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Full length article



## The association of long-term exposure to criteria air pollutants, fine particulate matter components, and airborne trace metals with late-life brain amyloid burden in the Atherosclerosis Risk in Communities (ARIC) study

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## ARTICLE INFO

Handling Editor: Hanna Boogaard

## ABSTRACT

**Background:** Studies suggest associations between long-term ambient air pollution exposure and outcomes related to Alzheimer's disease (AD). Whether a link exists between pollutants and brain amyloid accumulation, a biomarker of AD, is unclear. We assessed whether long-term air pollutant exposures are associated with late-life brain amyloid deposition in Atherosclerosis Risk in Communities (ARIC) study participants.

**Methods:** We used a chemical transport model with data fusion to estimate ambient concentrations of PM<sub>2.5</sub> and its components, NO<sub>2</sub>, NO<sub>x</sub>, O<sub>3</sub> (24-hour and 8-hour), CO, and airborne trace metals. We linked concentrations to geocoded participant addresses and calculated 10-year mean exposures (2002 to 2011). Brain amyloid deposition was measured using florbetapir amyloid positron emission tomography (PET) scans in 346 participants without dementia in 2012–2014, and we defined amyloid positivity as a global cortical standardized uptake value ratio  $\geq$  the sample median of 1.2. We used logistic regression models to quantify the association between amyloid positivity and each air pollutant, adjusting for putative confounders. In sensitivity analyses, we considered whether use of alternate air pollution estimation approaches impacted findings for PM<sub>2.5</sub>, NO<sub>2</sub>, NO<sub>x</sub>, and 24-hour O<sub>3</sub>.

**Results:** At PET imaging, eligible participants (N = 318) had a mean age of 78 years, 56% were female, 43% were Black, and 27% had mild cognitive impairment. We did not find evidence of associations between long-term exposure to any pollutant and brain amyloid positivity in adjusted models. Findings were materially

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<https://doi.org/10.1016/j.envint.2023.108200>

Received 26 April 2023; Received in revised form 13 August 2023; Accepted 11 September 2023

Available online 17 September 2023

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unchanged in sensitivity analyses using alternate air pollution estimation approaches for PM<sub>2.5</sub>, NO<sub>2</sub>, NO<sub>x</sub>, and 24-hour O<sub>3</sub>.

**Conclusions:** Air pollution may impact cognition and dementia independent of amyloid accumulation, though whether air pollution influences AD pathogenesis later in the disease course or at higher exposure levels deserves further consideration.

## 1. Introduction

Identifying modifiable risk factors for Alzheimer's disease (AD) remains a top priority for dementia-related research, as the failure rate for clinical trials of AD treatments remains staggeringly high (Cummings et al., 2014). Specifically, assessing the potential impact of environmental exposures on AD risk has important implications for primary prevention efforts since many are regulated at the population level. Recent growth in the literature linking long-term, ambient air pollution to AD-related outcomes has been dramatic. (Weuve et al., 2021) While the evidence remains mixed, multiple studies have reported associations between criteria air pollutants and cognitive decline (Tonne et al., 2014; Weuve et al., 2012; Duchesne et al., 2022), incident dementia (Oudin et al., 2016; Chen et al., 2017), progression from mild cognitive impairment to dementia (Wu et al., 2022), and magnetic resonance imaging (MRI)-based measures of brain morphology. (Casanova et al., 2016; Chen et al., 2015; Power et al., 2018; Wilker et al., 2015).

The mechanisms underlying such associations remain unclear. However, the beta-amyloid plaques that characterize AD may form in response to inflammation (McGeer and McGeer, 2013) and/or oxidative stress (Cai et al., 2011), suggesting a potential mechanism linking air pollution to AD. Animal studies show that concentrated air pollution exposure and some heavy metal components of particulate matter stimulate accumulation of reactive oxygen species (ROS) (Bai et al., 2020; Gurgueira et al., 2002) and induce oxidative stress in the brain (Durga et al., 2015). Likewise, particulate matter increases cerebral pro-inflammatory cytokines (Durga et al., 2015; Sahu et al., 2021) and promotes vascular inflammation (Sun et al., 2005). Mechanistic studies demonstrate that concentrated air pollution exposure increases cerebral AB42 and AB40 (the primary components of amyloid plaques) (Durga et al., 2015; Bhatt et al., 2015), the AB42:40 ratio (Patten et al., 2021), and amyloid plaque accumulation in rodents (Patten et al., 2021; Cacciottolo et al., 2017). Additionally, several studies report increases in oxidative stress, inflammation, and cerebral AB42 among dogs and humans living in Mexico City (Calderón-Garcidueñas et al., 2012; Calderón-Garcidueñas et al., 2008; Calderón-Garcidueñas et al., 2004), where average air pollution concentrations exceed US Environmental Protection Agency (EPA) air quality standards.

Findings from studies examining associations between ambient air pollution exposure and brain amyloid deposition in humans (Alemay et al., 2021; Iaccarino et al., 2021; Lee et al., 2020; Shaffer et al., 2021) have been inconsistent, with limited consideration of criteria air pollutants other than fine particulate matter (PM<sub>2.5</sub>). Moreover, particulate matter itself is a heterogeneous mixture of components including sulfates, nitrates, organic and elemental carbon, ammonium, and trace metals that may have different toxicity and impact on AD risk. To our knowledge, no study thus far has considered whether PM<sub>2.5</sub> components are associated with human brain amyloid deposition. Finally, existing epidemiologic studies of air pollution and brain amyloid deposition may not generalize to the broader US population because they have either enrolled persons who are already presenting with cognitive impairment (Iaccarino et al., 2021) or those with AD predisposition (Alemay et al., 2021), or are conducted in areas with ambient air pollution exposures well above those in the US (Lee et al., 2020). To address these gaps, we estimated the association between long-term exposure to criteria air pollutants, components of PM<sub>2.5</sub>, and airborne trace metals with late-life brain amyloid deposition in the Atherosclerosis Risk in Communities (ARIC) study cohort.

## 2. Methods

### 2a. Sample

The ARIC study recruited 15,792 participants from four US communities: Minneapolis suburbs, MN; Jackson, MS; Forsyth County, NC; and Washington County, MD. All participants were aged 45–64 years at recruitment, and all those recruited in MS were Black. The first four clinical visits took place roughly every three years (visit 1, 1987–1989; visit 2, 1990–1992; visit 3, 1993–1995; visit 4, 1996–1998). During visit 5 (2011–2013), participants with a prior ARIC brain MRI scan or evidence of cognitive impairment or decline and an age-stratified sample of those with normal cognition were invited to complete brain MRIs. A subset of those who completed MRIs at three ARIC study centers (MS, NC, and MD) and did not have dementia, heavy current alcohol use, renal dysfunction, or heart rate-corrected QT interval prolongation were invited for florbetapir (amyloid) positron emission tomography (PET) scans as part of the ARIC-PET ancillary study. Ultimately, 346 ARIC participants underwent amyloid-PET scans in 2012–2014. Study procedures were reviewed and approved by the institutional review board of each study center. All ARIC participants provided written informed consent.

