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Fine Particulate Matter, Residential Proximity to Major Roads, and Markers of Small Vessel Disease in a Memory Study Population

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Abstract

Background—Long-term exposure to ambient air pollution has been associated with impaired cognitive function and vascular disease in older adults, but little is known about these associations among people with concerns about memory loss.

Objective—To examine associations between exposures to fine particulate matter and residential proximity to major roads and markers of small vessel disease.

Methods—From 2004–2010, 236 participants in the Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort participated in neuroimaging studies. Residential proximity to major roads and estimated 2003 residential annual average of fine particulate air pollution (PM_{2.5}) were linked to measures of brain parenchymal fraction (BPF), white matter hyperintensities (WMH), and cerebral microbleeds. Associations were modeled using linear and logistic regression and adjusted for clinical and lifestyle factors.

Results—In this population (median age [interquartile range]=74[12], 57% female) living in a region with median 2003 PM_{2.5} annual average below the current Environmental Protection Agency (EPA) standard, there were no associations between living closer to a major roadway or for a 2 µg/m³ increment in PM_{2.5} and smaller BPF, greater WMH volume, or a higher odds of microbleeds. However, a 2 µg/m³ increment in PM_{2.5} was associated with –0.19 (95% Confidence Interval (CI): –0.37, –0.005) lower natural log-transformed WMH volume. Other associations had wide confidence intervals.

Conclusions—In this population, where median 2003 estimated PM_{2.5} levels were below the current EPA standard, we observed no pattern of association between residential proximity to major roads or 2003 average PM_{2.5} and greater burden of small vessel disease or neurodegeneration.

Keywords

Air pollution; small vessel disease; white matter hyperintensities; microbleeds

Introduction

Cerebrovascular small vessel disease has been identified as an important contributor to vascular-related cognitive impairment [1]. Evidence suggests that pathological changes involving small arteries, arterioles and veins including infarcts, white matter lesions, hemorrhages, and microbleeds are common in aging populations and associated with poorer cognitive function [2–4] and they are often observed in participants with dementia[5]. Although a number of lifestyle risk factors for early changes in cognitive function, which may precede clinical diagnosis, have been detected using neuroimaging [6–8], the role of environmental factors remains less well understood.

Ambient air pollution has been associated with cardiovascular morbidity and mortality [9] as well as a higher odds of cerebrovascular disease [10, 11] and cognitive impairment [12]. Studies have shown that long-term exposure to ambient air pollution is associated with a higher odds of developing dementia[13] and a higher rate of first hospital admission for dementia diagnosis[14]. Potential mechanisms for neurodegenerative effects have implicated inflammatory pathways and oxidative stress [15]. Evidence of direct neurotoxicity due to air pollution is more limited, but long-term exposures have been associated with smaller brain volume, especially white matter volume, and covert brain injuries [16, 17]. However, previous epidemiologic studies have focused on relatively healthy population-based samples. Whether air pollution is associated cerebrovascular changes among older people with dementia and concerns about their cognitive performance has not been investigated.

We hypothesized that patients who visit a memory clinic may be particularly susceptible to effects of air pollution on vascular and small vessel disease pathology. We therefore investigated the associations between a one year average of estimated exposure to ambient air pollution as a surrogate for long-term exposure to ambient air pollution and magnetic resonance imaging (MRI) markers of small vessel disease and neurodegeneration among participants in the Massachusetts Alzheimer's Disease Research Center (MADRC) Longitudinal Cohort in Boston, MA.

Materials and Methods

Study Population

Participants were enrolled in an ongoing longitudinal study at the MADRC, which is one of the 28 federally funded ADRCs across the United States that contributes to the National Alzheimer's Coordinating Center [18]. The longitudinal cohort that has enrolled cognitively

intact subjects, subjects with mild cognitive impairment (MCI), and subjects with dementia. All enrolled subjects signed a written informed consent. For this study, we included individuals with memory concerns (Clinical Dementia Rating (CDR) between 0 and 3) who had a complete structural MRI study of the brain in 2004 or later and a clinical evaluation performed within 1 year of the scan. We excluded patients with nonlacunar ischemic stroke or intracerebral hemorrhage (ICH) at the time of the scan because of the potential impact of these lesions on cognitive function trajectory. We also restricted to people with residential home addresses that could be geocoded. Our final analytic sample was comprised of 236 participants who resided in New England or New York. The Institutional Review Boards of Beth Israel Deaconess Medical Center and Massachusetts General Hospital have approved this study.

