Title

Long-Term Exposure to Fine Particulate Matter, Residential Proximity to Major Roads and Measures of Brain Structure

Journal

Stroke, 46(5)

ISSN

0039-2499

Authors

Wilker, Elissa H
Preis, Sarah R
Beiser, Alexa S
et al.

Publication Date

2015-05-01

DOI

10.1161/strokeaha.114.008348

Peer reviewed

HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Stroke. 2015 May ; 46(5): 1161–1166. doi:10.1161/STROKEAHA.114.008348.

Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure

Elissa H. Wilker, ScD[1,2], **Sarah R. Preis, ScD**[3,4], **Alexa S. Beiser, PhD**[3,4,5], **Philip A. Wolf, MD**[4,5], **Rhoda Au, PhD**[3], **Itai Kloog, PhD**[6], **Wenyuan Li, MS**[7], **Joel Schwartz, PhD**[2,7], **Petros Koutrakis, PhD**[2], **Charles DeCarli, MD**[8], **Sudha Seshadri, MD**[4,5], and **Murray A. Mittleman, MD, DrPH**[1,7]

[1]Cardiovascular Epidemiology Research Unit, Beth Israel Deaconess Medical Center, Boston, MA

[2]Exposure Epidemiology and Risk program, Department of Environmental Health, Harvard T.H Chan School of Public Health, Boston MA

[3]Boston University School of Public Health, Department of Biostatistics, Boston MA

[4]Framingham Heart Study, Framingham MA

[5]Boston University School of Medicine, Department of Neurology, Boston MA

[6]Department of Geography and Environmental Development, Ben-Gurion University of the Negev, Beer Sheva, Israel

[7]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston MA

[8]Department of Neurology and Center for Neuroscience, University of California, Davis, Davis, CA

Abstract

Background and Purpose—Long-term exposure to ambient air pollution is associated with cerebrovascular disease and cognitive impairment, but whether it is related to structural changes in the brain is not clear. We examined the associations between residential long-term exposure to ambient air pollution and markers of brain aging using magnetic resonance imaging (MRI).

Methods—Framingham Offspring Study participants who attended the seventh examination, were at least 60 years old and free of dementia and stroke were included. We evaluated associations between exposures (fine particulate matter ($PM_{2.5}$) and residential proximity to major roadways) and measures of total cerebral brain volume, hippocampal volume, white matter hyperintensity volume (log-transformed and extensive white matter hyperintensity volume for age) and covert brain infarcts. Models were adjusted for age, clinical covariates, indicators of socioeconomic position, and temporal trends.

Elissa Wilker, ScD Cardiovascular Epidemiology Research Unit Beth Israel Deaconess Medical Center 375 Longwood Ave WMS/ 443 Boston, MA 02215 ewilker@bidmc.harvard.edu ph: 617.632.7654 fax: 617.632.7698.

Disclosures

None

Results—A 2 μg/m^3 increase in $PM_{2.5}$ was associated with -0.32% (95%CI: -0.59, -0.05) smaller total cerebral brain volume and 1.46 (95%CI: 1.10, 1.94) higher odds of covert brain infarcts. Living further away from a major roadway was associated with 0.10 (95%CI: 0.01, 0.19) greater log-transformed white matter hyperintensity volume for an interquartile range difference in distance, but no clear pattern of association was observed for extensive white matter.

Conclusions—Exposure to elevated levels of $PM_{2.5}$ was associated with smaller total cerebral brain volume, a marker of age-associated brain atrophy, and with higher odds of covert brain infarcts. These findings suggest that air pollution is associated with insidious effects on structural brain aging even in dementia-and stroke-free persons.