After excluding participants who were not White in MD or NC (due to small numbers in other race categories at these study centers, N = 8), who were missing exposure (N = 8) or covariate data (N = 10), and who did not consent to use of genetic data (N = 1), as well as one participant who was retroactively diagnosed with dementia at the time of PET scan, our final analytic sample included 318 participants.

### 2b. Exposure

We considered 10-year exposure to criteria air pollutants (PM<sub>2.5</sub>, nitrogen dioxide [NO<sub>2</sub>], oxides of nitrogen [NO<sub>x</sub>], 24-hour ozone [O<sub>3</sub>], 8-hour O<sub>3</sub>, and carbon monoxide [CO]), components of fine particulate matter (sulfates [SO<sub>4</sub>], ammonium [NH<sub>4</sub>], nitrates [NO<sub>3</sub>], elemental carbon [EC], and organic carbon [OC]), and airborne trace metals with prior evidence of toxicity and acceptable estimation model performance (copper [Cu], iron [Fe], mercury [Hg], nickel [Ni], lead [Pb], vanadium [V], and zinc [Zn]).

We used a chemical transport model with observational data fusion to predict annual average pollutant concentrations in nested 1.33-, 4-, and 12-km gridded rasters approximately centered on ARIC recruitment sites. We derived two separate sets of exposure predictions (CMAQ-NEI and CMAQ-EDGAR) (Byun and Schere, 2006) for each gridded raster. Both sets were derived using the Community Multiscale Air Quality (CMAQ) chemical transport model, incorporating data on emissions, biogenic emissions, and weather. The two sets of predictions differed only based on which emissions inventory was used in the process, either the National Emissions Inventory [NEI] or the Emissions Database for Global Atmospheric Research [EDGAR]). After exploratory analyses suggested minimal impact on accuracy of annual estimates, simulations were run for only four representative months (January, April, July, and October) of each year, in order to reduce computation time. For each representative month, hourly predictions from each month were aggregated to obtain monthly predictions, and then averaged again to obtain annual predictions for each calendar year. We then weighted the two sets of annual predictions (CMAQ-NEI and CMAQ-EDGAR) to maximize agreement with annual air pollution concentrations measured

at US EPA regulatory monitors. Finally, each weighted average annual prediction was fused with observational data to further mitigate any systematic bias in model predictions (Chen et al., 2014; Hu et al., 2017).

We conducted validation exercises using leave-one-out cross-validation to assess model accuracy. Specifically, we used data on annual average air pollution exposures at EPA National Ambient Air Quality Standards (NAAQS) monitor sites within the spatial domains covered by the 1.33-, 4-, and 12-km gridded rasters as available for all pollutants except trace metals. Model performance for estimated annual PM<sub>2.5</sub> levels from 2000 to 2012 was strong ( $R^2$  for 1.33-, 4-, and 12-km grid cells of 0.82, 0.77, and 0.78, respectively). Cross-validated  $R^2$  values for annual exposure to ammonium (0.97 for 1.33-km, 0.91 for 4-km, and 0.77 for 12-km grid cells), sulfates (0.98 for 1.33-km, 0.96 for 4-km, and 0.89 for 12-km grid cells), and nitrates (0.97 for 1.33-km, 0.85 for 4-km, and 0.84 for 12-km grid cells) were similarly high. Agreement was generally fair to moderate for gaseous pollutants ( $R^2$  for NO<sub>2</sub>, NO<sub>x</sub>, and CO in 1.33-km grid cells of 0.37, 0.46, and 0.66, respectively, and  $R^2$  for 24-hour and 8-hour O<sub>3</sub> in 4-km grid cells of 0.53 and 0.39, respectively), elemental carbon ( $R^2$  range across raster resolutions, as available: 0.19 to 0.63), and organic carbon ( $R^2$  range across raster resolutions: 0.32 to 0.51). Cross-validation procedures for trace metals in 12-km rasters were conducted among monitoring stations containing at least 12 pairs of prediction-observations after setting both predicted and observed annual averages at or below the minimum detectable limit (MDL) to the MDL value. Trace metal cross-validation  $R^2$  values were as follows: Cu, 0.71; Fe, 0.68; Hg, 0.88; Ni, 0.50; Pb, 0.86; V, 0.76; and Zn, 0.80.

Participant addresses collected at each ARIC visit and during annual telephone interviews were standardized to US postal service formats and geocoded by a commercial vendor with excellent accuracy (Whitsel et al., 2006; Whitsel et al., 2004). Geocoded participant address coordinates were then joined to grid cell-specific exposures whenever the geocoded addresses fell within the spatial domains for which 1.33-, 4-, or 12-km gridded estimates were created. Participant exposures were assigned based on the finest spatial resolution of air pollutant data available for participant residential addresses. To account for residential mobility, participant exposures were weighted by the amount of time spent at each recorded residential address within a given calendar year. Because amyloid plaque accumulates long before the onset of dementia symptoms (Villemagne et al., 2013), we averaged participant-specific air pollutant concentrations over ten years (from 2002 to 2011).

## 2c. Outcome

Brain amyloid deposition was measured with florbetapir PET scans. Detailed methods have been previously described (Gottesman et al., 2016). 3T MRI scans were conducted at ARIC study centers from 2011 to 2013. PET scans were conducted within one year of MRIs (from 2012 to 2014). Participants were injected with florbetapir isotope and underwent four 5-minute scans. The Johns Hopkins University PET image analysis center processed the data and calculated standardized uptake value ratios (SUVRs) in 34 manually drawn regions of interest using cerebellum gray matter as the reference. Global amyloid deposition was calculated as a weighted average of SUVRs in orbitofrontal, prefrontal, and superior frontal cortices; the lateral temporal, parietal, and occipital lobes; the precuneus; the anterior cingulate; and the posterior cingulate. Because global SUVR is heavily skewed, previous analyses in the ARIC-PET cohort have considered those with a global SUVR above the median of 1.2 to have elevated brain amyloid deposition (Gottesman et al., 2016; Gottesman et al., 2017). Given this prior work, and the use of multiple different cutoffs to historically define amyloid positivity in the literature (Jansen et al., 2015), we also use this cutoff to define amyloid positivity.

