistent pattern (Table 3). We observed consistent associations between PM_{2.5} and both FMD % and hyperemic flow velocity. We also observed log-linear associations between residential proximity to a major roadway and FMD % (Table 4).

Upon examination of the exposure-response relationships for FMD % and hyperemic flow velocity, we observed no evidence of departure from linearity (Figure). In multivariable-adjusted models, living at a location with higher PM_{2.5} was associated with both impaired FMD % and hyperemic flow velocity. In plots of residential proximity to a major road, a steeper slope was observed for FMD % than for hyperemic flow velocity, which was consistent with the findings from our analyses that examined the log-linear association and trend tests.

There was no evidence of differences in the observed associations between proximity to roadway or PM_{2.5} and FMD % or hyperemic flow velocity according to sex, diabetes, age>65 years, current smoking status or median income of the participants' census tract. There were also no differences when we stratified by antihypertensive and lipid-lowering medication use. Results were not materially altered when we excluded the two outliers from the PM_{2.5} distribution or restricted our PM_{2.5} analyses to people living within 1000 m of a major road; when we adjusted for hyperemic flow velocity or 1/baseline brachial diameter; or when we analyzed the data accounting for clustering by census tract using generalized estimating equations.

DISCUSSION

In this community-based study of individuals residing in urban and suburban areas who were exposed to relatively low levels of particulate air pollution within contemporary regulated limits, we observed that both residential proximity to a major roadway and long-term estimated exposure to PM_{2.5} were associated with impaired FMD %, a measure of conduit artery function. PM_{2.5} was also associated with poorer microvascular function as assessed by hyperemic flow velocity. Our results suggest that long-term exposure to particulate and traffic-related sources of air pollution are associated with subclinical changes that adversely affect the conduit artery and may also impair microvascular function. The associations that we observed for FMD % were not attenuated when we adjusted for baseline diameter or hyperemic flow velocity, and did not differ substantially across

potentially susceptible or vulnerable subgroups. Though the magnitude of the effect sizes that we observed for FMD % were small on the absolute scale, the association between living within 50 m of a major road and FMD % was similar in magnitude to 10 mm Hg higher systolic blood pressure in a previous study of the Framingham Offspring participants.¹³

Our results are consistent with the one previously published study of the association between long-term exposure to air pollution and brachial function.⁷ Most previous studies of ambient air pollution exposures and FMD have focused on short-term effects. Controlled human studies have shown associations between exposure to diesel or concentrated ambient particles and ozone with smaller baseline brachial diameter,^{3,4,6} but no difference in FMD.

Flow velocity measured in the brachial artery is in part determined by downstream resistance, which is regulated by microvascular function. To our knowledge, no prior published studies have evaluated long-term exposure to air pollution and measures of hyperemic flow velocity. A previous study examined pollutant levels on the day of and five days preceding brachial artery testing and found that gaseous pollutants were associated with impaired flow-mediated brachial artery dilation, while PM_{2.5}, PM₁₀, and NO₂ were associated with small artery reactive hyperemia after hand ischemia.¹⁹ In our study, consistent negative associations were observed between PM_{2.5} and both FMD % and hyperemic flow velocity. Differences in time windows of exposure assessed, brachial testing protocols, age and sex of participants could play a role explaining these findings. One study reported no association between short-term exposure to secondhand smoke and microvascular endothelial-dependent vasodilation,²⁰ but others have reported narrower retinal diameter, a measure of microvascular function, with short-and long-term exposures.^{8,21} Animal models suggest that inhalation of nanoparticles is associated with lower NO bioavailability in the microvasculature, and higher levels of reactive oxygen and nitrogen species.²² However, the mechanisms for associations between long-term exposures to ambient air pollution and hyperemic flow velocity are still not well understood.

The patterns in associations that we observed across the two hyperemic response outcomes were generally similar for both PM_{2.5} and residential proximity to a major road. Though the association between residential proximity to a major road and FMD % showed that living 50 m away was associated with poorer response than living 400 m away, the association with hyperemic flow velocity was not statistically significant. We hypothesized that this could be due to differences in the features of long-term exposure to air pollution captured by these two approaches. Residential proximity to a major roadway is an integrated measure that is correlated with higher levels of traffic-related particulate air pollution and ultrafine particles, but this measure does not account for the intensity of traffic at a given location or meteorology. In contrast, our modeled PM_{2.5} exposure data takes both locally and regionally-generated sources into account, including traffic density, elevation, and other land use, which may in part explain narrower confidence intervals observed. Further work is needed to elucidate the underlying biology of the effects of near roadway exposures and PM_{2.5} mass composition on microvascular function and to evaluate differences in biological mechanisms related to the sources and composition of exposure. It is also possible that differences are due to more limited power resulting from a smaller sample size, because

evaluation of hyperemic flow velocity began after the start of Examination 7 and, therefore, data were not collected on 22% of Offspring participants or because analyses of residential proximity to a major road were restricted to participants living within 1000 m of a major road, although, restricting our PM_{2.5} analyses to this region did not materially change our results.