Keywords

air pollution; white matter disease; brain imaging

Introduction

Long-term exposure to particulate air pollution has been associated with higher incidence of stroke[1] and impaired cognitive function in older adults.[2, 3] Long-term exposures have also been associated with changes in cerebral hemodynamics,[4] impaired microvascular reactivity[5] and greater carotid atherosclerotic burden.[6] Air pollution has been hypothesized to affect the central nervous system through activation of systemic inflammatory pathways and vascular dysfunction.[7] Particulate air pollution is a pervasive component of urban and suburban ambient air pollution. Animal models have shown that particles can translocate from the nose via the olfactory nerve into the brain and evidence of these particles has been found in the striatum, frontal cortex, and cerebellum.[8] However, it is not known whether long-term exposures to air pollution at urban background levels are related to measures of structural integrity and atrophy in the brains of older adults.

Magnetic Resonance Imaging (MRI) of the brain can detect early vascular impairment[9] that is associated with subsequent risk of dementia and stroke.[10] We therefore investigated the associations between exposure to fine particulate matter ($PM_{2.5}$) and residential proximity to major roadways with measures of total cerebral brain volume (TCBV), hippocampal volume (HV), white matter hyperintensity volume (WMHV), and covert brain infarcts (CBI) in the Framingham Offspring Study. We hypothesized that higher long-term exposure to ambient air pollution would be associated with subclinical damage as indicated by smaller TCBV and HV, larger WMHV and higher odds of CBI.

Materials and Methods

Study Participants

The design of the Framingham Offspring Study has been detailed previously.[10, 11] Community dwelling participants living in the New England Region with no history of dementia, stroke, or transient ischemic attack who attended the seventh examination (1998–2001) and were aged ≥60 years at the time of MRI were eligible for inclusion in this study (n=943). All participants provided written informed consent, and the Institutional Review

Boards at Beth Israel Deaconess Medical Center and Boston Medical Center approved the protocol.

Exposure Assessment

$PM_{2.5}$ satellite data—Participant primary addresses at the seventh examination were geocoded using ArcGIS 10 (ESRI, Redlands, CA) and census tract median household income was assigned (US Census 2000). Beginning in the year 2000, Moderate Resolution Imaging Spectroradiometer (MODIS) satellite-derived Aerosol Optical Density (AOD) measurements were used to predict daily $PM_{2.5}$ concentration at a 10×10 km spatial resolution across New England as previously described.[12, 13]

Near roadway exposure—Residential proximity to the nearest A1, A2, or A3 roadway was determined by US Census Features Class in ArcGIS. We categorized proximity based on the following cutpoints: <50, 50 to <100, 100 to <200, 200 to <400, and 400 to <1,000 meters. We also evaluated the continuous association between the natural logarithm of proximity to a major roadway and neuroimaging outcomes because we have previously reported that this exposure and mortality were linearly associated.[12] Participants living further than 1,000 m from a major road in rural areas were excluded in primary analyses because the exposures of individuals living in exurb areas beyond 1,000 meters away from a major roadway are likely to be different from those of people living in urban and suburban areas.

Volumetric Brain MRI

TCBV, HV, and WMHV assessments and inter-rater reliability have been described previously.[14-17] Total cranial volume was determined by manual delineation of the intracranial vault and total brain parenchymal volume was determined by mathematical modeling. TCBV was then computed as a ratio of brain parenchymal volume to total cranial volume. The T2-weighted double spin-echo coronal sequences were acquired in 4-mm contiguous slices. Extensive WMHV (EXT-WMHV) was determined as a binary outcome by whether the log(WMHV/total cranial volume) was >1 SD above the age-adjusted mean in this cohort.[10, 18] The presence of CBI was determined manually on the basis of size (≥3 mm), location, and characteristics of the lesions.[19]

Additional Covariates

History of cardiovascular disease was determined as previously described.[20] Prevalent diabetes was defined as a fasting glucose ≥126 mg/dL or oral hypoglycemic or insulin use at an examination or any previous history of diabetes (excluding gestational diabetes). Smoking status (never, current, former), pack-years smoked (<10 years, ≥10 years, missing), education (no high school, high school, some college, bachelor's or higher), and alcohol intake (0, 1-7 drinks per week, 7-14, 15 or more) were self-reported. Fasting homocysteine was measured in plasma. Systolic and diastolic seated blood pressures were calculated as the mean of two measurements taken during the clinical exam.