## 2d. Covariates

We used self-reported data to characterize age at the time of PET

scan, sex, and education (less than high school, high school or equivalent, greater than high school). We collapsed race and study center to derive a race-center variable (Black in MS, White in NC, and White in MD). Procedures for adjudicating cognitive status in ARIC have been previously described (Knopman et al., 2016); briefly, participants were administered the Delayed Word Recall Test (Knopman and Ryberg, 1989), the Digit Symbol Substitution Test (Wechsler and WAIS-R: Manual, 1981), and the Word Fluency Test (Benton et al., 1981) at ARIC visits 2, 4, and 5, and an additional cognitive testing battery (including the Mini-Mental State Examination [MMSE] (Tombaugh and McIntyre, 1992), the Clinical Dementia Rating [CDR] scale (Morris, 1993), and the Functional Activities Questionnaire [FAQ] (Pfeffer et al., 1982)) at visit 5. Mild cognitive impairment was adjudicated if a participant had low scores in any one cognitive domain, evidence of cognitive decline, an FAQ score less than 6, and a CDR score between 0.5 and 3 (Knopman et al., 2016). Diagnoses were confirmed by expert consensus. We identified those with at least one APOE e4 allele via genotyping.

We used measures from visit 4 (1996–1998), the closest visit preceding our air pollution exposure period of interest, to characterize potential confounders. Smoking and alcohol consumption were self-reported and categorized as current, former, or never. Body mass index (BMI) was calculated as participants' weight in kilograms divided by their squared height in meters. Hypertension, diabetes, and coronary heart disease status were defined using medication data, hospital surveillance, measured blood pressure or blood glucose levels (where applicable), and self-reported medical histories. Finally, we operationalized neighborhood socioeconomic status (nSES) using census tract-level measures of log of median household income; log of median housing value; percent of households earning interest, dividends, or net rental income; proportion of adults with high school degrees; proportion of adults with college degrees; and proportion of adults in executive, managerial, or professional occupations (Roux et al., 2001). Z-scored versions of these variables were summed to produce a time-varying overall measure of nSES at participant addresses (Roux et al., 2001), from which we derived a 10-year average nSES for each participant (from 2002 to 2011).

## 2e. Statistical Analyses

We quantified characteristics of persons with and without elevated brain amyloid at visit 5. We assessed differences in continuous variables with Student's t-tests and used chi-square tests for categorical variables. We also described distributions of 2002–2011 averages of each exposure and calculated partial correlations between each exposure, adjusting for study center.

Multivariable-adjusted logistic regression models were used to quantify the association between 2002 and 2011 average air pollutant exposure and elevated amyloid deposition in 2012–2014. Associations were scaled to represent the effects of different exposure contrasts for each pollutant: 1  $\mu\text{g}/\text{m}^3$  for PM<sub>2.5</sub>; 1 ppb for NO<sub>2</sub>, NO<sub>x</sub>, 24-hour O<sub>3</sub>, and 8-hour O<sub>3</sub>; 100 ppb for CO; 0.1 ppb for sulfates, ammonium, nitrates, elemental carbon, and organic carbon; 10  $\text{ng}/\text{m}^3$  for Fe; and 1  $\text{ng}/\text{m}^3$  for Cu, Hg, Ni, Pb, V, and Zn. We ran unadjusted models (Model 1); models adjusted for age at PET scan, sex, education, race-center, and cognitive status (normal/MCI) at visit 5 (Model 2); and a fully adjusted model additionally adjusting for APOE e4 status (Model 3).

Because APOE e4 allele status has been shown to modify the association between air pollution and risk of dementia (Cacciottolo et al., 2017) and cognitive status (Schikowski et al., 2015) in prior studies, we explored potential effect measure modification by including a multiplicative interaction term (i.e., pollutant \* APOE e4 allele status) in Model 3. We also explored interactions with race-center, cognitive status, and number of vascular risk factors (i.e., current smoking, hypertension, diabetes, BMI  $\geq 30$ , and total cholesterol  $\geq 200$  mg/dL; N = 316 for analyses of effect measure modification by number of vascular

risk factors) (Gottesman et al., 2017).

In sensitivity analyses, we explored the effect of further covariate adjustment on resulting odds ratios for amyloid positivity. Of our remaining covariates of potential interest, only nSES and BMI were associated with at least one exposure and the outcome, thus meeting the minimum criteria as potential confounders in our sample, and were adjusted for in Model 4 (Model 3 + neighborhood SES) and Model 5 (Model 4 + BMI). For analyses of PM<sub>2.5</sub> components, we further explored adjusting for total PM<sub>2.5</sub> in Model 6 (Model 3 + total PM<sub>2.5</sub>); doing so changed the interpretation to the effect of a higher proportion of the component within total PM<sub>2.5</sub> exposure on late-life amyloid burden as opposed to higher absolute concentrations of each component.

As an additional sensitivity analysis, we explored whether using exposures generated from alternate air pollution estimation approaches impacted associations given evidence from epidemiologic literature that model choice may significantly impact associations with health outcomes (Klompaker et al., 2021; Sellier et al., 2014; Yap et al., 2012). Briefly, we used two additional methods to estimate PM<sub>2.5</sub>: (i) a satellite-based approach incorporating output from a chemical transport model (CTM) and monitor data (Hammer et al., 2020; van Donkelaar et al., 2019), and (ii) a regionalized universal kriging approach that uses partial least squares regression (PLSR)-resolved land use regression (LUR), temporal trend back-extrapolation, and spatial smoothing (Keller et al., 2015; Kirwa et al., 2021). We also used the regionalized universal kriging approach with LUR and PLSR to derive exposure estimates for NO<sub>2</sub> and 24-hour O<sub>3</sub>. Finally, we used a national log-normal ordinary kriging model (Liao et al., 2006) for additional concentration estimates of NO<sub>2</sub>, NO<sub>x</sub>, and 24-hour O<sub>3</sub>. Because data from the national log-normal ordinary kriging model were not available for every participant address, we imputed missing values as estimated exposures from the nearest residential address with available data within 1 km. Those who lived farther than 1 km from a residence with available data were excluded from analyses using the national log-normal ordinary kriging model (N = 13).

Further, we used inverse probability weights to better estimate what our results may look like had the ARIC-PET sample included participants with dementia. First, we obtained weights constructed by the ARIC cohort that account for the MRI study sampling strategy and study center-specific probability of participant refusal. Because inclusion in the PET sample further requires participants be free from dementia, we constructed another set of weights that, when applied to the PET sample, weighted it to better resemble the cognitive distribution of the MRI sample. A schematic for this approach is outlined in Supplemental Fig. 1. Using the combined MRI and cognitive distribution weights accounts for both the systematic sampling of the MRI study and the exclusion of participants with dementia in the PET study, and therefore better reflects the distribution of cognitive status in all ARIC visit 5 participants.

