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The Association of Long-Term Exposure to Particulate Matter Air Pollution with Brain MRI Findings: The ARIC Study

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Background: Increasing evidence links higher particulate matter (PM) air pollution exposure to late-life cognitive impairment. However, few studies have considered associations between direct estimates of long-term past exposures and brain MRI findings indicative of neurodegeneration or cerebrovascular disease.

Objective: Our objective was to quantify the association between brain MRI findings and PM exposures approximately 5 to 20 y prior to MRI in the Atherosclerosis Risk in Communities (ARIC) study.

Methods: ARIC is based in four U.S. sites: Washington County, Maryland; Minneapolis suburbs, Minnesota; Forsyth County, North Carolina; and Jackson, Mississippi. A subset of ARIC participants underwent 3T brain MRI in 2011–2013 ($n = 1{,}753$). We estimated mean exposures to PM with an aerodynamic diameter less than 10 or 2.5 μm (PM_{10} and $PM_{2.5}$) in 1990–1998, 1999–2007, and 1990–2007 at the residential addresses of eligible participants with MRI data. We estimated site-specific associations between PM and brain MRI findings and used random-effect, inverse variance–weighted meta-analysis to combine them.

Results: In pooled analyses, higher mean $PM_{2.5}$ and PM_{10} exposure in all time periods were associated with smaller deep-gray brain volumes, but not other MRI markers. Higher $PM_{2.5}$ exposures were consistently associated with smaller total and regional brain volumes in Minnesota, but not elsewhere.

Conclusions: Long-term past PM exposure in was not associated with markers of cerebrovascular disease. Higher long-term past PM exposures were associated with smaller deep-gray volumes overall, and higher $PM_{2.5}$ exposures were associated with smaller brain volumes in the Minnesota site. Further work is needed to understand the sources of heterogeneity across sites. https://doi.org/10.1289/EHP2152

Introduction

Common environmental pollutants may promote cognitive decline, cognitive impairment, and dementia. In particular, recent epidemiologic studies have reported that higher exposure to particulate air pollution is associated with increased risk of cognitive decline, cognitive impairment, and dementia (Power et al. 2016a; Tzivian et al. 2016; Xu et al. 2016). Although this body of work is highly suggestive, work linking air pollution to MRI markers of brain injury may provide mechanistic insight and would allay concerns about residual confounding by sociodemographic and socioeconomic characteristics that are common to studies of air pollution and cognition (Casanova et al. 2016; Chen et al. 2015; Wilker et al. 2015; Wilker et al. 2016). However, relatively little work has been done to examine the link between particulate air pollution and available markers of brain injury, and prior studies exclusively report on associations between recent air pollution exposures and markers of brain injury (Chen et al. 2015; Power et al. 2016a; Wilker et al. 2015). However, current brain health is a result of cumulative causes of brain injury that likely accumulate over decades, including aggregating proteins, ischemic injury, inflammation and oxidative stress, or exposure to toxins. As such, it is reasonable to expect that air pollution exposures over the prior years to decades may significantly contribute to current brain health. In addition, prior studies on air pollution and markers of brain injury are limited by lack of understanding of the selection process by which persons were selected for neuroimaging, which may lead to bias (Weuve et al. 2015).

To address these limitations, we conducted a study to quantify the association of long-term past exposure to particulate matter air pollution with MRI markers of neurodegeneration and subclinical cerebrovascular disease in older adults from the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). We hypothesized that long-term past exposure to particulate matter (PM) air pollution, specifically PM <2.5 μm in aerodynamic diameter ($PM_{2.5}$), would be associated with smaller total brain volumes, as atrophy is an etiologically nonspecific indicator of cumulative brain damage, and increased risk of subclinical cerebrovascular disease. We also considered associations with regional brain volumes, given focal atrophy may suggest that

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PM exposures contribute to the pathogenesis of specific neurodegenerative processes.

Methods

Study Population

In 1987–1989 (Visit 1), the ARIC Study recruited 15,792 participants from four U.S. communities: Minneapolis, Minnesota suburbs; Jackson, Mississippi; Washington County, Maryland; and Forsyth County, North Carolina. Participants have since been invited to complete four additional study visits: Visit 2, 1990–1992; Visit 3, 1993–1995; Visit 4, 1996–1998; and Visit 5, 2011–2013. A sample of participants who attended Visit 5 were invited to undergo brain MRI as part of the ARIC-NCS (Knopman et al. 2015). Briefly, at each site, excluding those with contraindications to MRI, all persons who had any indication of cognitive impairment at Visit 5, all persons who had previously completed brain MRI as part of an ARIC substudy, and a stratified random sample of the remaining participants (stratified by age) were invited to complete a brain MRI. Of those who completed brain MRI ($n = 1{,}978$), we excluded those with a history of surgery or radiation to the head, multiple sclerosis, or brain tumor ($n = 15$), all nonblack or nonwhite participants from any study site and all black individuals from Minnesota or Maryland ($n = 15$), those with an implausible estimated intracranial volume (eTIV) ($n = 2$), and those for whom we were unable to estimate historical air pollution exposures ($n = 193$). This study was approved by the institutional review boards of all participating institutions. All subjects provided written informed consent to participate at each study visit.

Particulate Matter Air Pollution Exposures

Based on each participant's residential address, which was updated at each ARIC study visit, we estimated monthly exposures to $PM_{2.5}$ and PM_{10} (PM with an aerodynamic diameter $<10\ \mu m$) using validated spatiotemporal statistical models (Paciorek et al. 2009; Yanosky et al. 2014; Yanosky et al. 2008; Yanosky et al. 2009). These models used PM monitoring, and geographic and meteorological covariates, in conjunction with spatial smoothing, to describe monthly $PM_{2.5}$ and PM_{10} levels with high spatial resolution. Given national monitoring data were available for $PM_{2.5}$ only for 1999 onward, separate spatiotemporal models for $PM_{2.5}$ were fit for the 1988–1998 and 1999–2007 time periods. The $PM_{2.5}$ model for the earlier time period (1988–1998) relied on PM_{10} model predictions and had a simpler space–time structure. The $PM_{2.5}$ models for both time periods had high predictive accuracy [cross-validation (CV) $R^2 = 0.77$ for both 1988–1998 and 1999–2007]. The predictive ability of the PM_{10} model was slightly lower (CV $R^2 = 0.58$ for both 1988–1998 and 1999–2007). Models generally performed well in both urban and rural areas and across seasons, though predictive performance varied somewhat by region [CV $R^2 = 0.81$, 0.81, 0.83, 0.72, 0.69, 0.50, and 0.60 for the Northeast, Midwest, Southeast, Southcentral, Southwest, Northwest, and Central Plains regions, respectively, for $PM_{2.5}$ from 1999–2007 (Yanosky et al. 2014)]. As our study sites are located in the Northeast, Midwest, and Southeast, predictive performance is expected to be similar across study sites.