Statistical Methods

Linear and logistic regression models were used to evaluate continuous outcomes (TCBV, HV, and WMHV) and dichotomous outcomes (EXT-WMHV and CBI) respectively. We first adjusted for age at MRI, [age at MRI]^2, sex, time from exam 7 to MRI, median household income, date of MRI, smoking status, pack-years smoked, education, alcohol intake, and sine and cosine of MRI date to account for seasonal trends (Model 1). We then added covariates thought to be potential confounders that could also be mediators of the associations between particulate air pollution and brain structure including: natural logarithm of homocysteine, systolic blood pressure, diabetes, cardiovascular disease, history of atrial fibrillation, hypertension medications, and obesity (body mass index [BMI]≥30 kg/m^2) (Model 2).

We tested whether observed associations differed by factors related to biological susceptibility and socioeconomic position as an evaluation of effect modification using cross-product terms for: sex, diabetes, obesity, current and former smoking (versus never smoking), and median household income < 25th percentile (≤$44,901).

In sensitivity analyses, we accounted for clustering by census tract to further control confounding by socioeconomic position using generalized estimating equations with exchangeable working correlation matrix. Nonlinearity was evaluated using restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. We evaluated associations with $PM_{2.5}$ restricting to participants living within 1000 m of a major road. We also considered whether adjusting for CBI altered findings for associations between exposures of interest and TCBV.[16]

Models of $PM_{2.5}$ were scaled to 2 μg/m^3, which approximates the interquartile range (IQR, 1.7 μg/m^3). We present the results of log-linear residential proximity to major roadway within 1000m analyses for an IQR. All analyses were performed in SAS version 9.3 or STATA Version 12. Plots were created using the POSTRCSPLINE package in Stata.[21]

Results

Table 1 shows population characteristics. The median (interquartile range (IQR)) of $PM_{2.5}$ exposure was 11.1 (1.7) μg/m^3. Participants lived a median distance [25th to 75th percentile] from a major road of 173 [48 to 415] meters (Table 2). The Spearman's rank correlation between the natural logarithm of residential distance from a major road and $PM_{2.5}$ was -0.15.

Higher $PM_{2.5}$ was associated with smaller TCBV and 1.46 times (95%CI: 1.10, 1.94) higher odds of CBI (Tables 3 and 4). A 2 μg/m^3 increase in $PM_{2.5}$ was associated with a 0.32 unit difference in TCBV (95%CI: -0.59,-0.05). There was no clear pattern of association between $PM_{2.5}$ and HV, WMHV, or EXT-WMHV.

An IQR difference in residential proximity to a major road was associated with 0.10 (95%CI: 0.01, 0.19) higher WMHV. A similar pattern was observed with categories of

distance. However, there was no evidence of an association between proximity to a major road and EXT-WMHV, nor was it associated with TCBV, HV, or CBI.

There was no evidence of effect modification for the observed associations by sex, diabetes diagnosis, obesity, smoking, or median income below the 25th percentile.

Only the association between $PM_{2.5}$ and TCBV met criteria for significant deviation from linearity, suggesting a stronger association at lower exposure levels and wide confidence intervals at high levels (Supplemental Figure I). We found no material differences when we considered restricting $PM_{2.5}$ analyses to regions within 1000 m of a major road or clustering by socioeconomic position. Adjustment for covert brain injury did not alter the association between $PM_{2.5}$ and TCBV.