Finally, to confirm our results were not driven by our definition of amyloid positivity, we transformed global cortical SUV<sub>R</sub>s into centiloids following the equation derived by Navitsky et al for Avid VOIs (Navitsky et al., 2018). We estimated the association between each individual air pollutant and centiloids (treated continuously) adjusting for confounders used in Model 2. All analyses were completed using SAS 9.4 (Cary, NC) and RStudio version 1.4.1717.

### 3. Results

Characteristics of all eligible participants, those with elevated amyloid burden (“amyloid positive”), and those without elevated amyloid burden (“amyloid negative”) are presented in Table 1. A significantly higher proportion of amyloid positive participants compared to amyloid negative participants were Black in MS, female, lived in areas of lower socioeconomic status, and had vascular risk factors. Amyloid positive participants were also more likely to have MCI and be APOE e4 carriers.

**Table 1**  
Characteristics of eligible ARIC-Amyloid PET Study participants (N = 318)  
a,b.

	Overall (N = 318)	Amyloid Negative (N = 153)	Amyloid Positive (N = 165)	P-value
Age in years at PET scan, mean (SD)	78.0 (5.3)	77.3 (5.4)	78.7 (5.1)	0.03
Female, N (%)	179 (56.3%)	76 (49.7%)	103 (62.4%)	0.02
Race-center, N (%)				0.001
Black in Jackson, MS	135 (42.5%)	49 (32.0%)	86 (52.1%)	
White in Forsyth County, NC	63 (19.8%)	35 (22.9%)	28 (17.0%)	
White in Washington County, MD	120 (37.7%)	69 (45.1%)	51 (30.9%)	
Education, N (%)				0.23
Less than high school	51 (16.0%)	19 (12.4%)	32 (19.4%)	
High school or equivalent	135 (42.5%)	69 (45.1%)	66 (40.0%)	
Greater than high school	132 (41.5%)	65 (42.5%)	67 (40.6%)	
Cognitive status at visit 5, N (%)				<0.001
MCI	86 (27.0%)	27 (17.6%)	59 (35.8%)	
Cognitively normal	232 (73.0%)	126 (82.4%)	106 (64.2%)	
At least one APOE e4 allele, N (%)	97 (30.5%)	30 (19.6%)	67 (40.6%)	<0.001
2002–2011 average neighborhood SES z- score sum, mean (SD)	−1.6 (5.2)	−0.6 (5.2)	−2.6 (5.1)	<0.001
BMI (kg/m <sup>2</sup> ), mean (SD)	29.2 (5.2)	28.4 (4.8)	30.0 (5.5)	0.008
Smoking status, N (%) <sup>c</sup>				0.93
Current	32 (10.1%)	15 (9.9%)	17 (10.3%)	
Former	132 (41.6%)	62 (40.8%)	70 (42.4%)	
Never	153 (48.3%)	75 (49.3%)	78 (47.3%)	
Alcohol consumption, N (%) <sup>c</sup>				0.43
Current	143 (45.1%)	74 (48.7%)	69 (41.8%)	
Former	95 (30.0%)	44 (28.9%)	51 (30.9%)	
Never	79 (24.9%)	34 (22.4%)	45 (27.3%)	
Diabetes, N (%) <sup>c</sup>	39 (12.3%)	14 (9.3%)	25 (15.2%)	0.11
Hypertension, N (%)	141 (44.3%)	60 (39.2%)	81 (49.1%)	0.08
Coronary heart disease, N (%) <sup>c</sup>	8 (2.6%)	4 (2.7%)	4 (2.5%)	0.90
Number of vascular risk factors, N (%) <sup>c</sup>				<0.001
0	57 (18.0%)	35 (23.2%)	22 (13.3%)	
1	112 (35.4%)	63 (41.7%)	49 (29.7%)	
2+	147 (46.5%)	53 (35.1%)	94 (57.0%)	

a. Time-varying covariates were measured at visit 4 (1996–1998) unless otherwise specified.

b. P-values from student's T-tests (for continuous variables) or chi-square tests (for categorical variables).

c. 1 participant missing data on smoking status, 1 participant missing data on alcohol consumption, 2 participants missing data on diabetes, 7 participants missing data on coronary heart disease, 2 participants missing data on number of vascular risk factors.

Abbreviations: BMI, body mass index; MCI, mild cognitive impairment; MD, Maryland; MS, Mississippi; NC, North Carolina; nSES, neighborhood socioeconomic status; PET, positron emission tomography; SD, standard deviation.

Distributions of air pollutants at participant residential addresses are presented in Fig. 1 and Supplemental Table 1, and partial correlations between pollutants are provided in Supplemental Fig. 2. Notably, elemental carbon and all airborne trace metals were highly correlated with each other (Pearson's  $r \geq 0.9$ ). Additionally, over 98% of participants were assigned to 1.33-km resolution exposures for all pollutants modeled using the primary estimation method.

Although unadjusted associations suggested protective effects, higher air pollution exposures were not significantly associated with amyloid positivity in fully adjusted models (Fig. 2, Supplemental Table 2). Additional adjustment for nSES and BMI in Models 4 and 5 (Supplemental Table 2) and adjusting for total PM<sub>2.5</sub> in analyses considering PM<sub>2.5</sub> components in Model 6 (Supplemental Table 3, Supplemental Fig. 3) did not materially change our results.

We did not see support for effect measure modification of associations between any pollutant and amyloid burden by APOE e4 allele status, cognitive status, or number of vascular risk factors (all  $p$ -values  $> 0.05$ ). Race-center appeared to modify the association between 24-hour O<sub>3</sub> and amyloid burden ( $p$ -value for interaction = 0.028); however, given the number of models considered in our analyses, this is likely a chance finding.

Results from sensitivity analyses were largely consistent with our main findings. Despite low to moderate correlation of PM<sub>2.5</sub>, NO<sub>2</sub>, NO<sub>x</sub>, and 24-hour O<sub>3</sub> estimates across approaches (Supplemental Fig. 4), there was little support for the hypothesized associations between average ten-year exposures and brain amyloid positivity when using alternate air pollution estimation approaches. Of note, estimates using the national log-normal kriging model had wider confidence intervals (Fig. 3), reflecting smaller variability in air pollution estimates using this approach. Results were materially unchanged when we weighted participants to better reflect the cognitive status distribution of all ARIC participants at visit 5 (Fig. 4) and when global SUVs were converted to centile ranks (Supplemental Table 4).