Our study has several limitations. Although we accounted for individual level and area-level characteristics of education and median household income, we cannot exclude possible residual confounding by socioeconomic or other characteristics. However, the results from our analysis which took spatial clustering by census tract into account were similar to those from the multivariable-adjusted results and are supported by a recent study that showed that correlations between socioeconomic position and PM_{2.5} exposures are low within urban areas.²³ We do not have data on time activity patterns reflective of microenvironments, which may have led to exposure misclassification, potentially biasing results towards the null. Because our study was performed with community-based volunteers, it would not have been appropriate to administer an NO donor as previous smaller, clinic-based studies have done, and we cannot distinguish between endothelium dependent and independent mechanisms. Also, we did not withhold medications that act upon the cardiovascular system prior to the brachial examination, although we note that similar results were observed when we restricted to those participants not using statins and antihypertensive medications and data suggest that there are no major differences in brachial reactivity measures after acutely withholding non-nitrate vasoactive medications in subjects taking these medications long-term.²⁴ Our study did not include repeated measures from study participants; therefore we cannot infer causality. Our PM_{2.5} data are based on an average for the year 2001 as a surrogate for long term exposure. Using a one year average of long-term exposure is an approach that has been used in other cohort studies.^{7,25} This approach limits the influence of secular trends in exposure while capturing the rank ordering of the spatial distribution of average PM_{2.5} level at the residence of study participants. Finally, these results may not be generalizable to other populations and people living in other geographic areas.

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Figure 1. Associations between distance to major road and PM_{2.5} with FMD and Hyperemic Flow Velocity using restricted cubic splines (knots=5)*

*Multivariable-adjusted associations between the natural logarithm of distance from a major road and PM_{2.5} and measures of flow-mediated dilation and hyperemic flow velocity. Models were adjusted for all Model 2 covariates (see text). There were no substantial deviations from linearity for the associations evaluated.

Table 1

Characteristics of Study Participants

Clinical Characteristics	mean $\pm$ SD or n (%)
Age at Examination (years)	49 $\pm$ 14
Female	2731 (53%)
Body Mass Index (kg/m ²)	27.6 $\pm$ 5.4
Systolic Blood Pressure (mm Hg)	122 $\pm$ 17
Diastolic Blood Pressure (mm Hg)	75 $\pm$ 10
Heart rate (beats per minute)	63 $\pm$ 10
Triglycerides (mg/dL)	125 $\pm$ 92
Total cholesterol/HDL	3.9 $\pm$ 1.4
Diabetes Mellitus	360 (7%)
Hypertension medications	1062 (21%)
Lipid medications	724 (14%)
Post-menopausal hormone use	488 (10%)
Current Smokers	371 (7%)
Former Smokers	2124 (42%)
Education (Years)	
<High school degree	121 (2%)
High school degree	1063 (21%)
12-some college, technical school or associate's degree	1584 (31%)
+ bachelor's degree or higher	2294 (45%)
Missing	50 (1%)
Third Generation	2828 (55%)
Vascular Measures	
Baseline Brachial Diameter (mm)	4.2 $\pm$ 0.9
Flow-mediated Dilation (%)	4.5 $\pm$ 3.6
Baseline Mean Flow, cm/s	7.5 $\pm$ 4.3
Hyperemic Mean Flow, cm/s	57.2 $\pm$ 20.4

Table 2

Distributions of Fine Particulate Matter Exposures and Proximity to Roadway Measures

Exposure	Median (IQR) or n (%)	Range
Proximity to Major Roadway (m) *	197 (346)	0.05--999.7
Fine Particulate Matter ($\mu\text{g}/\text{m}^3$)	10.9 (1.99)	7.3--21.7
Residential Proximity in Categories (meters)		
<50	1034 (20%)	
50-<100	463 (9%)	
100-<200	816 (16%)	
200-400	1088 (21%)	
400-1000	1181 (23%)	
>1000 *	530 (10%)	

IQR indicates Interquartile Range;

* 530 (10%) excluded because analyses were restricted major road.

Table 3

Baseline - Long term exposures to ambient air pollution and measures of baseline brachial diameter and baseline mean flow (cm/s).

	Model 1 [*]			Model 2 [†]		
	estimate	95%CI	p-value	estimate	95%CI	p-value
Baseline Brachial Diameter (mm) [‡]						
Categories of Residential Proximity to major road						
<50m	0.02	[-0.02, 0.07]	0.42	0.03	[-0.02, 0.07]	0.38
50 to <100m	0.09	[0.03, 0.15]		0.09	[0.03, 0.15]	
100 to <200m	0.01	[-0.03, 0.06]		0.02	[-0.03, 0.07]	
200 to <400m	0.05	[0.01, 0.09]		0.05	[0.01, 0.10]	
Distance 400m	--	--	--	--	--	--
Log of Distance to Major Road (m) [§]	-0.01	[-0.03, 0.01]	0.38	-0.01	[-0.03, 0.01]	0.34
PM _{2.5} (µg/m ³)	0.01	[-0.01, 0.03]	0.25	0.01	[-0.01, 0.03]	0.25
Baseline Flow (cm/s) [¶]						
Categories of Residential Proximity to major road						
<50m	-0.05	[-0.42, 0.32]	0.94	-0.07	[-0.43, 0.29]	0.94
50 to <100m	-0.06	[-0.53, 0.42]		-0.03	[-0.50, 0.44]	
100 to <200m	0.10	[-0.30, 0.49]		0.06	[-0.33, 0.45]	
200 to <400m	-0.14	[-0.50, 0.23]		-0.17	[-0.53, 0.18]	
Distance 400m	--	--	--	--	--	--
Log of Distance to Major Road (m) [§]	0.01	[-0.16, 0.19]	0.87	0.02	[-0.15, 0.20]	0.78
PM _{2.5} (µg/m ³)	-0.03	[-0.18, 0.12]	0.72	-0.03	[-0.17, 0.12]	0.73