Discussion

In this study, we observed that an increase in $PM_{2.5}$ within the range of exposures observed at urban and suburban background levels in New England was associated with smaller -0.32 (95%CI: -0.59, -0.05) TCBV and with 1.46 times (95%CI: 1.10, 1.94) higher odds of CBI. These findings support the hypothesis that higher long-term exposures to ambient air pollution are associated with structural changes in the brain that could precede cognitive impairment and overt cerebrovascular damage.[22-24]

To our knowledge, there are no published studies of associations between air pollution and brain volume or CBI in older adults. Though CBI may appear asymptomatic, these small infarcts typically located in deep regions of the brain have been associated with neurological abnormalities, poorer cognitive function[25] onset of dementia,[24] and are thought to reflect small vessel disease.[26] Smaller TCBV has been associated subsequent stroke among Framingham Offspring participants,[27] and also with poorer performance on tests of attention, executive and visuospatial function.[16] The magnitude of association that we observed for a 2 μg/m^3 increase in $PM_{2.5}$ was similar to approximately one year of brain aging computed as the ratio of the coefficients for $PM_{2.5}$ and age in the model. Adjustment for CBI did not alter this association, suggesting that atrophy was independent of the presence of asymptomatic injury and not merely a direct result of the presence of cerebral infarction.

The mechanisms through which air pollution may affect brain aging remain unclear, but systemic inflammation resulting from deposition of fine particles in alveoli is likely important. Upregulation of a pro-inflammatory state has been associated both with elevated risk of stroke[7, 28] and cognitive decline.[29] Circulating levels of biomarkers indicative of systemic inflammation have been associated with lower brain volume.[30]

Our findings are largely consistent with previous studies showing that long-term exposure to ambient air pollution is associated with vascular impairment.[4, 5, 12] Several prior studies have reported associations between long-term pollution exposure and living close to major roads with incident stroke[1, 31, 32] and poorer cognitive function in older adults.[2, 3, 33] Living in a high air pollution region in Mexico City was associated with greater accumulation of β-amyloid-42 in the frontal cortex and hippocampus than living in a non-polluted area.[34]

Though evidence regarding the associations between long-term air pollution exposures and white matter damage is limited, an ecological study in Mexico reported associations between higher levels of air pollution and white matter damage in children and dogs.[35] Our findings of a positive association between WMHV and living further from a major road but no association with EXTWMHV were unexpected. However, among Framingham Offspring Study participants, EXTWMHV was associated with poorer cognitive function[18] and elevated risk of stroke[10] but WMHV was not, suggesting a threshold for these associations. Different findings may have distinct underlying pathophysiologic mechanisms. To evaluate this will require additional studies in experimental models designed to address these questions.

There were some differences in associations we observed for $PM_{2.5}$ and residential proximity to a major roadway. While both capture features of long-term exposure to ambient air pollution, proximity is an integrated measure of exposure to traffic which includes vehicle emissions, noise, ultrafine particles, road dust, and gaseous pollutants such as nitrogen dioxide, carbon monoxide, and volatile organic compounds but does not specifically account for the intensity of traffic or meteorological conditions at a given location. In contrast, modeled $PM_{2.5}$ incorporates both locally and regionally generated air pollution. Hence they represent different aspects of ambient pollutant exposures.

Our study is not without limitations. Although we accounted for individual-level and area-level characteristics of socioeconomic position, there may be residual confounding. However, the results from our analysis taking spatial clustering into account were similar to our primary results and previous literature using modeled $PM_{2.5}$ has also shown that correlations between socioeconomic position and $PM_{2.5}$ are low within urban areas.[36] The Framingham Offspring population is comprised of mostly white participants. Therefore, these results may not be generalizable to other populations. Recent addresses were stable, with 91% of participants reporting the same address at the 6^{th} and 7^{th} examination cycles. Our $PM_{2.5}$ data are based on an average for the year 2001 similar to other large epidemiologic studies.[12, 31] This approach limits the influence of secular trends in exposure, while capturing the spatial distribution of average $PM_{2.5}$. This study also has several strengths, including a relatively large, community-based sample, inclusion of both men and women, quantitative brain MRI, and individual-level estimates of exposures.