Input data were available from 1988 onward; we generated PM estimates at the residential address of each participant from 1990–2007, given lower confidence in PM estimates in the first few years covered by the model and our goal to quantify associations with long-term past exposures. We did not use moving averages to avoid issues of bias due to secular trends in air pollution coupled with differences in brain health for those who underwent MRI early or late in the study period.

Specifically, among those participants with complete air pollution exposure estimates, we created three exposure summaries for use in our analyses. First, we considered average exposures from 1990–2007, which represents the period approximately 22 to 5 y prior to neuroimaging. We hypothesized that these long-term cumulative exposures would be most relevant to current brain health. Structural brain changes detectable on MRI considered here are expected to represent the culmination of years of brain injury; thus, long-term cumulative average exposure would be expected to be relevant to the severity of brain injury detectable on MRI. In addition, we also separately considered average exposures from 1990–1998 (approximately 14 to 22 y prior to neuroimaging) and from 1999–2007 (approximately 14 to 5 y prior to neuroimaging), to explore whether changes to exposure model before and after 1999 impacted our findings. However, we recognize that, if observed, differences in association across averaging periods could also be attributable to true differences in the impact of exposure based on the timing of exposure relative to outcome assessment.

Neuroimaging Measures

At each study site, participants completed 3T MRI scans according to a standardized protocol. Pulse sequences included a sagittal T1-weighted 3-D volumetric magnetization-prepared gradient echo (MPRAGE) pulse sequence, axial T2 fluid-attenuated inversion recovery and axial T2* weighted gradient echo. The ARIC MRI reading center (Mayo Clinic, Minnesota) analyzed all images.

Regional gray-matter volumes were quantified with FreeSurfer (version 5.1; Laboratory for Computational Neuroimaging at the Athinoula A. Martinos Center for Biomedical Imaging), and total brain and intracranial volumes were estimated using in-house algorithms (Jack et al. 2014). In our analyses, we consider gray-matter volumes of the total brain, the four lobes (frontal, parietal, temporal, occipital), the hippocampus, the deep-gray structures (thalamus, caudate, putamen, and pallidum), and total volume of multiple gray-matter regions known to atrophy preferentially in Alzheimer's disease (parahippocampal, entorhinal, and inferior parietal lobules, hippocampus, precuneus, and cuneus), which we refer to as the AD signature region (Dickerson et al. 2011).

White matter hyperintensity (WMH) volumes were measured using an in-house algorithm. (Raz et al. 2013) As WMH volumes were not normally distributed, we created a dichotomous severe WMH variable defined as present if WMH volume is $>5\%$ of total white matter volume. Brain infarcts and microbleeds were identified, counted, and measured by a trained imaging technician and confirmed by a radiologist (Knopman et al. 2015). Lacunar infarcts were subsequently identified based on location and size (3–15 mm in diameter) (Wardlaw et al. 2013). Microbleeds were subsequently classified as lobar or subcortical based on location. In our analyses, we characterized infarcts, lacunar infarcts, microbleeds, lobar microbleeds, and subcortical microbleeds as present or absent.

Covariates

We used data collected at Visits 1 and 4 to define participant age, gender (male/female), education ($\leq$high school, $>$high school), body mass index (BMI; normal/overweight/obese), and smoking status (current/former/never). BMI was defined as measured weight (kg) divided by the square of measured height (m), while all other covariates were defined via self-report. We also considered two measures of area-level socioeconomic status (SES), the proportion of the residential census tract population below the U.S. poverty line, and a summary measure of neighborhood

wealth/income, education, and occupation combining U.S. Census tract–level characteristics denoted the Neighborhood SES score (Diez Roux et al. 2001). Each measure of SES was categorized into three levels (bottom quintile, middle three quintiles, top quintile) using center-specific cutoffs.

Statistical Analysis

We initially conducted all analyses stratified by study site. Brain volumes were z-transformed prior to use in analyses based on the mean and standard deviation (SD) of volumes in those individuals who met eligibility criteria for inclusion in our study. We used weighted linear or logistic regression to quantify the site-specific association between a 1-$\mu g/m^3$-higher PM exposure measure and each of our neuroimaging features. The weights accounted for the stratified random sampling used to select participants from each site from ARIC Visit 5 into the ARIC MRI sample; thus, our site-specific analyses can be interpreted as the association that would be observed in the full Visit 5 ARIC sample at each site. All models were adjusted for age, gender, race, education, and eTIV. Associations with 1990–1998 and 1990–2007 exposure summaries were adjusted for covariate values at the time of Visit 1 (1987–1989), while associations with 1999–2007 exposure summaries were adjusted for covariate values at the time of Visit 4 (1996–1998). To provide a summary estimate combining data from all four sites, we combined site-specific estimates using random effects meta-analysis (DerSimonian and Laird 1986). Use of random effects meta-analysis was chosen given potential heterogeneity in association due to differences in PM composition or other factors across study sites. It also allowed for formal evaluation of the evidence for heterogeneity across estimates using the I^2 test. Moreover, this method has the benefit of allowing us to derive a summary measure of association despite evidence of intractable confounding by site; exposure and confounder distributions across sites did not always overlap.