#### 4. Discussion

We did not find significant associations between 10-year exposure to criteria air pollutants, components of PM<sub>2.5</sub>, or airborne trace metals and late-life elevated amyloid deposition among older adults without dementia living in three US communities.

This study contributes to the growing literature examining potential mechanisms underlying associations between air pollution and accelerated cognitive decline or heightened dementia risk in observational studies (Weuve et al., 2021). To date, similar studies of long-term (i.e. greater than one-year) exposure to air pollution and human brain amyloid burden measured *in vivo* have been inconsistent. Iaccarino and colleagues reported that elevated PM<sub>2.5</sub> was associated with a 10% increase (95% CI: 5%, 15%) in odds of amyloid positivity among 18,178 Medicare-eligible adults with MCI or dementia of uncertain etiology (Iaccarino et al., 2021). However, no significant association was found with 8-hour O<sub>3</sub>. Among a sample of 156 participants in Barcelona, 97% of whom reported a family history of AD, no effect was detected for PM<sub>2.5</sub> (Alemany et al., 2021). However, higher NO<sub>2</sub> exposure was associated with higher amyloid deposition only among the subset of participants who had decreased AB42/40 ratios measured in cerebrospinal fluid. As our sample excludes those with dementia, and we lack cerebrospinal fluid measures, direct comparison of these studies to our findings is difficult. Finally, a study of 309 cognitively unimpaired individuals in South Korea reported significantly higher odds of amyloid positivity among those in the highest tertile of 5-year exposure to particulate matter (PM<sub>10</sub>), approximately 48 to 67  $\mu\text{g}/\text{m}^3$  (Lee et al., 2020), which is high relative to levels found in most of the US and those experienced by the participants in our sample.

There is some evidence to suggest that air pollution exposure may influence AD primarily in later stages of the disease process, which may help explain the observed heterogeneity across studies. A recent study

conducted using data from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) cohort found that the hazard ratio for air pollution exposure and progression to dementia among participants with cognitive impairment, no dementia (CIND) at baseline was stronger than that for incident CIND among unimpaired participants, suggesting air pollution may exert stronger effects later in the disease process (Wu et al., 2022). If the effects of air pollution on dementia and its pathological processes are modified by clinical progression, this could explain why our findings do not support the significant findings of prior studies. The study by Alemany et al. reported that NO<sub>2</sub> exposure was associated with amyloid-PET positivity only in those with evidence of AD pathology in cerebrospinal fluid (Alemany et al., 2021), and the study by Iaccarino et al. (Iaccarino et al., 2021) of Medicare beneficiaries included only those who had either MCI or dementia, suggesting the association may be limited to those who are farther along the disease pathway. In contrast, our sample was comprised of persons without dementia, 73% of whom had normal cognition.

Additionally, there is some evidence to suggest that the relationship between air pollution exposures and AD is nonlinear. This may also contribute to heterogeneity in findings across studies. For example, investigators reported nonlinear relationships between both PM<sub>2.5</sub> and PM<sub>10</sub> with incident CIND in the SNAC-K cohort (Wu et al., 2022). This is echoed by the pattern of findings linking particulate matter to markers of AD pathology. For example, a study conducted among community-dwelling residents around Seattle that reported 10-year mean PM<sub>2.5</sub> levels of 8.2  $\mu\text{g}/\text{m}^3$  (Shaffer et al., 2021Preprint:1–13.) found no association between long-term PM<sub>2.5</sub> exposure and three measures of AD pathology at autopsy (Shaffer et al., 2021Preprint:1–13.), mirroring our own US-based findings. On the other hand, studies on AD pathology conducted in Asia, where air pollution levels tend to be much higher, reported significant associations linking PM<sub>2.5</sub> with AB42/40 ratios in cerebrospinal fluid (Ma et al., 2022) and linking PM<sub>10</sub> exposure with amyloid-PET positivity (Lee et al., 2020). If the effect of air pollution exposures on AD risk is most pronounced at higher levels of exposure, this could help explain the observed pattern of findings.

We did not find evidence of effect measure modification by APOE e4 status. This is consistent with previous epidemiologic studies of air pollution and brain amyloid burden in humans (Alemany et al., 2021; Lee et al., 2020). However, this contradicts findings in related work on the effect of air pollution on brain amyloid accumulation in animal and ecologic studies. For example, in an experiment conducted with mice, APOE e4 carriers exposed to particulate matter had higher amyloid deposition compared to unexposed APOE e4 carriers, while no difference was detected between exposed and unexposed APOE e3 carriers (Cacciottolo et al., 2017). Similarly, in young adults and children living in Mexico City exposed to very high levels of air pollution, those with at least one APOE e4 allele had greater AB42 accumulation compared to APOE e3 carriers (Calderón-Garcidueñas et al., 2008). As there are also epidemiologic studies suggesting stronger associations between air pollution and cognitive change among APOE e4 carriers (Cacciottolo et al., 2017; Schikowski et al., 2015; Kulick et al., 2020), it may be worth examining whether APOE e4 modifies air pollution's effect on alternate pathological pathways known to increase risk of accelerated cognitive decline and dementia, or whether APOE e4 only modifies the effect of air pollution on amyloid accumulation at high levels of exposure.

Our study has several important strengths. We extended the scope of prior work to consider associations with multiple criteria air pollutants, components of PM<sub>2.5</sub>, and airborne trace metals. Full address histories were available, limiting the potential for exposure misclassification due to residential moves and allowing the use of a 10-year average exposure window that represents an etiologically relevant exposure window based on our current understanding of AD pathogenesis. We considered the impact of using alternate modeling approaches to estimate air pollution exposures, which confirmed that our findings were not specific to our choice of air pollution estimation approach. We also acknowledge that this study has limitations. Like prior studies, we do not account for