Exposure Assessment

Residential proximity to major roads—Participant primary addresses based on clinical records were geocoded using ArcGIS 10 (ESRI, Redlands, CA). Neighborhood-level socioeconomic characteristics, including median household income were assigned at the census block group level from US Census 2000 data. Distance to the nearest A1, A2, or A3 road (US Census Features Class) was determined for each subject home address at the time of the exam. We have previously observed that the natural logarithm of residential proximity to a major roadway and mortality and vascular function are linearly associated [19–22]. We therefore tested the natural log of proximity to a major roadway and measures of cognitive performance and neuroimaging. As in prior studies, participants living further than 1,000 m from a major road in rural areas beyond background were excluded from the roadway analyses[16, 21].

PM_{2.5} levels from a high-resolution spatial-temporal model—Residential PM_{2.5} exposures at home address were calculated using spatio-temporal modeled estimates. This approach incorporates the spatial resolution of land use regression models and the spatio-temporal resolution of satellite remote sensing [23]. A new Multi-Angle Implementation of Atmospheric Correction (MAIAC) code was used for processing Moderate Resolution Imaging Spectroradiometer (MODIS) aerosol optical density (AOD) measurements. Subsequently, these were used to predict PM_{2.5} levels at a spatial resolution of 1 × 1 km level [23] across the northeastern USA (New England, New York, and New Jersey) [24]. We first regressed ground PM_{2.5} measurements from 161 monitoring stations against the corresponding AOD values, adjusting for meteorological and land use regression variables (including temperature, wind speed, visibility, elevation, traffic density, population density, point emissions, area emissions and percentage of land use). The fit of this calibration model was used to predict daily PM_{2.5} concentrations in grid cells with available AOD measurements that were missing monitors. In order to estimate PM_{2.5} for cells with missing AOD measurements on a specific day, a model with a smooth function of latitude and longitude, the mean PM_{2.5} from monitors within 60 km of the cell, and a random intercept for each cell was used. For each monitoring site, residuals from this model were regressed against local spatial and temporal variables at each monitoring site. The fit of this final model was used to estimate daily-localized predictions for each residential address, which represent deviations from the 1 × 1 km grid predictions. To estimate annual average PM_{2.5},

we first summed the daily 1×1 km grid prediction and localized residual $PM_{2.5}$ prediction corresponding to each residential address location. We then averaged these daily total $PM_{2.5}$ predictions over the year. The first-stage calibration yielded excellent out-of-sample 10-fold cross-validated R^2 (mean out of sample $R^2 = 0.88$; year-to-year variation 0.82–0.90) values and a slope of observed versus predicted $PM_{2.5}$ of 0.99 (year-to-year variation 0.98–1.01) for the cross-validated results [24]. We selected the year 2003 for the annual average $PM_{2.5}$, because it is the first year for which data were available and this index year preceded all neuroimaging outcome data included in this study. A similar approach has been used in our prior work in FHS [16, 21] and in the Women's Health Initiative study of $PM_{2.5}$ and mortality [11].

$PM_{2.5}$ and proximity to roadway capture different features of long-term exposures to traffic. Residential proximity to a major road is an integrated exposure that includes noise and road dust and is correlated with higher traffic-related particulate air pollution and higher levels of ultrafine particles and gaseous air pollutants. However, this exposure metric does not account for traffic density and meteorological conditions. In contrast, the modeled $PM_{2.5}$ exposure reflects the actual particle levels, which are associated with local and regional air pollution sources [25].

Outcome Assessment

All neuroimaging data were collected at the Massachusetts General Hospital Athinoula A. Martinos Imaging Center on either a GE 1.5 Tesla Signa (General Electric Company, Fairfield, CT) or a Siemens 3 Tesla Trio whole-body scanner (Siemens Medical Systems, Iselin, NJ) with a TIM 12-channel matrix head coil that minimizes gradient distortions. We examined three outcomes: brain parenchymal fraction, a measure of brain atrophy which has also been associated with poorer cognitive function [26]; cerebral micro-bleeds, deposits of hemosiderin seen as focal lesions [27]; and white matter hyperintensities, which reflect ischemia and disruption of the blood-brain barrier [28].