Summary

In conclusion, we observed evidence suggesting that long-term exposure to $PM_{2.5}$ is associated with lower TCBV and more CBI among a community-based sample of participants free of dementia and stroke. These findings suggest that relatively low urban background levels of particulate air pollution may contribute to the acceleration of atrophic changes and small vessel disease in older adults. Future studies will be necessary to confirm or refute these findings, extend the work to include longitudinal assessments, and to determine factors that mediate this association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding

This work was supported by grants from the NIH (ES022243, ES000002, AG08122, AG033193, AG016495, NS17950 and N01-HC-25195) and the United States Environmental Protection Agency (USEPA) (RD834798). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the USEPA. No funding organization had any role in the design and conduct of the study; collection; management, analysis and interpretation of the data; and preparation of the manuscript. Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the funders. Further, USEPA does not endorse the purchase of any commercial products or services mentioned in the publication.

References

1. Ljungman PL, Mittleman MA. Ambient air pollution and stroke. Stroke. 2014; 45:3734–3741. [PubMed: 25300971]
2. Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A 3rd, Schwartz J. Traffic-related air pollution and cognitive function in a cohort of older men. Environ Health Perspect. 2011; 119:682–687. [PubMed: 21172758]
3. Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. Arch Intern Med. 2012; 172:219–227. [PubMed: 22332151]
4. Wellenius GA, Boyle LD, Wilker EH, Sorond FA, Coull BA, Koutrakis P, et al. Ambient fine particulate matter alters cerebral hemodynamics in the elderly. Stroke. 2013; 44:1532–1536. [PubMed: 23709640]
5. Adar SD, Klein R, Klein BE, Szpiro AA, Cotch MF, Wong TY, et al. Air pollution and the microvasculature: A cross-sectional assessment of in vivo retinal images in the population-based multi-ethnic study of atherosclerosis (mesa). PLoS Med. 2010; 7:e1000372. [PubMed: 21152417]
6. Adar SD, Sheppard L, Vedal S, Polak JF, Sampson PD, Diez Roux AV, et al. Fine particulate air pollution and the progression of carotid intima-medial thickness: A prospective cohort study from the multi-ethnic study of atherosclerosis and air pollution. PLoS Med. 2013; 10:e1001430. [PubMed: 23637576]
7. Iadecola C, Anrather J. The immunology of stroke: From mechanisms to translation. Nat Med. 2011; 17:796–808. [PubMed: 21738161]
8. Elder A, Gelein R, Silva V, Feikert T, Opanashuk L, Carter J, et al. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environ Health Perspect. 2006; 114:1172–1178. [PubMed: 16882521]
9. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2011; 42:2672–2713. [PubMed: 21778438]
10. Debette S, Beiser A, DeCarli C, Au R, Himali JJ, Kelly-Hayes M, et al. Association of mri markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: The framingham offspring study. Stroke. 2010; 41:600–606. [PubMed: 20167919]
11. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The framingham offspring study. Am J Epidemiol. 1979; 110:281–290. [PubMed: 474565]
12. Wilker EH, Ljungman PL, Rice MB, Kloog I, Schwartz J, Gold DR, et al. Relation of long-term exposure to air pollution to brachial artery flow-mediated dilation and reactive hyperemia. Am J Cardiol. 2014; 113:2057–2063. [PubMed: 24793676]