In sensitivity analyses, we reestimated our site-specific and combined estimates of association *a*) additionally adjusting for BMI, smoking status, and our two measures of area-level SES; *b*) excluding persons with documented stroke before MRI; *c*) restricting to persons who did not move during follow-up; *d*) considering white participants only (there were too few black participants in the North Carolina site to allow a site-specific estimate among blacks or a pooled estimate combining the North Carolina and Mississippi site estimates); *e*) incorporating inverse probability of attrition weighting (Hernán et al. 2000; Power et al. 2016b) to account for potentially informative attrition from Visit 1 to Visit 5; *f*) excluding potential outliers in our exposure estimates through application of the generalized extreme studentized derivative test (Rosner 1983); *g*) using log-transformed WMH volumes as an outcome in linear regression models; and *h*) in models omitting weighting. We also reestimated our site-specific estimates of association using a 1-SD unit increase in site-specific exposure as the exposure contrast. All analyses were completed using SAS (version 9.4; SAS Institute Inc.) or Stata (version 14.0; StataCorp).

Results

In total, 1,753 persons met our eligibility criteria and were included in the analyses. At the time of MRI, participants were on average 76 y old, 40% were male, and 45% had greater than a high school education. Table 1 provides demographic and clinical characteristics of the study participants, as well as information on our MRI outcomes by study site. Overall, the Minnesota site was the most affluent of the four sites, followed in order by North Carolina, Maryland, and Mississippi.

Table 1. Selected characteristics for eligible ARIC-NCS participants by study site.

Characteristic	MN ($n=419$) % or mean ± SD	MD ($n=443$) % or mean ± SD	NC ($n=446$) % or mean ± SD	MS ($n=441$) % or mean ± SD	p-Value[a]
Age at baseline, y	53 ± 5	53 ± 5	54 ± 5	52 ± 5	0.0004
Age at MRI, y	76 ± 5	77 ± 5	77 ± 5	75 ± 5	
Male	48	37	43	33	<0.0001
Black	0	0	6	100	<0.0001
>HS education	55	30	53	45	<0.0001
Smoking at baseline					<0.0001
Current	15	13	17	19	
Former	40	31	32	26	
Never	45	56	52	55	
BMI at baseline, kg/m^2	27 ± 4	27 ± 5	25 ± 4	29 ± 5	<0.0001
Neighborhood SES score at baseline	4.4 ± 3.1	−0.4 ± 2.8	−3.4 ± 5.1	−4.6 ± 4.6	<0.0001
Proportion of residential census track below U.S. poverty line at baseline	0.05 ± 0.03	0.08 ± 0.05	0.07 ± 0.06	0.31 ± 0.14	<0.0001
Estimated intracranial volume, cm^3	1436 ± 154	1378 ± 150	1406 ± 159	1308 ± 134	<0.0001
Total brain volume, cm^3	1048 ± 109	1009 ± 104	1022 ± 108	967 ± 98	0.05
Frontal lobe volume, cm^3	155 ± 15	149 ± 15	153 ± 17	143 ± 14	<0.0001
Parietal lobe volume, cm^3	111 ± 12	106 ± 12	107 ± 12	99 ± 11	<0.0001
Occipital lobe volume, cm^3	43 ± 5	41 ± 5	41 ± 5	37 ± 5	<0.0001
Temporal lobe volume, cm^3	105 ± 12	101 ± 11	102 ± 12	98 ± 11	<0.0001
Deep-gray volume, cm^3	30 ± 3	30 ± 3	30 ± 3	29 ± 3	0.004
Hippocampal volume, cm^3	7.0 ± 0.9	6.7 ± 0.9	6.9 ± 1.0	6.8 ± 1.0	0.002
AD signature region volume, cm^3	62 ± 7	59 ± 7	59 ± 7	56 ± 6	<0.0001
Severe WMH[b]	22	26	25	28	<0.0001
Infarcts present	24	25	27	27	0.01
Lacunes present	17	18	18	19	0.07
Microbleeds present	24	20	27	28	<0.0001
Subcortical microbleeds present	20	17	22	23	0.0005
Lobar microbleeds present	10	7	10	9	0.0003

Note: ARIC-NCS, Atherosclerosis Risk in Communities Neurocognitive Study; BMI, body mass index; HS, high school; MD, Maryland; MN, Minnesota; MS, Mississippi; NC, North Carolina; SD, standard deviation; SES, socioeconomic status; WMH, white matter hyperintensities.
[a]Chi-square of F-test p-value for comparison of characteristics by site, after weighting; p-values for brain volumes are additionally adjusted for estimated intracranial volume.
[b]Severe WMH defined as WMH volume >5% of white matter volume.

Of the four sites, Minnesota and Mississippi had the lowest PM exposures, while Maryland and North Carolina had the highest (Table 2). Variation in exposure to PM_{10} was generally larger than variation in exposure to $PM_{2.5}$. Site-specific coefficients of variation for our exposure estimates ranged from 0.03 to 0.11 $\mu g/m^3$ for PM_{10} and 0.02 to 0.10 $\mu g/m^3$ for $PM_{2.5}$.

As there was evidence of moderate to high heterogeneity ($I^2 > 40\%$) across sites when considering analyses of $PM_{2.5}$ and brain volumes, we discuss both the site-specific and pooled analyses (Table 3). In the Minnesota site, higher $PM_{2.5}$ exposures were generally associated with smaller total and regional brain volumes, with slightly stronger associations observed when considering the 1990–1998 exposure period compared to the 1999–2007 exposure period. This pattern was not observed in the other three sites. Results from the Maryland and North Carolina sites were consistently null. In the Mississippi site, there was some evidence to support a protective association between higher PM exposures and larger AD signature region, temporal lobe, and occipital lobe volumes, regardless of exposure period; associations with other regions were typically null. When site-specific associations were pooled via meta-analysis, the resulting effect estimates were generally null. However, consistently adverse associations between $PM_{2.5}$ exposure from 1999–2007 and frontal lobe volumes across sites resulted in a small, marginally significant pooled association [beta: −0.02 SD units per 1-$\mu g/m^3$ higher exposure; 95% confidence interval (CI): −0.04, 0.00] Similarly, consistently adverse associations between higher $PM_{2.5}$ exposures in all three time periods and smaller deep-gray volumes across the Minnesota, Maryland, and North Carolina sites resulted in small, marginally significant pooled associations (e.g., for mean $PM_{2.5}$ from 1990–2007, beta: −0.03 SD units per 1-$\mu g/m^3$ higher exposure; 95% CI: −0.08, 0.00). The overall pattern of site-specific and combined results was similar across our sensitivity analyses, including analyses implementing inverse probability weighting (Tables S1 and S2) and those omitting use of sampling weights (Table S3).

