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Association between Fine Particulate Matter Exposure and Cerebrospinal Fluid Biomarkers of Alzheimer's Disease among a Cognitively Healthy Population-Based Cohort

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Background: Epidemiological evidence suggests air pollution adversely affects cognition and increases the risk of Alzheimer's disease (AD), but little is known about the biological effects of fine particulate matter ($PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm) on early predictors of future disease risk.

Objectives: We investigated the association between 1-, 3-, and 5-y exposure to ambient and traffic-related $PM_{2.5}$ and cerebrospinal fluid (CSF) biomarkers of AD.

Methods: We conducted a cross-sectional analysis using data from 1,113 cognitively healthy adults (45–75 y of age) from the Emory Healthy Brain Study in Georgia in the United States. CSF biomarker concentrations of $A\beta_{42}$, tTau, and pTau, were collected at enrollment (2016–2020) and analyzed with the Roche Elecsys system. Annual ambient and traffic-related residential $PM_{2.5}$ concentrations were estimated at a 1-km and 250-m resolution, respectively, and computed for each participant's geocoded address, using three exposure time periods based on specimen collection date. Associations between $PM_{2.5}$ and CSF biomarker concentrations, considering continuous and dichotomous (dichotomized at clinical cutoffs) outcomes, were estimated with multiple linear/logistic regression, respectively, controlling for potential confounders (age, gender, race, ethnicity, body mass index, and neighborhood socioeconomic status).

Results: Interquartile range (IQR; IQR = 0.845) increases in 1-y [β: −0.101; 95% confidence interval (CI): −0.18, −0.02] and 3-y (β: −0.078; 95% CI: −0.15, −0.00) ambient $PM_{2.5}$ exposures were negatively associated with $A\beta_{42}$ CSF concentrations. Associations between ambient $PM_{2.5}$ and $A\beta_{42}$ were similar for 5-y estimates (β: −0.076; 95% CI: −0.160, 0.005). Dichotomized CSF variables revealed similar associations between ambient $PM_{2.5}$ and $A\beta_{42}$. Associations with traffic-related $PM_{2.5}$ were similar but not significant. Associations between $PM_{2.5}$ exposures and tTau, pTau tTau/$A\beta_{42}$, or pTau/$A\beta_{42}$ levels were mainly null.

Conclusion: In our study, consistent trends were found between 1-y $PM_{2.5}$ exposure and decreased CSF $A\beta_{42}$, which suggests an accumulation of amyloid plaques in the brain and an increased risk of developing AD. https://doi.org/10.1289/EHP13503

Introduction

As life expectancy rises and the US population pyramid continues to age, we are seeing an increase in chronic noncommunicable age-related conditions, including Alzheimer's disease (AD). With the multifactorial nature of AD pathogenesis, building evidence around preventable environmental exposures may ultimately reduce inequities and improve health outcomes. In this regard, accumulating epidemiological evidence demonstrates an association between exposure to air pollution and the prevalence of AD. Most of the evidence to date has focused on links between fine particulate matter ($PM_{2.5}$, fine particulate matter with aerodynamic diameter ≤ 2.5 μm), a mixture of fine particles in the air, and cognitive function, incident cognitive impairment, or dementia.[1–4] Incident dementia is often studied using diagnostic codes on insurance billing claims and medical records, facilitating studies with large sample sizes; however, billing data are known to miss some true dementia cases,[1,5] and there are no diagnostic codes for the preclinical stages of dementia. $PM_{2.5}$ can pass through the lung gas–blood barrier or through the gut–brain axis, or it can directly enter brain tissue via the olfactory nerve to promote oxidative stress and inflammation, processes directly related to AD pathogenesis.[6,7] Growing evidence also suggests that cerebrovascular damage may contribute to dementia and $PM_{2.5}$ exposure is associated with biomarkers of endothelial injury in blood and cerebrospinal fluid (CSF), further implicating the adverse effect of $PM_{2.5}$ on CSF biomarkers.[8] Because $PM_{2.5}$ is a heterogeneous mixture, different sources of exposure often have varying degrees of toxicity, and most existing studies have focused on ambient exposure, rather than those merely from traffic-related emissions. Understanding the impact of $PM_{2.5}$ from both ambient and traffic-related sources on preclinical stages of dementia in older at-risk adults is crucial from a public health perspective, because it will improve the estimation of the burden of disease in association with air pollution by identifying more affected individuals.