13. Kloog I, Nordio F, Coull BA, Schwartz J. Incorporating local land use regression and satellite aerosol optical depth in a hybrid model of spatiotemporal pm(2.5) exposures in the mid-atlantic states. Environ Sci Technol. 2012; 46:11913–11921. [PubMed: 23013112]
14. Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, et al. Stroke risk profile predicts white matter hyperintensity volume: The framingham study. Stroke. 2004; 35:1857–1861. [PubMed: 15218158]
15. DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, et al. Measures of brain morphology and infarction in the framingham heart study: Establishing what is normal. Neurobiol Aging. 2005; 26:491–510. [PubMed: 15653178]
16. Seshadri S, Wolf PA, Beiser A, Elias MF, Au R, Kase CS, et al. Stroke risk profile, brain volume, and cognitive function: The framingham offspring study. Neurology. 2004; 63:1591–1599. [PubMed: 15534241]
17. DeCarli C, Maisog J, Murphy DG, Teichberg D, Rapoport SI, Horwitz B. Method for quantification of brain, ventricular, and subarachnoid csf volumes from mr images. J Comput Assist Tomogr. 1992; 16:274–284. [PubMed: 1545026]
18. Au R, Massaro JM, Wolf PA, Young ME, Beiser A, Seshadri S, et al. Association of white matter hyperintensity volume with decreased cognitive functioning: The framingham heart study. Arch Neurol. 2006; 63:246–250. [PubMed: 16476813]
19. DeCarli C, Miller BL, Swan GE, Reed T, Wolf PA, Garner J, et al. Predictors of brain morphology for the men of the nhlbi twin study. Stroke. 1999; 30:529–536. [PubMed: 10066847]
20. Cupples LA, D'Agostino R. Some risk factors related to the annual incidence of cardiovascular disease and death using pooled repeated biennial measurements: Framingham study, 30-year follow-up. The framingham study: An epidemiological investigation of cardiovascular disease. 1987:87–203.
21. Buis, Maarten L. [September 13, 2014] POSTRCSPLINE: Stata module containing post-estimation commands for models using a restricted cubic spline. 2009. http://ideas.repec.org/c/boc/bocode/s456928.html
22. Vermeer SE, Den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Incidence and risk factors of silent brain infarcts in the population-based rotterdam scan study. Stroke. 2003; 34:392–396. [PubMed: 12574548]
23. Bernick C, Kuller L, Dulberg C, Longstreth WT Jr. Manolio T, Beauchamp N, et al. Silent mri infarcts and the risk of future stroke: The cardiovascular health study. Neurology. 2001; 57:1222–1229. [PubMed: 11591840]
24. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. 2003; 348:1215–1222. [PubMed: 12660385]
25. Price TR, Manolio TA, Kronmal RA, Kittner SJ, Yue NC, Robbins J, et al. Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. The cardiovascular health study. Chs collaborative research group. Stroke. 1997; 28:1158–1164. [PubMed: 9183343]
26. Vermeer SE, Longstreth WT Jr. Koudstaal PJ. Silent brain infarcts: A systematic review. The Lancet. Neurology. 2007; 6:611–619. [PubMed: 17582361]
27. Weinstein G, Beiser AS, Decarli C, Au R, Wolf PA, Seshadri S. Brain imaging and cognitive predictors of stroke and alzheimer disease in the framingham heart study. Stroke. 2013; 44:2787–2794. [PubMed: 23920020]
28. McColl BW, Allan SM, Rothwell NJ. Systemic infection, inflammation and acute ischemic stroke. Neuroscience. 2009; 158:1049–1061. [PubMed: 18789376]
29. Gorelick PB. Role of inflammation in cognitive impairment: Results of observational epidemiological studies and clinical trials. Ann N Y Acad Sci. 2010; 1207:155–162. [PubMed: 20955439]
30. Jefferson AL, Massaro JM, Wolf PA, Seshadri S, Au R, Vasan RS, et al. Inflammatory biomarkers are associated with total brain volume: The framingham heart study. Neurology. 2007; 68:1032–1038. [PubMed: 17389308]

31. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med. 2007; 356:447–458. [PubMed: 17267905]

32. Stafoggia M, Cesaroni G, Peters A, Andersen ZJ, Badaloni C, Beelen R, et al. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: Results from 11 european cohorts within the escape project. Environ Health Perspect. 2014; 122:919–925. [PubMed: 24835336]