Similarly, there was some evidence to suggest heterogeneity of association across sites when considering analyses of PM_{10} and brain volumes (Table 4). Site-specific analyses suggested adverse associations between higher mean PM_{10} over 1999–2007 or 1990–2007 and smaller total brain volumes, occipital lobe volumes, and deep-gray volumes in Minnesota (Table 4). As with the $PM_{2.5}$ analyses, we also observed protective associations between higher long-term PM_{10} exposure and larger occipital lobe, temporal lobe, and AD signature region volumes in Mississippi. As with $PM_{2.5}$, there was little evidence of an association between long-term PM_{10} exposure and total or regional brain volumes in pooled analyses, with the exception of an adverse association between higher mean PM_{10} in all three time periods and smaller deep-gray-region volumes (e.g., the PM_{10} 1990–2007 time period, beta: −0.02; 95% CI: −0.04, 0.00). As above, the overall pattern of site-specific and combined results was similar across sensitivity analyses, including analyses implementing inverse probability weighting (Tables S4 and S5) and those omitting use of sampling weights (Table S6).

When considering the relation between $PM_{2.5}$ or PM_{10} and the presence of MRI markers of cerebrovascular disease, there was little statistical evidence of heterogeneity of association across the four sites; thus, we focused on the analyses pooling estimates from all four sites via meta-analysis. Overall, there was little conclusive evidence to support an association between higher exposure to $PM_{2.5}$ or PM_{10} in any time period and the presence of MRI markers of cerebrovascular disease in pooled analyses combining all four sites (Tables S7 and S8). However, the odds ratios (ORs) for the pooled associations between a 1-$\mu g/m^3$-higher mean $PM_{2.5}$ exposure and either lacunes or subcortical microbleeds were consistently in the range of 1.04 to 1.10, although these associations were not statistically significant. Similarly, although the ORs for the pooled associations between a 1-$\mu g/m^3$-higher mean PM_{10} exposure and microbleeds were consistently in the range of 1.04 to 1.05; these associations were also not statistically significant. Results from our sensitivity analyses were broadly consistent with our primary analysis findings, including analyses implementing inverse probability weighting or omitting use of sampling weights (Tables S9 to S14).

Table 2. Distribution of exposure by site and exposure averaging time period for eligible ARIC-NCS participants.

Exposure	Site	Time period	Mean	SD	Minimum	25th Percentile	75th Percentile	Maximum
$PM_{2.5}$	MN	1990–1998	9.4	0.4	7.7	9.2	9.6	11.5
$PM_{2.5}$	MN	1999–2007	13.1	0.7	9.3	12.9	13.4	16.7
$PM_{2.5}$	MN	1990–2007	11.2	0.5	9.0	11.1	11.5	13.9
$PM_{2.5}$	MD	1990–1998	15.1	1.0	11.8	14.6	15.9	18.2
$PM_{2.5}$	MD	1999–2007	19.1	1.8	9.9	18.5	20.1	22.9
$PM_{2.5}$	MD	1990–2007	17.1	1.3	11.4	16.5	17.9	20.5
$PM_{2.5}$	NC	1990–1998	15.7	0.5	13.8	15.4	16.0	17.7
$PM_{2.5}$	NC	1999–2007	11.4	0.7	8.7	11.1	11.7	18.9
$PM_{2.5}$	NC	1990–2007	13.6	0.5	11.6	13.4	13.8	16.7
$PM_{2.5}$	MS	1990–1998	12.4	0.3	11.6	12.2	12.5	13.3
$PM_{2.5}$	MS	1999–2007	10.2	0.3	8.7	10.1	10.4	11.3
$PM_{2.5}$	MS	1990–2007	11.3	0.2	10.4	11.2	11.4	12.3
PM_{10}	MN	1990–1998	17.0	1.2	12.1	16.6	17.6	20.0
PM_{10}	MN	1999–2007	16.6	1.8	10.5	16.2	17.5	21.6
PM_{10}	MN	1990–2007	16.8	1.4	11.5	16.3	17.5	20.6
PM_{10}	MD	1990–1998	23.3	2.3	16.2	22.0	25.1	30.2
PM_{10}	MD	1999–2007	19.4	2.1	13.5	18.0	20.9	25.5
PM_{10}	MD	1990–2007	21.4	2.1	15.5	20.1	22.9	27.8
PM_{10}	NC	1990–1998	21.9	0.9	18.6	21.3	22.3	24.8
PM_{10}	NC	1999–2007	18.2	0.8	14.4	17.7	18.5	20.8
PM_{10}	NC	1990–2007	20.0	0.8	16.9	19.5	20.4	22.7
PM_{10}	MS	1990–1998	18.7	0.5	17.1	18.3	18.9	20.0
PM_{10}	MS	1999–2007	17.4	0.5	15.9	17.1	17.6	18.9
PM_{10}	MS	1990–2007	18.0	0.5	16.6	17.7	18.3	19.4

Note: ARIC-NCS, Atherosclerosis Risk in Communities Neurocognitive Study; MD, Maryland; MN, Minnesota; MS, Mississippi; NC, North Carolina; PM, particulate matter; SD, standard deviation.

Table 3. Adjusted association between a 1-$\mu g/m^3$-higher past $PM_{2.5}$ exposure and SD-unit brain volumes in 2011–2013 in the ARIC-NCS study.