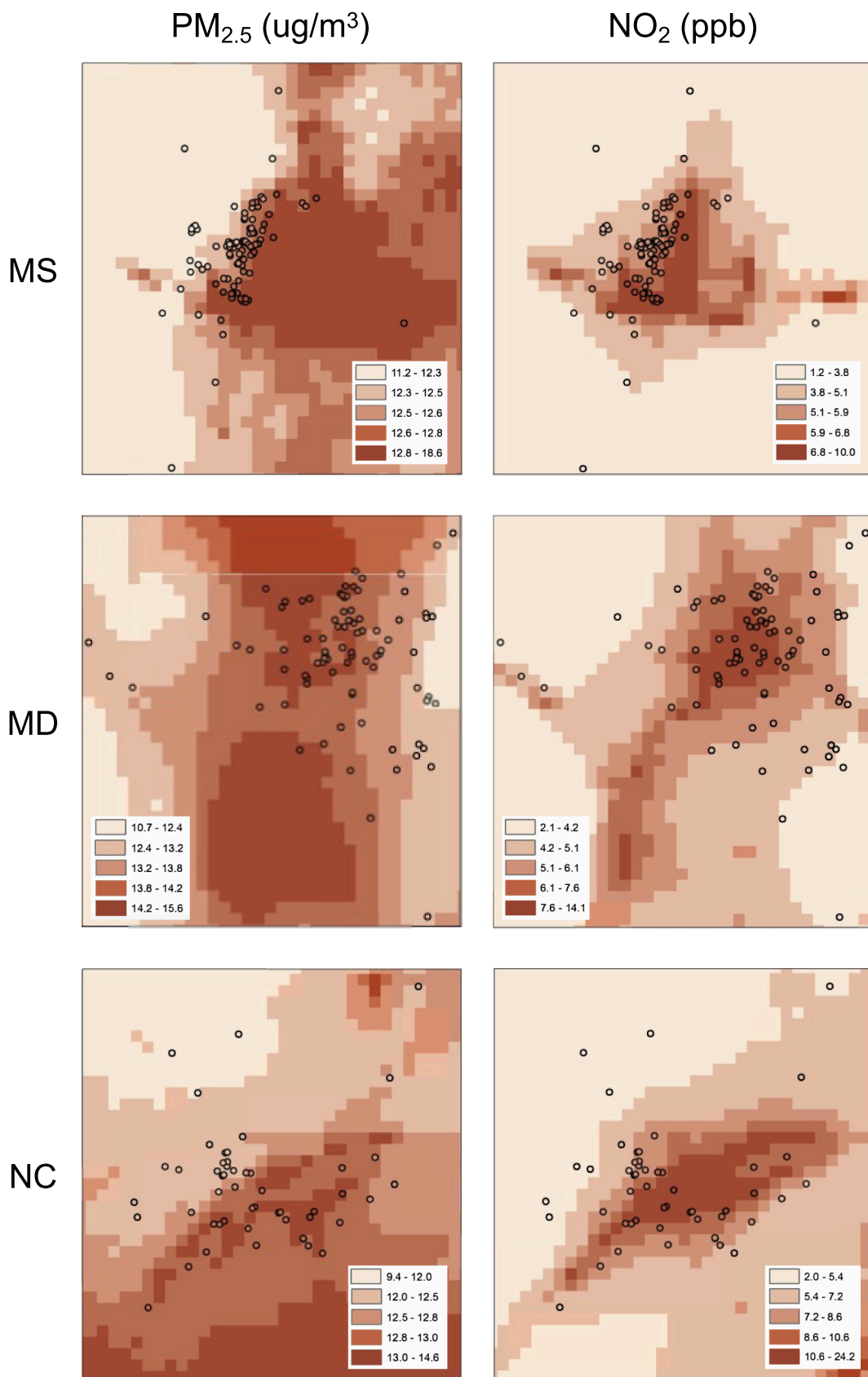
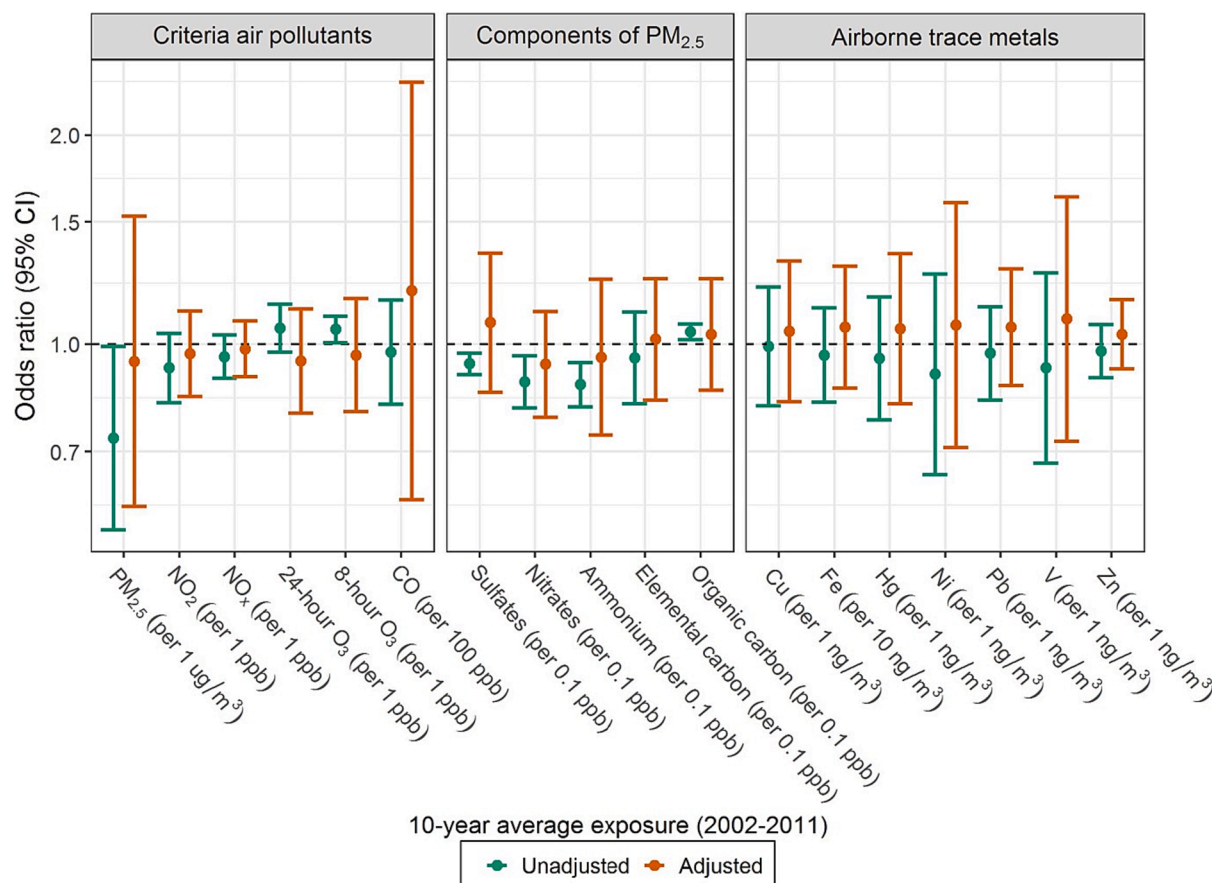
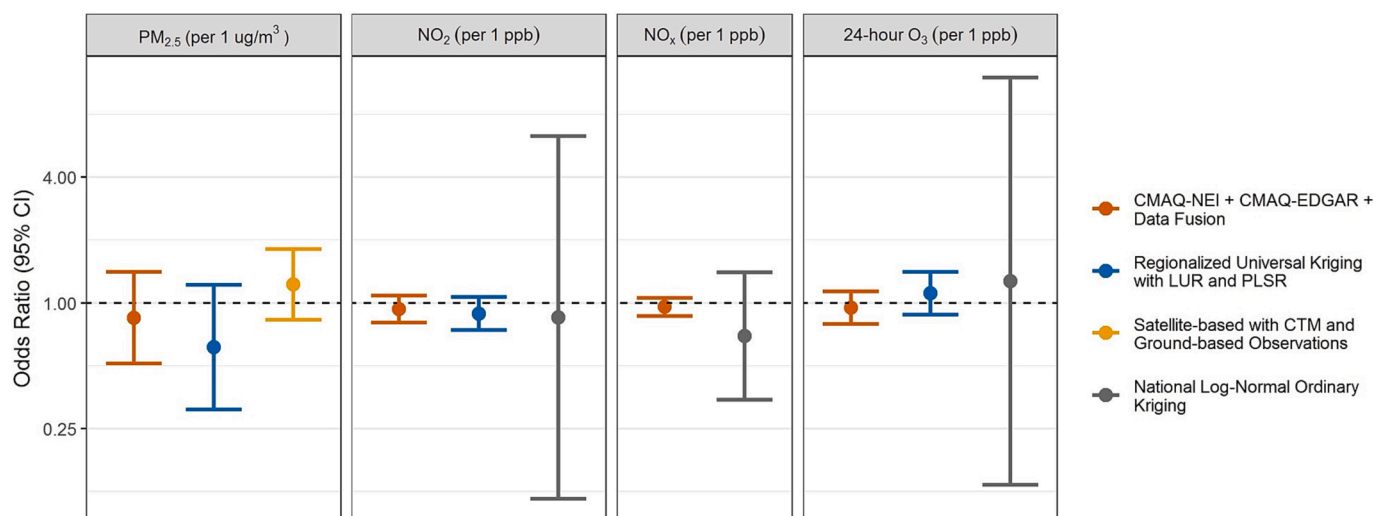