33. Wellenius GA, Boyle LD, Coull BA, Milberg WP, Gryparis A, Schwartz J, et al. Residential proximity to nearest major roadway and cognitive function in community-dwelling seniors: Results from the mobilize boston study. J Am Geriatr Soc. 2012; 60:2075–2080. [PubMed: 23126566]

34. Calderon-Garciduenas L, Reed W, Maronpot RR, Henriquez-Roldan C, Delgado-Chavez R, Calderon-Garciduenas A, et al. Brain inflammation and alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol. 2004; 32:650–658. [PubMed: 15513908]

35. Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, Gomez-Garza G, Barragan-Mejia G, Broadway J, et al. Air pollution, cognitive deficits and brain abnormalities: A pilot study with children and dogs. Brain Cogn. 2008; 68:117–127. [PubMed: 18550243]

36. Brochu PJ, Yanosky JD, Paciorek CJ, Schwartz J, Chen JT, Herrick RF, et al. Particulate air pollution and socioeconomic position in rural and urban areas of the northeastern united states. Am J Public Health. 2011; 101(Suppl 1):S224–230. [PubMed: 21836114]

Table 1

Population characteristics (n=943).

Characteristic	Median [IQR] or N(%)
Age at MRI (yr)	68 [9]
Systolic Blood Pressure (mmHg)	129 [25]
Diastolic Blood Pressure (mmHg)	72 [13]
Male	456 (48%)
Prevalent Cardiovascular Disease	130 (14%)
Smoking Status	
Current	73 (8%)
Former	532 (56%)
Never	337 (36%)
Missing	1 (<1%)
Prevalent Heart Failure	46 (5%)
Diabetes	134 (14%)
Hypertension Medication Use	366 (39%)
Homocysteine	8.3 [3.1]
Education	
Less than high school	51 (5%)
High school	311 (33%)
Some college /associate's degree	275 (29%)
Bachelor's or higher	298 (32%)
Missing Education	8 (<1%)
Median Household Income	63,479 [29,270]
Total Cerebral Brain Volume	78.41 [4.39]
Hippocampal Volume	0.33 [0.07]
Log White Matter Hyperintensity Volume	−2.69 [1.30]
Extensive White Matter Hyperintensity	135 (14%)
Covert Brain Infarcts	133 (14%)

Table 2

Exposure characteristics

Exposure	Median [IQR] or n(%)	Range
PM2.5 (μg/m^3)*	11.1 [1.7]	7.7–17.6
Distance to Major Road (m)†	173 [367]	0-993
Distance by category (m)		
<50	226 (24%)	
50 to <100	87 (9%)	
100 to<200	149 (16%)	
200 to<400	186 (20%)	
400 to<1000	226 (24%)	
≥1000	69 (7%)	

*Estimates unavailable on 13 participants.

†69 participants living ≥1000 m from a major road excluded.

Table 3

Associations between exposures and continuous volumetric outcomes.