		$PM_{2.5}$ 1990–1998			$PM_{2.5}$ 1999–2007			$PM_{2.5}$ 1990–2007		
Outcome and site	n	Beta (95% CI)	p-Value	I^2/p-Value for heterogeneity	Beta (95% CI)	p-Value	I^2/p-Value for heterogeneity	Beta (95% CI)	p-Value	I^2/p-Value for heterogeneity
Total brain	—	—	—	—	—	—	—	—	—	—
MN	419	−0.09 (−0.16, −0.01)	0.02	—	−0.07 (−0.11, −0.03)	<0.01	—	−0.1 (−0.16, −0.05)	<0.01	—
MD	443	0.01 (−0.03, 0.05)	0.58	—	0 (−0.02, 0.02)	0.84	—	0 (−0.03, 0.03)	0.96	—
NC	446	0.03 (−0.05, 0.11)	0.47	—	−0.02 (−0.09, 0.05)	0.54	—	0 (−0.09, 0.08)	0.93	—
MS	441	0.07 (−0.09, 0.23)	0.38	—	0.04 (−0.08, 0.16)	0.52	—	0.07 (−0.09, 0.22)	0.39	—
Combined	—	0 (−0.06, 0.05)	0.87	58.1/0.07	−0.02 (−0.07, 0.02)	0.31	72.9/0.01	−0.02 (−0.09, 0.04)	0.5	75.8/0.01
Frontal lobe	—	—	—	—	—	—	—	—	—	—
MN	417	−0.1 (−0.2, 0)	0.04	—	−0.05 (−0.11, 0.01)	0.08	—	−0.09 (−0.17, 0)	0.04	—
MD	442	−0.01 (−0.06, 0.04)	0.76	—	−0.01 (−0.04, 0.01)	0.27	—	−0.02 (−0.05, 0.02)	0.36	—
NC	446	0.02 (−0.09, 0.13)	0.69	—	−0.01 (−0.09, 0.06)	0.75	—	0 (−0.11, 0.11)	1	—
MS	440	0.07 (−0.08, 0.23)	0.36	—	−0.02 (−0.15, 0.11)	0.72	—	0.02 (−0.14, 0.18)	0.81	—
Combined	—	−0.01 (−0.07, 0.04)	0.63	35.8/0.20	−0.02 (−0.04, 0)	0.08	0/0.66	−0.02 (−0.05, 0.01)	0.13	0/0.41
Occipital lobe	—	—	—	—	—	—	—	—	—	—
MN	417	−0.09 (−0.2, 0.03)	0.13	—	−0.06 (−0.13, 0)	0.06	—	−0.1 (−0.19, 0)	0.05	—
MD	442	0 (−0.06, 0.06)	0.97	—	0 (−0.03, 0.02)	0.82	—	0 (−0.04, 0.04)	0.91	—
NC	446	0.01 (−0.13, 0.14)	0.92	—	−0.07 (−0.16, 0.03)	0.17	—	−0.06 (−0.2, 0.08)	0.43	—
MS	440	0.23 (−0.02, 0.47)	0.07	—	0.15 (−0.01, 0.31)	0.06	—	0.23 (0.02, 0.45)	0.04	—
Combined	—	0 (−0.08, 0.08)	1	46.5/0.13	−0.02 (−0.08, 0.04)	0.59	63.5/0.04	−0.01 (−0.1−0.1, 0.08)	0.79	64.0/0.04
Parietal lobe	—	—	—	—	—	—	—	—	—	—
MN	417	−0.1 (−0.2, −0.01)	0.04	—	−0.07 (−0.14, 0.01)	0.08	—	−0.1 (−0.2, 0)	0.05	—
MD	442	0.01 (−0.04, 0.06)	0.65	—	0 (−0.03, 0.02)	0.83	—	0 (−0.04, 0.04)	0.99	—
NC	446	0.01 (−0.08, 0.1)	0.82	—	−0.03 (−0.09, 0.03)	0.34	—	−0.02 (−0.11, 0.07)	0.63	—
MS	440	0.09 (−0.1, 0.29)	0.36	—	0.05 (−0.1, 0.19)	0.54	—	0.08 (−0.11, 0.27)	0.39	—
Combined	—	−0.01 (−0.07, 0.05)	0.77	44.4/0.15	−0.01 (−0.04, 0.01)	0.33	15.3/0.15	−0.02 (−0.07, 0.03)	0.48	34.4/0.21
Temporal Lobe	—	—	—	—	—	—	—	—	—	—
MN	417	−0.08 (−0.17, 0.01)	0.08	—	−0.05 (−0.1, 0.01)	0.09	—	−0.07 (−0.15, 0)	0.05	—
MD	442	−0.01 (−0.07, 0.04)	0.59	—	0 (−0.03, 0.02)	0.82	—	−0.01 (−0.04, 0.03)	0.75	—
NC	446	0.03 (−0.07, 0.13)	0.54	—	0 (−0.08, 0.08)	0.91	—	0.02 (−0.09, 0.13)	0.71	—
MS	440	0.24 (0.03, 0.45)	0.02	—	0.11 (−0.04, 0.26)	0.14	—	0.21 (0.01, 0.41)	0.04	—
Combined	—	0.01 (−0.07, 0.09)	0.85	65.5/0.03	−0.01 (−0.04, 0.03)	0.68	35.7/0.20	0 (−0.07, 0.07)	0.99	62.5/0.05
Deep gray	—	—	—	—	—	—	—	—	—	—
MN	417	−0.08 (−0.21, 0.04)	0.19	—	−0.06 (−0.13, 0.01)	0.07	—	−0.09 (−0.2, 0.01)	0.07	—
MD	442	−0.04 (−0.1, 0.02)	0.15	—	−0.01 (−0.04, 0.01)	0.29	—	−0.03 (−0.06, 0.01)	0.18	—
NC	446	−0.04 (−0.18, 0.1)	0.55	—	−0.04 (−0.13, 0.05)	0.35	—	−0.06 (−0.19, 0.07)	0.38	—
MS	440	0.11 (−0.1, 0.32)	0.3	—	0.04 (−0.12, 0.21)	0.61	—	0.09 (−0.12, 0.29)	0.39	—
Combined	—	−0.04 (−0.09, 0.01)	0.1	0/0.48	−0.02 (−0.04, 0)	0.09	0/0.46	−0.03 (−0.07, 0)	0.07	1.5/0.38
Hippocampus	—	—	—	—	—	—	—	—	—	—
MN	416	−0.01 (−0.14, 0.12)	0.87	—	−0.05 (−0.12, 0.02)	0.15	—	−0.06 (−0.17, 0.05)	0.28	—
MD	442	−0.02 (−0.1, 0.05)	0.53	—	0 (−0.03, 0.04)	0.83	—	0 (−0.05, 0.05)	1	—
NC	443	0.07 (−0.05, 0.2)	0.27	—	−0.04 (−0.17, 0.1)	0.6	—	0 (−0.15, 0.16)	0.99	—
MS	437	0.07 (−0.32, 0.45)	0.74	—	0.12 (−0.16, 0.41)	0.39	—	0.13 (−0.25, 0.51)	0.5	—
Combined	—	0 (−0.06, 0.06)	0.99	0/0.63	−0.01 (−0.04, 0.02)	0.64	0/0.40	−0.01 (−0.05, 0.04)	0.71	0/0.68
AD signature	—	—	—	—	—	—	—	—	—	—
MN	417	−0.09 (−0.19, 0.02)	0.11	—	−0.03 (−0.1, 0.04)	0.39	—	−0.06 (−0.15, 0.03)	0.2	—
MD	442	0.01 (−0.05, 0.06)	0.8	—	−0.01 (−0.03, 0.02)	0.7	—	0 (−0.04, 0.03)	0.86	—
NC	446	0.01 (−0.09, 0.11)	0.85	—	−0.02 (−0.09, 0.05)	0.57	—	−0.01 (−0.12, 0.09)	0.8	—
MS	440	0.2 (−0.02, 0.42)	0.07	—	0.12 (−0.03, 0.27)	0.12	—	0.2 (−0.01, 0.4)	0.06	—
Combined	—	0 (−0.07, 0.07)	0.97	48.8/0.12	−0.01 (−0.03, 0.02)	0.63	9.2/0.35	0 (−0.06, 0.05)	0.86	41.0/0.17