Fig. 1. Maps of 10-year average PM<sub>2.5</sub> and NO<sub>2</sub> exposure distributions within the 1.33 km estimation area containing each study site. Dots represent approximate participant locations for participants who did not move within the 10 year averaging period and for whom 1.33 km exposure resolution data were available for all 10 years within the averaging period. Abbreviations: m, meter; MD, Maryland; MS, Mississippi; NC, North Carolina; NO<sub>2</sub>, nitrogen dioxide; PM<sub>2.5</sub>, fine particulate matter; ppb, parts per billion; ug, micrograms.

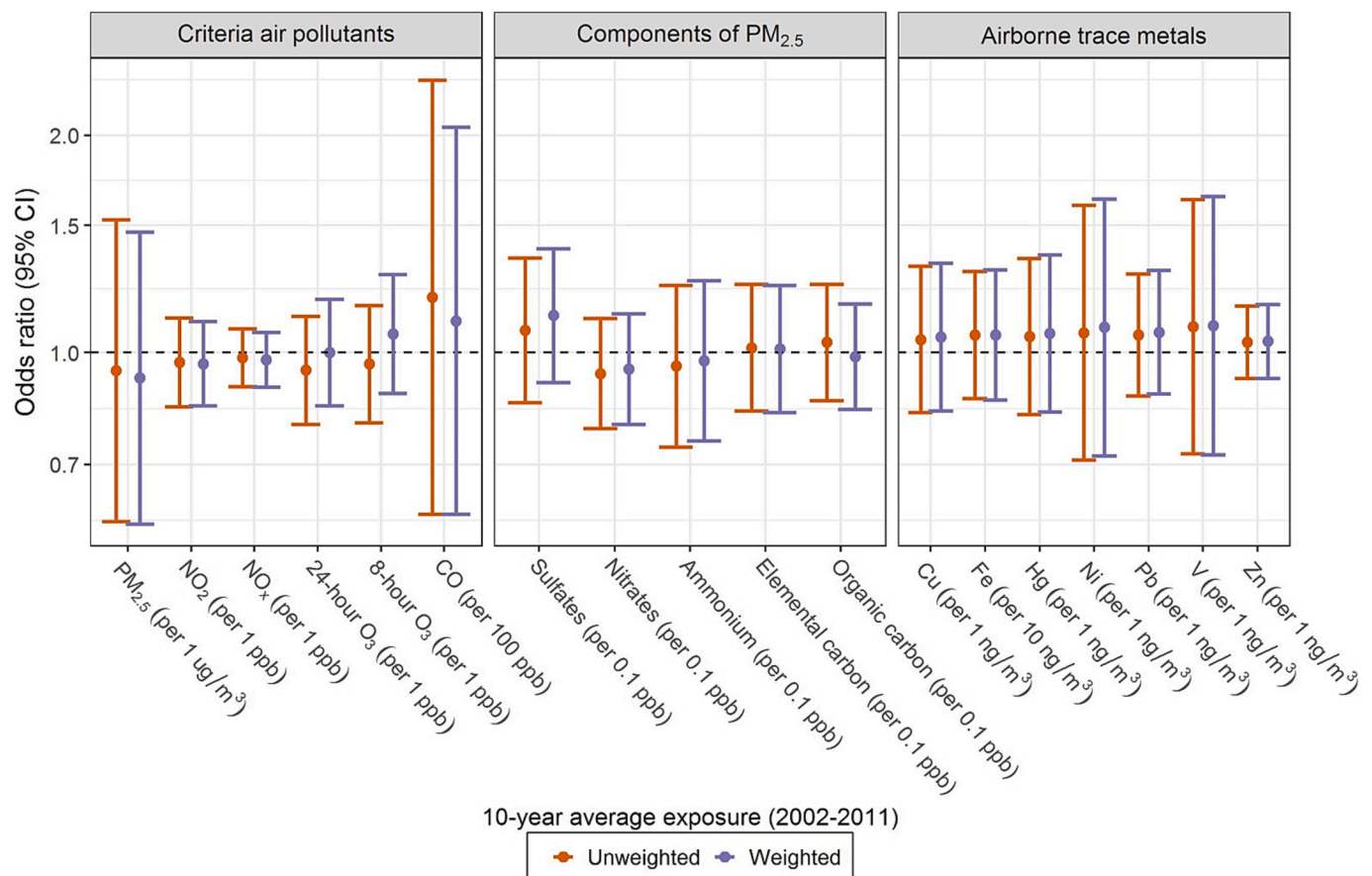


**Fig. 2. Associations of 10-year exposure to criteria air pollutants, PM<sub>2.5</sub> components, and airborne trace metals with elevated late-life amyloid burden among ARIC-PET participants (N = 318).** Adjusted models include age at PET scan, sex, race-center, education, cognitive status, and APOE e4 allele status (Model 3). Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; CO, carbon monoxide; Cu, copper; Fe, iron; Hg, mercury; m, meter; ng, nanograms; Ni, nickel; NO<sub>x</sub>, oxides of nitrogen; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; Pb, lead; PET, positron emission tomography; PM<sub>2.5</sub>, fine particulate matter; ppb, parts per billion; ug, micrograms; V, vanadium; Zn, zinc.



**Fig. 3. Associations between PM<sub>2.5</sub>, NO<sub>2</sub>, NO<sub>x</sub> and 24-hour O<sub>3</sub> and elevated late-life amyloid burden using alternate air pollution modeling approaches.** Models presented are adjusted for age at PET scan, sex, race-center, education, cognitive status, and APOE e4 allele status (Model 3). Abbreviations: CI, confidence interval; CMAQ, Community Multiscale Air Quality; CTM, chemical transport model; EDGAR, Emissions Database for Global Atmospheric Research; LUR, land use regression; m, meter; NEI, National Emissions Inventory; NO<sub>2</sub>, nitrogen dioxide; NO<sub>x</sub>, oxides of nitrogen; O<sub>3</sub>, ozone; PLSR, partial least squares regression; PM<sub>2.5</sub>, fine particulate matter; ppb, parts per billion; ug, micrograms.





**Fig. 4.** Associations between criteria air pollutants, components of PM<sub>2.5</sub>, and airborne trace metals and elevated late-life amyloid burden, unweighted vs. weighted. Models presented are adjusted for age at PET scan, sex, race-center, education, cognitive status, and APOE e4 allele status (Model 3). Abbreviations: CI, confidence interval; CO, carbon monoxide; Cu, copper; Fe, iron; Hg, mercury; m, meter; ng, nanograms; Ni, nickel; NO<sub>x</sub>, oxides of nitrogen; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; Pb, lead; PM<sub>2.5</sub>, fine particulate matter; ppb, parts per billion; ug, micrograms; V, vanadium; Zn, zinc.

daily mobility when estimating participant exposures; as regulation targets ambient pollutant concentrations, our results remain relevant to health policy considerations. Our limited sample size may have reduced our ability to detect significant effects; however, our sample size was similar to that of other PET imaging studies that reported significant associations (Alemany et al., 2021; Lee et al., 2020). Though we used additional air pollution estimation models for four air pollutants, alternate approaches were unavailable for components of PM<sub>2.5</sub> or airborne trace metals, and we cannot determine which air pollution method used in this study has the highest accuracy or reliability. As adjusting for study center effectively modifies the interpretation of results to looking at within-site exposure contrasts, we assume our approach here accurately captures local contrasts; however, we are unable to compare these findings with those using other approaches that may better