		Model 1*			Model 2†		
Outcome	**Exposure**	**β**	**95%CI**	**n**	**β**	**95%CI**	**n**
Hippocampal Volume	<50	0.004	(−0.005, 0.014)	865	0.005	(−0.004, 0.015)	853
	50 to <100	0.003	(−0.011, 0.016)		0.003	(−0.010, 0.017)	
	100 to <200	0.005	(−0.006, 0.016)		0.005	(−0.006, 0.016)	
	200 to <400	0.003	(−0.007, 0.013)		0.003	(−0.007, 0.013)	
	400 to <1000	REF			REF		
	Log(distance)‡	−0.002	(−0.007, 0.003)	865	0.003	(−0.008, 0.002)	853
	$PM_{2.5}$§	0.0001	(−0.005, 0.005)	921	0.0004	(−0.005, 0.005)	909
Log (White Matter Hyperintensities)	<50	−0.17	(−0.35, 0.01)	873	−0.16	(−0.34, 0.02)	861
	50 to <100	−0.13	(−0.37, 0.11)		−0.12	(−0.36, 0.11	
	100 to <200	−0.07	(−0.27, 0.13)		−0.06	(−0.26, 0.13)	
	200 to <400	0.02	(−0.16, 0.21)		0.03	(−0.15, 0.22)	
	400 to <1000	REF			REF		
	Log(distance)‡	0.10	(0.010, 0.19)	873	0.09	(−0.0004, 0.18)	861
	$PM_{2.5}$§	−0.06	(−0.16, 0.03)	929	−0.08	(−0.17, 0.01)	917
Total Cerebral Brain Volume	<50	0.23	(−0.29, 0.75)	873	0.09	(−0.42, 0.60)	861
	50 to <100	0.45	(−0.24, 1.14)		0.47	(−0.21, 1.16)	
	100 to <200	−0.02	(−0.60, 0.56)		−0.14	(−0.71, 0.43)	
	200 to <400	−0.19	(−0.73, 0.35)		−0.30	(−0.84, 0.23)	
	400 to <1000	REF			REF		
	Log(distance)‡	−0.15	(−0.41, 0.11)	873	−0.10	(−0.36, 0.16)	861
	$PM_{2.5}$§	−0.32	(−0.59, −0.05)	929	−0.26	(−0.53, 0.004)	917

*Model 1 adjusted for age, age , sex, time from exam 7 to MRI, median household income, date of MRI, smoking status, pack-years smoked, education (no high school, high school, some college, bachelor's or higher), drinking categories and sine and cosine of MRI date to account for seasonal trends.

†Model 2 adjusted for model 1 covariates + log (homocysteine), systolic blood pressure, diabetes, cardiovascular disease, history of AF, hypertension medications, and obesity.

‡Scaled to difference between 25^{th} and 75^{th} percentile of distance (367 m).

§Scaled to 2μg/m^3 difference in $PM_{2.5}$.

Table 4

Associations between exposures and binary outcome

		Model 1*			Model 2†		
Outcome	**Exposure**	**OR**	**95%CI**	**n**	**OR**	**95%CI**	**n**
Extensive White Matter Hyperintensity Volume for Age	<50	0.88	(0.51, 1.52)	873	0.94	(0.53, 1.67)	861
	50 to <100	0.56	(0.25, 1.29)		0.59	(0.25, 1.38)	
	100 to <200	0.86	(0.46, 1.60)		0.96	(0.51, 1.83)	
	200 to <400	1.05	(0.60, 1.84)		1.16	(0.65, 2.06)	
	400 to <1000	REF				REF	
	Log(distance)‡	1.11	(0.84, 1.48)	873	1.09	(0.81, 1.47)	861
	$PM_{2.5}$§	1.00	(0.76, 1.32)	929	0.94	(0.70, 1.26)	917
Covert Brain Infarcts	<50	1.21	(0.67, 2.17)	870	1.29	(0.70, 2.36)	861
	50 to <100	1.25	(0.58, 2.67)		1.16	(0.53, 2.56)	
	100 to <200	1.17	(0.61, 2.23)		1.10	(0.56, 2.15)	
	200 to <400	1.69	(0.95, 3.00)		1.72	(0.95, 3.11)	
	400 to <1000	REF			REF		
	Log(distance)‡	1.05	(0.79, 1.40)	870	1.02	(0.75, 1.37)	861
	$PM_{2.5}$§	1.46	(1.10, 1.94)	926	1.37	(1.02, 1.85)	917

*Model 1 adjusted for age, age , sex, time from exam 7 to MRI, median household income, date of MRI, smoking status, pack-years smoked, education (no high school, high school, some college, bachelor's or higher), drinking categories and sine and cosine of MRI date to account for seasonal trends.

†Model 2 adjusted for model 1 covariates + log (homocysteine), systolic blood pressure, diabetes, cardiovascular disease, history of AF, hypertension medications, and obesity.

‡Scaled to difference between 25^{th} and 75^{th} percentile of distance (367 m).

§Scaled to 2μg/m^3 difference in $PM_{2.5}$.