Note: Adjusted for age, gender, race, education and estimated intracranial volume. —, no data; ARIC-NCS, Atherosclerosis Risk in Communities Neurocognitive Study; CI, confidence interval; MD, Maryland; MN, Minnesota; MS, Mississippi; NC, North Carolina; PM, particulate matter.

Table 4. Adjusted association between a 1-$\mu g/m^3$-higher past PM_{10} exposure and SD-unit brain volumes in 2011–2013 in the ARIC-NCS study.

		$PM_{2.5}$ 1990–1998			$PM_{2.5}$ 1999–2007			$PM_{2.5}$ 1990–2007		
Outcome and site	n	Beta (95% CI)	p-Value	I^2/p-Value for heterogeneity	Beta (95% CI)	p-Value	I^2/p-Value for heterogeneity	Beta (95% CI)	p-Value	I^2/p-value for heterogeneity
Total brain	—	—	—	—	—	—	—	—	—	—
MN	419	−0.01 (−0.03, 0.01)	0.56	—	−0.02 (−0.05, 0)	0.06	—	−0.02 (−0.04, 0.01)	0.16	—
MD	443	0 (−0.01, 0.02)	0.75	—	0.01 (−0.01, 0.02)	0.51	—	0 (−0.01, 0.02)	0.64	—
NC	446	0.01 (−0.05, 0.07)	0.85	—	0.01 (−0.06, 0.07)	0.85	—	0.01 (−0.06, 0.07)	0.83	—
MS	441	0.03 (−0.05, 0.11)	0.42	—	0.03 (−0.03, 0.09)	0.27	—	0.04 (−0.04, 0.11)	0.31	—
Combined	—	0 (−0.01, 0.01)	0.96	0/0.77	0 (−0.02, 0.02)	0.9	41.8/0.16	0 (−0.02, 0.01)	0.86	7.9/0.35
Frontal lobe	—	—	—	—	—	—	—	—	—	—
MN	417	0.01 (−0.02, 0.04)	0.49	—	−0.01 (−0.04, 0.02)	0.52	—	0 (−0.03, 0.03)	0.87	—
MD	442	0 (−0.03, 0.02)	0.69	—	0 (−0.03, 0.02)	0.84	—	0 (−0.03, 0.02)	0.75	—
NC	446	0 (−0.08, 0.08)	0.99	—	0.03 (−0.05, 0.11)	0.51	—	0.01 (−0.07, 0.1)	0.73	—
MS	440	0.02 (−0.05, 0.1)	0.54	—	0 (−0.06, 0.06)	1	—	0.01 (−0.06, 0.09)	0.74	—
Combined	—	0 (−0.01, 0.02)	0.81	0/0.82	0 (−0.02, 0.01)	0.7	0/0.86	0 (−0.02, 0.02)	0.86	0/0.96
Occipital lobe	—	—	—	—	—	—	—	—	—	—
MN	417	−0.02 (−0.05, 0.01)	0.24	—	−0.03 (−0.05, 0)	0.05	—	−0.03 (−0.06, 0)	0.09	—
MD	442	0 (−0.03, 0.03)	0.87	—	0.01 (−0.02, 0.04)	0.64	—	0 (−0.03, 0.03)	0.9	—
NC	446	0.01 (−0.09, 0.12)	0.82	—	0.03 (−0.08, 0.13)	0.62	—	0.02 (−0.09, 0.13)	0.72	—
MS	440	0.1 (−0.02, 0.22)	0.1	—	0.1 (0.01, 0.19)	0.02	—	0.11 (0, 0.22)	0.05	—
Combined	—	0 (−0.03, 0.02)	0.77	21.6/0.28	0.01 (−0.03, 0.05)	0.6	66.8/0.03	0 (−0.03, 0.04)	0.86	54.3/0.09
Parietal lobe	—	—	—	—	—	—	—	—	—	—
MN	417	0.01 (−0.02, 0.04)	0.42	—	−0.02 (−0.05, 0.01)	0.29	—	−0.01 (−0.03, 0.02)	0.65	—
MD	442	0 (−0.02, 0.03)	0.72	—	0 (−0.02, 0.03)	0.84	—	0 (−0.02, 0.03)	0.78	—
NC	446	0.02 (−0.05, 0.09)	0.6	—	0.04 (−0.02, 0.1)	0.22	—	0.03 (−0.04, 0.1)	0.38	—
MS	440	0.04 (−0.05, 0.14)	0.38	—	0.05 (−0.02, 0.13)	0.18	—	0.06 (−0.04, 0.15)	0.24	—
Combined	—	0.01 (−0.01, 0.02)	0.31	0/0.85	0 (−0.02, 0.03)	0.71	31.8/0.22	0 (−0.01, 0.02)	0.75	0/0.51
Temporal lobe	—	—	—	—	—	—	—	—	—	—
MN	417	0.01 (−0.02, 0.03)	0.65	—	−0.01 (−0.04, 0.02)	0.57	—	0 (−0.04, 0.03)	0.84	—
MD	442	−0.01 (−0.03, 0.01)	0.47	—	−0.01 (−0.03, 0.02)	0.58	—	−0.01 (−0.03, 0.02)	0.5	—
NC	446	0.02 (−0.05, 0.09)	0.66	—	0.04 (−0.02, 0.11)	0.2	—	0.03 (−0.04, 0.1)	0.39	—
MS	440	0.12 (0.02, 0.23)	0.02	—	0.1 (0.02, 0.17)	0.01	—	0.12 (0.03, 0.22)	0.01	—
Combined	—	0.01 (−0.02, 0.04)	0.52	51.1/0.11	0.02 (−0.02, 0.05)	0.37	65.2/0.03	0.01 (−0.02, 0.05)	0.43	61.0/0.05