capture small-scale variation. Amyloid positivity prevalence estimates were slightly different in our study compared to those published in a recent meta-analysis (Jansen et al., 2015), possibly because Black individuals, who make up 42.5% of our study population, have higher calculated global SUVRs across categories of cognitive status (Gottesman et al., 2016). Finally, our sample excluded individuals with dementia, precluding investigation of associations in this potentially sensitive group. Though we conducted sensitivity analyses upweighting the small number of those who transition to dementia by visit 6 to approximate a sample including those at all disease stages, these analyses are unlikely to fully reflect the effect that would have been found in a sample that included participants with dementia.

In conclusion, we did not find evidence of associations between criteria air pollutants, components of PM<sub>2.5</sub>, and airborne trace metals

and late-life brain amyloid deposition among individuals without dementia recruited from three sites in the US. While this suggests that air pollution may impact cognition and dementia independent of amyloid accumulation, whether air pollution influences AD pathogenesis later in the disease course or at higher exposure levels deserves further consideration.

#### CRediT authorship contribution statement

**Erin E. Bennett:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Ziwei Song:** Validation, Writing – review & editing. **Katie M. Lynch:** Validation, Writing – review & editing. **Chelsea Liu:** Validation, Writing – review & editing. **Emma K. Stapp:** Validation, Writing – review & editing. **Xiaohui Xu:** Conceptualization, Writing – review & editing. **Eun Sug Park:** Conceptualization, Writing – review & editing. **Qi Ying:** Methodology, Resources, Writing – review & editing. **Richard L. Smith:** Conceptualization, Writing – review & editing. **James D. Stewart:** Methodology, Resources, Data curation, Writing – review & editing, Visualization. **Eric A. Whitsel:** Conceptualization, Methodology, Resources, Data curation, Writing – review & editing. **Thomas H. Mosley:** Resources, Data curation, Writing – review & editing, Funding acquisition. **Dean F. Wong:** Methodology, Resources, Writing – review & editing. **Duanping Liao:** Methodology, Resources, Data curation, Writing – review & editing. **Jeff D. Yanosky:** Methodology, Resources, Data curation, Writing – review & editing. **Adam A. Szpiro:** Methodology, Resources, Data curation, Writing – review & editing. **Joel D. Kaufman:** Methodology, Resources, Data curation, Writing – review &

editing. **Rebecca F. Gottesman:** Methodology, Resources, Writing – review & editing, Funding acquisition. **Melinda C. Power:** Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Data availability

Data may be made available on request.

### Acknowledgements

This work is supported by grant R01ES029509 from NIH/NIEHS, awarded to MCP. The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (75N92022D00001, 75N92022D00002, 75N92022D00003, 75N92022D00004, 75N92022D00005). The ARIC Neurocognitive Study is supported by U01HL096812, U01HL096814, U01HL096899, U01HL096902, and U01HL096917 from the NIH (NHLBI, NINDS, NIA and NIDCD). Brain MRI examinations performed in the 2004–06 Brain MRI study were funded by R01HL70825. Brain PET scans in 2011–2013 were funded by R01AG040282. Avid Radiopharmaceuticals provided the isotope (florbetapir) for the study, but had no role in study design or interpretation. The authors thank the staff and participants of the ARIC study for their important contributions.

### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2023.108200>.

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