Recent systematic reviews highlight the need to expand the scope of current studies on air pollution and dementia risk to include neuropathologically relevant outcomes, such as early indicators of dementia, including AD CSF and plasma-based biomarkers, which can be assessed at the late stage of the preclinical phase.[1,4,9] A recent study found positive associations between $PM_{2.5}$ and amyloid β-protein (Aβ)1–40 from plasma in longitudinal analyses, but no associations were detected between $PM_{2.5}$ and Aβ1–42 or the ratio of Aβ1–42/Aβ1–40.[10] Blood-based biomarkers of protein pathology are less predictive of brain pathology and have shown insignificant changes in Aβ levels as in comparison with CSF Aβ biomarkers in AD patients.[11] So far, three clinically validated CSF biomarkers [$A\beta_{42}$, total Tau (tTau), and phosphorylated Tau (pTau)] have been

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noted as valid proxies for neuropathological changes of AD,[9,12] and specifically, $A\beta_{42}$ has been linked to the abnormal pathological state of cerebral Aβ in both animal and human models. Lower levels of $A\beta_{42}$ in CSF are observed in AD, reflecting the deposition of amyloid plaques in the brain—a defining feature of the disease. Elevated levels of tTau in CSF reflect increased neuronal damage and degeneration, indicative of the neurofibrillary tangle formation—another hallmark of AD pathology. Increased concentrations of pTau signify the presence of abnormally phosphorylated Tau proteins, further emphasizing the Tau pathology associated with AD. The interplay between these biomarkers reflects the complex cascade of events in AD, from Tau-related neurodegenerative processes (tTau and pTau) to the accumulation of Aβ. Because pathological changes related to AD can begin decades before symptoms appear,[13] quantifying the relationship between both ambient and traffic-related $PM_{2.5}$ pollution, and CSF biomarkers reflective of AD-positive changes will elucidate how exposure influences dementia risk.[14]

So far, two epidemiological studies have reported associations between $PM_{2.5}$ and CSF $A\beta_{42}$ in cognitively healthy individuals whereas no relationships with tTau or pTau have been noted.[15,16] However, there are several limitations with these prior studies, including *a*) the exposure assessments in Alemany et al.[16] and Li et al.[15] only focused on 1- or 2-y average $PM_{2.5}$ prior to the biomarker assessment; *b*) the relatively small sample size ($n = 156$) in Alemany et al.,[16] and *c*) the outcome assessment in Li et al.,[15] which relied on the Innotest-AMYLOID(1-42) ELISA assay, an unstandardized manual method, showing a high correlation with the automated Elecsys method but higher intra- and interlaboratory variations.[17,18]

To address these limitations in prior studies and grow our understanding of the impact of air pollution on preclinical dementia risk, here we conducted a cross-sectional analysis to characterize the association between long-term ambient and traffic-related $PM_{2.5}$ exposure (1, 3, and 5 y prior to biomarker assessment) and CSF biomarker composition ($A\beta_{42}$, tTau, and pTau, assessed with Elecsys AD CSF assays) in a dementia-free, aging population, as part of the Emory Healthy Brain Study (EHBS). Increased levels of exposure to residential $PM_{2.5}$ were hypothesized to be associated with decreased $A\beta_{42}$ and increased Tau levels. We also tested for effect modification by several well-known risk factors for AD-related outcomes, including APOE-ε4 status, the strongest genetic risk factor for AD.

Methods

Study Design and Population

The EHBS is a gerontology-based prospective research study focusing on the cognitive health of older adults. The EHBS is nested within the Emory Healthy Aging Study (EHAS) and includes participants from the Atlanta metropolitan region in the state of Georgia in the United States. Our cross-sectional analysis includes data from the baseline visits, which were conducted between 2016 and 2020. The primary aim of the EHBS is to characterize psychological and psychosocial factors associated with normal and abnormal aging through assessment of the central nervous system among adults 45–75 y of age who were free of cognitive impairment in addition to several other chronic conditions (e.g., congestive heart failure, multiple sclerosis, human immunodeficiency virus) at enrollment; more details on recruitment and eligibility have been published elsewhere.[19]

Demographic characteristics were collected with the online Health History Questionnaire (HHQ).[19] Individual-level information was self-reported for gender, age, race, Hispanic ethnicity, educational attainment, and residential address. Participants could choose one or more race(s) from a five-item list (White/Caucasian, Black/African American, Asian, American Indian/Alaska Native, Hawaiian/Other Pacific Islander). Hispanic ethnicity (Yes/No) was addressed in a separate HHQ question. Data on education was also self-reported with seven possible categories: Less than high school; High school diploma/GED; Some college credit, but no degree; associate's degree (e.g., AA AS); bachelor's degree (e.g., BA, BS); master's degree (e.g., MA, MS, MBA); professional or doctorate degree. EHBS biennial study visits include neuropsychology tests, biospecimen collection (blood, CSF), cardiovascular measures, and brain imaging. All measures, including anthropometric, were collected by trained clinical research staff for use in the diagnosis and prediction of chronic illness.[19] All participants completed an online consent process prior to enrollment and provided informed consent. The study was approved by the local ethics committee and the Emory University institutional review board (IRB).