The high-resolution scan includes sagittal T1-weighted images and axial T2-weighted, FLAIR, and gradient echo and SWI sequences [29]. Brain parenchymal fraction was quantified on T1-weighted images using FSL's FLIRT for image registration to an atlas brain (Montreal Neurological Institute 152), and subsequently the SIENAX processing stream, as previously described [29]. White matter was segmented on FLAIR images using a validated semi-automated procedure [30]. A region of interest map was generated using MRICro software (University of Nottingham School of Psychology, Nottingham, UK) and created by signal intensity thresholding and manual correction, if necessary. Normalization for head size was performed using a previously validated method [31]. Manual editing of white matter hyperintensity maps was performed by consensus of two experienced readers (ICC = 0.98). Cerebral microbleeds were identified as round foci ≤ 5 mm in diameter on gradient-echo images [27, 32–34]. Each lesion is marked electronically by a reader on the screen and all lesions are recorded for each exam [35] (ICC = 0.97) [34].

Statistical Analysis

White matter hyperintensity volumes were natural-log transformed to improve the normality of the distribution. We used linear regression to calculate beta coefficients and 95% CIs for the association between measures of ambient air pollution and brain parenchymal fraction (%) and the log of white matter hyperintensity volume (cc). We used logistic regression to calculate the odds ratios (ORs) and 95% CIs for the association between exposures and presence of microbleeds. We first modeled these associations adjusting for a basic set of covariates: age, age-squared, MRI date, sex, level of education (<16 years, 16 years or more, missing), quartiles of median household income, smoking status (current, former, never, or missing) and sine and cosine of season to account for seasonal trends (Model 1). We then further adjusted for additional covariates that could be potential mediators or confounders of the associations such as diagnoses (dementia or other), diabetes, statin use, hypertension, or stroke history not previously excluded (Model 2). We also performed stratified secondary analyses to evaluate associations among participants with a diagnosis of probable Alzheimer's disease separately from other study participants.

We conducted several sensitivity analyses to evaluate the robustness of our results. In primary models, we evaluated the shape of exposure response relationships using restricted cubic splines with three degrees of freedom and tested for deviation from linearity using likelihood ratio tests. We additionally modeled the number of microbleed counts using categories in an ordinal logistic model (0, 1–3, and >3 microbleeds). We restricted our PM_{2.5} estimates from Model 1 to participants living within 1,000 m of a major road, which we considered the area of urban background levels. Additionally, we adjusted models for scanner strength (1.5 Tesla or 3 Tesla).

We scaled the estimates to reflect the association for a 2 µg/m³ difference in PM_{2.5} or the difference between living 50 m away from a major road (i.e., residential proximity to a major road,) versus living 400 m away from a major road, with proximity modelled as a the natural log of the continuous term for distance. We carried out data management and analysis in SAS 9.3 (SAS Institute Inc., Cary, NC) and created plots using the Plotrix package (v. 3.5–12) in R v. 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Restricted cubic splines were modeled in Stata v.12 (Statacorp, College Station, TX) [36].

Results

The median age of participants was 74 years (interquartile range (IQR): 12) and the majority were women (Table 1). There were 62 participants (26%) with a diagnosis of probable Alzheimer's disease. Brain parenchymal fraction was available on a subset of participants having T1 scans with sufficient quality for post-processing procedures (n=202). The median (IQR) of ambient PM_{2.5} in 2003 was 11.0 (1.5) µg/m³. Among participants living within 1,000 m of a major road, the median residential distance from a major road was 260 m (with an interquartile range of 387 m). Forty-six participants (19%) lived within 100 m of a major road, 33 (14%) lived 100 to 200 m away, 50 (21%) lived 200 to 400 m away, 60 (25%) lived 400 to 1000 m away, and 47 (20%) lived 1000 or more meters away.

In our primary analyses, there was no clear evidence of associations between either PM_{2.5} or residential proximity to a major road and greater evidence of small vessel disease. We did observe an association between higher levels of PM_{2.5} and smaller white matter hyperintensity volume. A similar pattern of association was observed for the association between residential proximity to major roads and white matter hyperintensity volume, such that living closer to a major road was associated with lower white matter hyperintensity volume, but associations had confidence intervals that included the null. Estimates remained similar when we adjusted for additional covariates that could be potential confounders or mediators (Table 2 and 3).

When we stratified by diagnosis of probable Alzheimer's disease as a secondary analysis (Figure 1), similar results were observed in both groups for associations with brain parenchymal fraction and had wide confidence intervals. Living closer to a major road was associated with higher white matter hyper-intensity volume among participants with a diagnosis of probable Alzheimer's disease (0.27 log(white matter hyperintensity volume), 95%CI: -0.05, 0.58), but smaller white matter volume in study participants with other diagnoses (-0.30 95%CI: -0.51, -0.09). An increase in PM_{2.5} was associated with a higher odds of microbleeds among people with probable Alzheimer's disease (OR: 2.81 95%CI: 0.78, 10.16) compared to those with other diagnoses (OR: 0.59, 95%CI: 0.33, 1.06), but there were no clear differences in the association by roadway proximity.