Deep gray	—	—	—	—	—	—	—	—	—	—
MN	417	−0.01 (−0.04, 0.01)	0.27	—	−0.03 (−0.05, 0)	0.04	—	−0.02 (−0.05, 0)	0.04	—
MD	442	−0.02 (−0.05, 0.01)	0.12	—	−0.02 (−0.05, 0.01)	0.15	—	−0.02 (−0.05, 0.01)	0.12	—
NC	446	−0.04 (−0.14, 0.06)	0.44	—	−0.01 (−0.11, 0.09)	0.78	—	−0.03 (−0.14, 0.08)	0.59	—
MS	440	0.05 (−0.05, 0.15)	0.33	—	0.04 (−0.04, 0.12)	0.3	—	0.05 (−0.04, 0.14)	0.28	—
Combined	—	−0.02 (−0.03, 0)	0.07	0/0.57	−0.02 (−0.04, 0)	0.03	0/0.45	−0.02 (−0.04, 0)	0.02	0/0.49
Hippocampus	—	—	—	—	—	—	—	—	—	—
MN	416	−0.01 (−0.04, 0.03)	0.69	—	−0.02 (−0.04, 0.01)	0.13	—	−0.02 (−0.04, 0.01)	0.24	—
MD	442	−0.02 (−0.05, 0.02)	0.35	—	−0.01 (−0.04, 0.03)	0.75	—	−0.01 (−0.05, 0.02)	0.5	—
NC	443	0.06 (−0.03, 0.16)	0.2	—	0.08 (−0.02, 0.19)	0.1	—	0.08 (−0.03, 0.19)	0.14	—
MS	437	0.05 (−0.14, 0.24)	0.62	—	0.08 (−0.05, 0.22)	0.23	—	0.08 (−0.1, 0.25)	0.38	—
Combined		−0.01 (−0.03, 0.02)	0.58	0/0.46	0 (−0.03, 0.04)	0.87	47.9/0.12	−0.01 (−0.03, 0.02)	0.7	25.1/0.26
AD signature	—	—	—	—	—	—	—	—	—	—
MN	417	0 (−0.02, 0.03)	0.88	—	−0.01 (−0.04, 0.01)	0.28	—	−0.01 (−0.03, 0.02)	0.49	—
MD	442	0 (−0.02, 0.02)	0.99	—	0 (−0.03, 0.02)	0.93	—	0 (−0.03, 0.02)	0.96	—
NC	446	0.02 (−0.06, 0.1)	0.59	—	0.05 (−0.03, 0.14)	0.2	—	0.04 (−0.05, 0.13)	0.36	—
MS	440	0.1 (−0.01, 0.21)	0.07	—	0.12 (0.03, 0.2)	0.01	—	0.12 (0.02, 0.23)	0.02	—
Combined	—	0 (−0.01, 0.02)	0.6	12.0/0.33	0.02 (−0.02, 0.06)	0.35	70.1/0.02	0.01 (−0.02, 0.04)	0.54	53.5/0.09

Note: Adjusted for age, gender, race, education, and estimated intracranial volume. —, no data; ARIC-NCS, Atherosclerosis Risk in Communities Neurocognitive Study; MD, Maryland; MN, Minnesota; MS, Mississippi; NC, North Carolina; PM, particulate matter.

Discussion

In pooled analyses combining all four sites, higher mean $PM_{2.5}$ and PM_{10} exposures in the 5 to 20 y prior were associated with smaller deep-gray regional brain volumes and higher $PM_{2.5}$ exposures 5–14 y prior were marginally associated with smaller frontal lobe volumes. We found little evidence in support of an association between higher long-term exposure to $PM_{2.5}$ or PM_{10} over our three time periods of exposure and other brain volume measures or markers of cerebrovascular and small vessel disease in pooled analyses. However, there was evidence of significant heterogeneity in associations between PM and brain volumes by study site. When considering site-specific associations, we consistently observed smaller total and regional brain volumes with greater long-term exposure to $PM_{2.5}$ in the Minnesota site, but not the other three sites. Throughout, where there was evidence of an association between PM exposure and brain volumes, the magnitude of these associations was similar to that seen in prior analyses in this sample, considering the association between midlife blood pressure and brain volumes. (Power et al. 2016b) For reference, the −0.05 to −0.1 SD unit effect size observed in the Minnesota site can be interpreted as loss of approximately 0.5% to 1% of regional brain volume.