$PM_{2.5}$ Exposure Assessment

Because evidence suggests a relationship between both ambient $PM_{2.5}$ and traffic-related $PM_{2.5}$ exposure and cognitive decline and because traffic-related $PM_{2.5}$ is a major exposure source in urban environments like Atlanta,[20] we used both measures of $PM_{2.5}$ in our analyses.

We obtained ambient $PM_{2.5}$ exposure data from the publicly available Socioeconomic Data and Application Center (SEDAC) air quality dataset for health-related applications.[21] The dataset consists of yearly average ambient $PM_{2.5}$ levels (in $\mu g/m^3$) estimated at a 1-km spatial resolution, using a well-validated ensemble-based prediction model for the contiguous United States (2000–2016), which was reduced to annual $PM_{2.5}$ estimates in the state of Georgia for our analyses. As described by Di et al., three machine-learning algorithms: random forest, neural network, and gradient boosting were used to predict ambient $PM_{2.5}$ and included a variety of predictor variables from satellite data, land use, meteorological variables, and chemical transport model simulations.[22] The ensemble model then combined these $PM_{2.5}$ predictions with a generalized additive model that allowed for the contribution of each machine-learning algorithm to vary by location.[22] The ensemble model was trained on $PM_{2.5}$ levels measured at 2,156 US EPA monitors, was validated with 10-fold cross-validation, and produced high-resolution annual $PM_{2.5}$ predictions with an average R^2 of 0.89.[22]

As described previously,[23] annual traffic-related $PM_{2.5}$ exposure concentrations at 200–250 m resolution (in $\mu g/m^3$) for the Atlanta metropolitan area for the period 2012–2019 were predicted via a land-use random forest model built on training data comprising the 2015 annual concentrations of traffic-related $PM_{2.5}$ from Atlanta Reginal Commission, road inventory and traffic monitoring data based on measurements from the Georgia Department of Transportation that considered road geometry and traffic volume, land cover data from the National Land Cover Database, and ambient $PM_{2.5}$ data from the Atmospheric Composition Analysis. The random forest model was trained with the R package *randomForest*. The resulting 200–250 m resolution annual traffic-related $PM_{2.5}$ predictions had an average R^2 of 0.80. Given that the traffic-related $PM_{2.5}$ exposure estimates covered only 20 of the 159 counties in Georgia, the analytic sample for these models was reduced to include only the participants located within this area ($n = 1{,}080$) in comparison with ambient $PM_{2.5}$ exposures ($n = 1{,}113$).

For both ambient and traffic-related $PM_{2.5}$ exposures, we spatially matched geocoded residential addresses to the closest centroid of grids (based on 1-km^2 or 200–250 m^2 grids) to assign annual exposures. 1-y exposure predictions (1 year prior to specimen collection) were calculated by averaging the daily predictions in each year for every grid cell.[22] We further calculated individual 3- and 5-y exposures by averaging yearly predictions

prior to specimen collection. Participants' geocoded addresses were mapped using QGIS mapping software, and air pollution exposures were assigned based on air pollution model grid cell of residence.