Associations did not show evidence of departure from linearity based on likelihood ratio tests. Odds ratios for microbleeds based on categories of microbleed count (0, 1–3, and >3 microbleeds) using ordinal logistic regression analysis showed similar results. Results were not materially different when we restricted models of PM_{2.5} to within 1000 m of a major road or when we included an indicator for 1.5 or 3 T MRI.

Discussion

In this population of participants with mild cognitive complaints or early dementia, we observed no consistent pattern of associations between higher one year estimated average exposure to ambient air pollution or residential proximity to major roads and markers of small vessel disease. However, a 2 µg/m³ increase in PM_{2.5} was associated with lower white matter hyperintensity volume. To our knowledge, this is the first study to investigate these associations among patients attending a memory clinic, with a majority of the sample classified as having clinically recognized changes in cognitive function.

We had hypothesized that we would observe positive associations between indicators of long-term exposures to ambient air pollution and markers of small vessel disease. Studies in the greater Boston area and elsewhere have shown that higher levels of long-term exposure to air pollution are associated with elevated risk of incident stroke, impaired cognitive function, and subclinical brain injuries among older people [11] [16, 17, 37, 38]. Associations have also been reported between higher levels of long-term exposure to ambient air pollution and residential proximity to major roads with markers of atherosclerosis including greater burden of coronary artery calcification and carotid intima media thickness [39–42]. These associations are thought to be primarily mediated through

inflammatory pathways, oxidative stress and vascular changes affecting blood flow to the brain [15, 43, 44].

The major findings from this study differ from those of population-based samples in that there was no clear pattern of association with brain volume. However, the negative association between higher levels of PM_{2.5} and lower white matter hyperintensity volume may be explained in part by recent evidence from the Women's Health Initiative which showed that the association between ambient air pollution exposures and lower brain volume is related primarily to white matter volume loss [17] and are somewhat similar to those in the Framingham Offspring Study, where there was some evidence of a negative association between residential proximity to major roads and lower white matter hyperintensity volume [16]. Prior studies have shown that aging and other vascular disease may result in lower white matter volume prior to the onset of clinically identifiable mild cognitive impairment [45] [46]. Therefore, it is possible that with less white matter volume susceptible to developing white matter hyperintensities, an analysis examining the impact of PM_{2.5} or proximity to roadway on white matter hyperintensities as a proportion of white matter volume may result in estimates that are not in the anticipated direction. However, it is also possible that this association is due to other mechanisms or that it is a chance finding.

While most our results were similar across subgroups of patients with different levels of cognitive impairment, we observed some evidence to suggest that there could be differences in associations by these clinical characteristics. Because participants in this population represent a heterogeneous group, including people with probable Alzheimer's disease, those with vascular disease and those who had only limited impairment in cognitive status at the time of examination, it may be particularly difficult to evaluate the exposure- response relationship appropriately taking into account relevant timing of exposures. Since it may be possible to observe associations within more homogenous well-defined patient populations who have a clearly defined diagnosis, we conducted an analysis restricted to those with probable Alzheimer's disease and found that in this subgroup, living close to a major road was associated with higher white matter hyperintensities. However, differences could also be related to other health factors or chance. Further research with larger populations and longitudinal data could help to answer these questions.

In this study, we did not have information on the participants' long-term residential history, which may lead to some exposure misclassification, particularly if people moved to a new location because of changes in their cognitive status, or if early life or occupational exposures are particularly relevant. However, we restricted our study to participants living at residential addresses and excluded people living in skilled nursing and assisted living facilities. We also cannot rule out the possibility of misclassification of the outcomes, although we observed good consistency in the readings of outcomes with high intraclass coefficients. Some studies have hypothesized that the location and number of microbleeds may in part explain the underlying pathology [47], such that microbleeds in deep brain regions may be more indicative of traditional vascular-risk factor related pathology than those in lobar regions which are strongly linked to vascular amyloid pathology [27]. However, only 8 participants had deep microbleeds and no other recognized pathophysiology, so we did not have statistical power to evaluate this association. Similarly,

given the small relatively small size of this population and the potential for heterogeneity in associations by diagnoses, we were not able to further investigate differences in exposure-response relationships by other factors that may modify these associations, such as age, sex and socioeconomic status.