Strengths of this study include the relatively large number of participants with MRI, our ability to use weighting to account for selection into the MRI subcohort in primary analyses and attrition from the baseline ARIC visit in sensitivity analyses, and consideration of long-term, cumulative past exposures. Our coefficients of variation for air pollution exposure estimates are similar to those calculated from other studies based in geographically constrained locations (albeit typically using shorter averaging periods) (Power et al. 2016a), suggesting that the variation in exposure at our four sites is similar to that found in other locations. However, the relatively small number of persons in each center limits our power to detect small true effects, systematically evaluate the potential for nonlinear associations, or assess effect modification by age or other personal factors. In addition, mild brain atrophy may have several root causes. Heterogeneity in the causes of neurodegeneration in our sample may contribute to the muted dose–response, especially if only a subset of the potential causes of neurodegeneration, including both neurodegenerative diseases and other sources of brain injury, are related to air pollution exposure. Similarly, our findings do not preclude the possibility of neurotoxic effects on the brain that are not captured by the considered MRI markers of brain injury; studies considering alternate markers (e.g., cortical thickness) may be useful. We did not consider associations with more recent exposures, or with cumulative exposures that include recent exposures. As such, we cannot comment on the relative importance of recent versus past exposures or whether recent exposures are an acceptable surrogate for long-term cumulative exposures. As with many recent studies of the health effects of air pollution, we used modeled exposure measures using residential address rather than personal exposure metrics, and we were unable to address the issue of indoor air pollution. Moreover, we cannot discount the possibility that regional variation in predictive accuracy of our model may complicate or invalidate comparison of site-specific effect estimates. Finally, we cannot exclude the possibility of chance findings.

There are a small number of reports considering the association between PM exposures and MRI-based measurements of brain structure or subclinical cerebrovascular disease. Collectively, including the current study, this body of literature fails to identify a consistent pattern of associations, as results are frequently null, with the few positive findings differing across studies. In a study nested within the Women's Health Initiative Memory Study (WHIMS), $PM_{2.5}$ air pollution exposures in 1999–2006 were not associated with gray-matter brain volumes assessed in 2005–2006 (Chen et al. 2015). However, higher $PM_{2.5}$ exposures were associated with smaller, normal-appearing white matter brain volumes, with magnitudes of association of roughly 0.01-SD units volume per interquartile range increase in exposure. Additional analyses in WHIMS using a voxel-based approach found $PM_{2.5}$ exposures in the 3 y prior to MRI were associated with areas of smaller cortical gray-matter and subcortical white-matter volumes (Casanova et al. 2016). Notably, the authors also report significant clusters of association whereby higher $PM_{2.5}$ was associated with larger deep gray–matter nuclei volumes in WHIMS participants (Casanova et al. 2016), opposite to our own observations of associations between higher PM and smaller regional gray-matter volumes in ARIC participants. In participants from the Framingham Offspring Study who lived in the New England region, higher past-year $PM_{2.5}$ exposure was associated with smaller total cerebral brain volumes and greater risk of covert brain infarcts, but not with WMH volumes, age-adjusted extensive WMH volumes, or hippocampal volumes (Wilker et al. 2015). Finally, in a study of participants from the Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort, there was no association between higher $PM_{2.5}$ exposures in 2003 and either brain parenchymal fraction (a measure of brain atrophy) or the presence of microbleeds at an MRI between 2004 and 2010, while there was a protective association between higher $PM_{2.5}$ exposure and smaller WMH volumes (Wilker et al. 2016).

Interestingly, studies of the relationship between air pollution and cognitive or related outcomes (e.g., MRI markers or neuropathology) that consider geographically localized samples are more likely to report null associations. In contrast, studies considering participants spread over larger geographic regions have been more likely to report adverse associations (Power et al. 2016a). We suggest several potential explanations. First, studies in geographically constrained locations are typically small, and the range of exposures tends to be smaller. Thus, such studies are likely underpowered to detect small effects. A meta-analytic approach, such as demonstrated here, for combining information about multiple small, geographically constrained studies in different locations can overcome this limitation without inducing concerns about strong or intractable confounding that may arise in pooled analyses. Second, studies with wider geographic distribution may be more susceptible to confounding by characteristics that vary regionally. As we have previously demonstrated elsewhere (Power et al. 2016a), it appears unlikely that residual confounding may fully account for the adverse findings in more geographically dispersed settings, given the characteristics such a confounder would have to have in order to fully account for previously observed associations. However, this possibility cannot be fully discounted, especially given evidence in this study that exposure and confounder distributions across sites do not always overlap. Thus, residual confounding may still lead to a biased estimate of the true association in more expansive settings when spatial confounding is strong and meta-analysis of site-specific associations is not used. Finally, it is possible that a focus on quantifying exposure based on particulate mass is contributing to this heterogeneity of findings. If specific PM species or other physical characteristics such as surface area confer the relevant toxic effect, geographically constrained studies may be studying the impact of less toxic exposures, while geographically broad studies may be capturing mixtures of these effects due to their larger study area. Our finding of heterogeneity in association across sites would support this hypothesis, and the finding of adverse associations in Minnesota but not the other three sites may be attributable not to chance, but to the relative toxicity of

exposures. Future work will be needed to understand the drivers of the divide in findings between these two study types in order to establish a causal effect of air pollution on late-life brain health.

Another potential explanation for the finding of adverse associations between $PM_{2.5}$ and brain volumes in the Minnesota site, but not the others, lies in the potential nonlinearity of the association. Minnesota had the lowest air pollution levels of the four sites, and previous studies have suggested a nonlinear relationship between PM and both total cerebral brain volume (Wilker et al. 2015) and cognitive function (Ailshire and Crimmins 2014; Oudin et al. 2015; Power et al. 2011), whereby the strongest associations were observed at the lowest levels of exposure. Given relatively small samples per site, we were not able to assess nonlinearity of exposure within site, but hope others may be able to follow up on this possibility in the future.

Conclusions

In conclusion, we found no associations between cumulative past PM exposure and MRI-based markers of cerebrovascular disease. Combining data across sites, higher past PM exposures were associated with smaller deep-gray volumes across sites, and higher $PM_{2.5}$ in 1999–2007 was marginally associated with smaller frontal lobe volumes. When considering individual sites, higher $PM_{2.5}$ exposures were associated with smaller brain volumes in the Minnesota site. Further work will be needed to replicate these findings and understand the sources of heterogeneity across sites, and will require consideration of a broader number of sites.

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