AD CSF Biomarker Concentrations

CSF biospecimens were collected by EHBS research staff via lumbar puncture at enrollment; CSF collection protocol has been previously described.[24] $A\beta_{42}$, tTau, and pTau CSF levels were quantified using the ElectroChemiLuminescense Immunoassay (ECLIA) Elecsys AD CSF portfolio on an automated Roche Diagnostics instrument (F. Hoffman-La Roche Ltd.). The assays have measuring ranges of 200–1,700 pg/mL ($A\beta_{42}$), 80–1,300 pg/mL (tTau), and 8–120 pg/mL (pTau). tTau and pTau levels were $\log_{10}$-transformed for normality in linear models in the statistical analyses. We also examined CSF biomarker ratio outcomes, namely, $tTau/A\beta_{42}$ and $pTau/A\beta_{42}$, which are highly predictive of amyloid positivity based on concordance with amyloid-PET, including for cognitively normal participants.[25] All AD CSF biomarker outcomes were kept as continuous variables for linear regression analyses in our main analyses and dichotomized based on the Elecsys AD CSF portfolio positive (+) cutoffs for logistic regression analyses in our sensitivity analyses to evaluate the robustness of our main findings ($A\beta_{42} \leq 1{,}030$ pg/mL; tTau >300 pg/mL; pTau >27 pg/mL; $tTau/A\beta_{42} > 0.28$ pg/mL; $pTau/A\beta_{42} > 0.023$ pg/mL).[9,26] The cutoff values for $A\beta_{42}$, $tTau/A\beta_{42}$, and $pTau/A\beta_{42}$ CSF were established and validated to demonstrate CSF biomarker concordance with Aβ PET visual read in the BioFINDER and ADNI studies, respectively.[27] Cutoff values for single Tau biomarkers, tTau and pTau, were derived and validated in a separate study based on the separation between mild cognitive impairment (MCI) patients with a higher vs. lower risk of cognitive decline and optimized for identification of AD patients vs. normal controls.[28]

Covariates

Sources of potential confounding were identified with a directed acyclic graph (DAG; Figure S1). Individual-level confounders were conceptualized as factors impacting both residential $PM_{2.5}$ exposure and the outcome measure. Potential confounding factors included in the analysis were self-reported gender, age, neighborhood socioeconomic status (N-SES), race/ethnicity, educational attainment, and body mass index (BMI). Due to historic racism and discriminatory land-use practices such as redlining, environmental exposures disproportionately affect low-income and minority populations. For this reason, neighborhood deprivation characteristics were also included as potential confounding variables and effect modifiers as done in our previous work.[29] Race has also been noted as an important factor when interpreting CSF biomarker results.[30] In addition, BMI influences biomarker concentrations and is also related to N-SES through characteristics such as neighborhood walkability, greenspace, and food access.[31,32] Furthermore, we believe age and self-reported gender can influence choice of neighborhood, which in turn may systematically affect air pollution exposure.

Because of the presence of multiancestral groups and small categories in self-reported race/ethnicity, we used a three-level race variable in the analysis: White/Caucasian, Black/African American, and Other, as well as a dichotomous ethnicity variable indicating Hispanic origin. Similarly, educational attainment was included as a three-level variable: master's degree or higher, college degree, less than a college degree. Height and weight measurements were used to calculate BMI (weight in kilograms divided by height in square meters), which was used as a continuous variable in all models. N-SES for each participant was established in this study with census-tract level American Community Survey (ACS)-defined principal components of neighborhood deprivation (see Li et al.[29] for details) and the Area Deprivation Index (ADI). As described previously in Li et al.,[29] three principal components of neighborhood deprivation were calculated based on estimates for 5-y ACS census tract–level data, including 16 indicators of 6 socioeconomic domains (poverty/income, racial composition, education, employment, occupation, and housing properties) (Table S1; Figure S2).[29] The ADI is provided in national percentile rankings at the block group level from 1 to 100, where 100 represents the most deprived neighborhood, and was calculated using census block group–level indicators and factor analysis to cluster indicators based on their ability to explain the variance between block groups.[33]

Statistical Analyses

We implemented multiple linear regression models to estimate the conditional relationship between residential $PM_{2.5}$ exposure and AD CSF biomarker levels at enrollment, including participants with complete demographic and clinical data. In our main models, continuous biomarker concentrations (linear regression models) were assigned as dependent variables and $PM_{2.5}$ exposures along with the selected covariates as independent variables ($n = 1{,}113$). Because the biomarkers had different ranges, we standardized all continuous biomarker measures by converting them to z-scores prior to employing regression analysis to increase comparability of results across different biomarkers. Z-scores were computed for each observation by subtracting the sample mean from each individual value and subsequently dividing by the sample standard deviation (SD). For ease of comparison between estimates using different exposure time periods, we standardized the $PM_{2.5}$ estimates to the 1-y $PM_{2.5}$ exposure distribution, by dividing all $PM_{2.5}$ exposure estimates by the IQR of 1-y ambient or traffic-related $PM_{2.5}$ exposure, respectively. The general form of the model for all analyses appears below:

$$\text{AD CSF Biomarker Outcome} = \alpha_0 + \beta_1 PM_{2.5} + \gamma_1 Age + \gamma_2 Gender + \gamma_3 Education + \gamma_4 Race + \gamma_5 Hispanic\ ethnicity + \gamma_6 BMI + \gamma_7 ADI + \gamma_8 nSES\ PC_1 + \gamma_9 nSES\ PC_2 + \gamma_{10} nSES\ PC_3 + \varepsilon,$$

where $PM_{2.5}$ represents either ambient or traffic-related $PM_{2.5}$ averages 1, 3, or 5 y prior to specimen collection, and ε represents the random error term, with an assumed mean of zero and constant variance $\sim n\ (0,\sigma^2)$.