In summary, in this study of patients attending a memory clinic, we did not observe clear evidence to suggest that long-term exposure to ambient air pollution as estimated by a one year average of ambient PM_{2.5} in 2003 or residential proximity to major roadway is associated with markers of small vessel disease. No prior studies have examined associations between long-term exposure to ambient air pollution and neuroimaging specifically among people with concerns about memory loss. Therefore, these findings add to our understanding of associations between exposure to ambient air pollution and the impact on the aging brain. A future study of a large sample of patients followed from the beginning of the onset of cognitive difficulties with detailed measures of neurodegeneration and cerebrovascular disease pathology research is necessary to determine whether individuals with pre-clinical or clinical cognitive impairment are particularly susceptible to long-term effects of air pollution on small vessel disease.

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Figure 1. Fine Particulate Matter, Residential Proximity to Major Roads, and Markers of Small Vessel Disease Results Stratified by Probable Alzheimer’s Disease Diagnosis

Model 1 estimates for stratified associations between exposures and outcomes. Living closer to a major road was associated with evidence of higher white matter hyperintensity volume among participants with probable Alzheimer’s disease (n=62) but not among participants with other diagnoses. Higher levels of PM_{2.5} were associated with higher odds of microbleeds among participants with a diagnosis of probable Alzheimer’s disease, but these associations also had wide confidence intervals.

Table 1

Population characteristics of 236 neuroimaging study participants, median [IQR] or n(%)

Age (years)	74 [12]
Women	134 (57%)
Smoking status	
current	8 (3%)
former	73 (31%)
never	103 (44%)
missing	52 (22%)
History of	
Hypertension	78 (33%)
Stroke	8 (3%)
Diabetes	24 (10%)
Heart disease	43 (18%)
Education	
<16 years	105 (44%)
College degree	101 (43%)
Missing	30 (13%)
Median household income (\$)	61,412 [35,460]
Dementia subtype	
Probable Alzheimer's disease	62 (26%)
Mild cognitive Impairment	123 (52%)
Other diagnoses	51 (21%)
Brain parenchymal fraction (%)	70.2 (3.6)
Microbleed presence	77 (33%)
Log(White Matter Hyperintensities(cc))	2.3 [1.4]
PM_{2.5} (µg/m³)	11.0 [1.5]
Distance to road (m)^a	260 [387]

^a n for distance to road =189 (49 participants with probable Alzheimer's disease).

Table 2

Association between PM_{2.5} and residential proximity to major road with MRI markers of small vessel disease.^a

outcome	Model 1 ^b			Model 2 ^c		
	exposure	beta	95%CI	beta	95%CI	
Brain Parenchymal Fraction (%)						
<i>Proximity to Major Road (m)</i>						
		0.04	(−0.46, 0.54)	0.04	(−0.46, 0.53)	
<i>PM_{2.5} in 2003 (µg/m³)</i>						
		0.02	(−0.52, 0.56)	−0.06	(−0.59, 0.47)	
Log(White Matter Hyperintensities(cc))						
<i>Proximity to major road (m)</i>						
		−0.13	(−0.31, 0.04)	−0.13	(−0.31, 0.04)	
<i>PM_{2.5} in 2003 (µg/m³)</i>						
		−0.19	(−0.37, −0.005)	−0.19	(−0.38, −0.01)	

^a Associations are scaled to a 2µg/m³ difference in PM_{2.5} or the difference between living 50 m versus living 400 m away from a major road.

^b Adjusted for age, age-squared, MRI date, sex, level of education(<16 years, 16 years), quartiles of census block group median household income, smoking status (current, former, never, or missing), sine and cosine of day of year.

^c Adjusted for model 1 covariates and additionally adjusted for diagnosis (dementia or other), diabetes, statin, hypertension and stroke history.

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Table 3

Associations between PM_{2.5} and residential proximity to major road with odds of microbleed presence.^a

	Model 1 ^b		Model 2 ^c	
	OR	95%CI	OR	95%CI
<i>Distance to major road (m)</i>	0.89	(0.58, 1.39)	0.89	(0.55, 1.43)
<i>PM_{2.5} in 2003 (µg/m³)</i>	0.79	(0.50, 1.26)	0.81	(0.49, 1.35)

^aAssociations are scaled to a 2 µg/m³ difference in PM_{2.5} or the difference between living 50 m versus living 400 m away from a major road.

^bModel 1 adjusted for age, age-squared, MRI date, sex, level of education (<16 years, 16 years), quartiles of census block group median household income, smoking status (current, former, never, or missing), sine and cosine of day of year.

^cModel 2 adjusted for model 1 covariates and additionally adjusted for diagnosis (dementia or other), diabetes, statin, hypertension stroke history.