^{*} Adjusted for age, age², BMI, sex, cohort, smoking status (never, former, current), date of examination, individual level education (No high school diploma, high school degree, some college, technical school or associate's degree and bachelor's degree or higher), median household income (quartiles), sine and cosine of season.

[†] Adjusted for model 1 variables and walk test administered before brachial examination, history of diabetes, lipid-lowering medications, anti-hypertensive medications current estrogen use, a history of cardiovascular disease, systolic blood pressure, diastolic blood pressure, heart rate, triglycerides and total cholesterol/HDL ratio.

[‡] Model 1 results include 4,574 observations for distance to roadway analyses and 5,104 for PM_{2.5}. Model 2 results include 4,557 observations for distance to roadway and 5,083 for PM_{2.5}.

[§] Natural Logarithm of proximity to a major road scaled to the difference between living 50m to the living 400 m away.

^{||} PM_{2.5} scaled to IQR (1.99 µg/m³)

[¶] Model 1 results include 4,036 observations for distance to roadway analyses and 4,528 for PM_{2.5}. Model 2 results include 4,020 observations for distance to roadway and 4,508 for PM_{2.5}.

Table 4

Hyperemic Response – Long term exposures to ambient air pollution and measures of FMD (%) and hyperemic flow velocity (cm/s).

		Model 1 [*]			Model 2 [†]		
	estimate	95%CI	p-value	estimate	95%CI	p-value	
Flow-Mediated Dilation							
(%)[‡]							
Categories of Residential Proximity to major road							
<50m	−0.34	[−0.60, −0.08]	0.01	−0.32	[−0.58, −0.06]	0.01	
50 to <100m	−0.33	[−0.67, 0.00]		−0.28	[−0.61, 0.05]		
100 to <200m	−0.02	[−0.30, 0.26]		−0.004	[−0.27, 0.28]		
200 to <400m	−0.23	[−0.48, 0.03]		−0.16	[−0.41, 0.09]		
Distance 400m	--	--	--	--	--		
Log of Distance to Major Road [§]	0.15	[0.02 0.27]	0.02	0.15	[0.02 0.27]	0.02	
PM _{2.5} (μg/m ³)	−0.16	[−0.27, −0.05]	0.003	−0.16	[−0.27, −0.05]	0.004	
Hyperemic Flow Velocity							
(cm/s)[¶]							
Categories of Residential Proximity to major road							
<50m	−0.81	[−2.44, 0.82]	0.14	−0.68	[−2.29 0.93]	0.14	
50 to <100m	−1.25	[−3.34, 0.84]		−1.02	[−3.08, 1.05]		
100 to <200m	0.34	[−1.41, 2.08]		0.44	[−1.28, 2.16]		
200 to <400m	0.53	[−1.07, 2.12]		0.88	[−0.70, 2.46]		
Distance 400m	--	--	--	--	--		
Log of Distance to Major Road [§]	0.56	[−0.21, 1.33]	0.15	0.59	[−0.17, 1.36]	0.13	
PM _{2.5}	−0.79	[−1.46, −0.12]	0.02	−0.72	[−1.38, −0.06]	0.03	

^{*} Adjusted for age, age², BMI, sex, cohort, smoking status (never, former, current), date of examination, individual level education (No high school diploma, high school degree, some college, technical school or associate's degree and bachelor's degree or higher), median household income (quartiles), sine and cosine of season

[†] Adjusted for model 1 variables and walk test administered before brachial examination, history of diabetes, lipid-lowering medications, anti-hypertensive medications current estrogen use, a history of cardiovascular disease, systolic blood pressure, diastolic blood pressure, heart rate, triglycerides and total cholesterol/HDL ratio.

[‡] Model 1 results include 4,574 observations for distance to roadway analyses and 5,104 for PM_{2.5}. Model 2 results include 4,557 observations for distance to roadway and 5,083 for PM_{2.5}.

[§] Natural Logarithm of proximity to a major road scaled to the difference between living 50m to the living 400m away.

^{||} PM_{2.5} scaled to IQR (1.99 μg/m³)

[¶] Model 1 results include 4,036 observations for distance to roadway analyses and 4,528 for PM_{2.5}. Model 2 results include 4,020 observations for distance to roadway and 4,508 for PM_{2.5}.