Sensitivity Analyses

We conducted several sensitivity analyses to evaluate the robustness of our findings. First, we used dichotomized AD CSF biomarker cutoffs (±) as dependent variables in logistic regression models instead of the continuous biomarker measurements to estimate the association between $PM_{2.5}$ exposures and cutoff variables that are commonly used to evaluate AD risk. Further, we included models estimating the relationship between residential ambient $PM_{2.5}$ exposures and AD CSF biomarker levels and positive cutoffs at enrollment, including only individuals with traffic-related $PM_{2.5}$ exposure data ($n = 1{,}080$). To account for the level of urbanicity across residences, we included models additionally controlling for the Rural and Urban Community Area (RUCA) code, which consists of whole number codes 1–10, to delineate metropolitan, micropolitan, small town, and rural commuting areas based on the size and direction of the primary (largest) commuting flows.[34] Because the majority of study participants resided within the Atlanta metropolitan area, RUCA was incorporated as a dichotomous variable: "rural" if >1 and "urban" if equal to 1. Finally, we included models additionally controlling for year of specimen collection to address potential confounding introduced by time trends of air pollution and dementia.

Table 1. Baseline descriptive characteristics for EHBS study participants (≥45 y of age).

Characteristics	Overall ($n = 1,113$)	Traffic-related $PM_{2.5}$ subset ($n = 1,080$)
Age (y)		
Mean (SD)	61.7 (6.73)	61.7 (6.75)
Median (min, max)	62.0 (45.0, 77.0)	62.0 (45.0, 77.0)
Gender		
Female	775 (69.6%)	748 (69.3%)
Male	338 (30.4%)	332 (30.7%)
BMI (kg/m^2)		
Mean (SD)	25.5 (3.55)	25.5 (3.55)
Median (min, max)	25.3 (16.8, 38.4)	25.3 (16.8, 38.4)
Race		
White/Caucasian	943 (84.7%)	910 (84.3%)
Black/African American	121 (10.9%)	121 (11.2%)
Asian	13 (1.2%)	13 (1.2%)
American Indian/Alaska Native, White/Caucasian	10 (0.9%)	10 (0.9%)
American Indian/Alaska Native	7 (0.6%)	7 (0.6%)
Asian, White/Caucasian	6 (0.5%)	6 (0.6%)
American Indian/Alaska Native, Black/African American, White/Caucasian	4 (0.4%)	4 (0.4%)
Native Hawaiian/Other Pacific Islander	3 (0.3%)	3 (0.3%)
Asian, Native Hawaiian/Other Pacific Islander, White/Caucasian	2 (0.2%)	2 (0.2%)
Asian, Black/African American	1 (0.1%)	1 (0.1%)
Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White/Caucasian	1 (0.1%)	1 (0.1%)
Asian, Native Hawaiian/Other Pacific Islander	1 (0.1%)	1 (0.1%)
Black/African American, White/Caucasian	1 (0.1%)	1 (0.1%)
Hispanic ethnicity		
Yes	32 (2.9%)	32 (3.0%)
No	1,081 (97.1%)	1,048 (97.0%)
Education		
Less than high school	1 (0.1%)	0 (0%)
High school diploma/GED	18 (1.6%)	18 (1.7%)
Some college credit, but no degree	128 (11.5%)	123 (11.4%)
Associate's degree (e.g., AA, AS)	69 (6.2%)	68 (6.3%)
Bachelor's degree (e.g., BA, BS)	409 (36.7%)	402 (37.2%)
Master's degree (e.g., MA, MS, MBA)	322 (28.9%)	309 (28.6%)
Professional or doctorate degree	166 (14.9%)	160 (14.8%)
Area Deprivation Index		
Mean (SD)	29.4 (20.1)	28.8 (19.7)
Median (min, max)	25.0 (1.00, 93.0)	25.0 (1.00, 93.0)
Urbanicity		
Urban	1,059 (95.1%)	1,051 (97.3%)
Rural	54 (4.9%)	29 (2.7%)
APOE-ε4 allele carriership		
No allele	591 (53.1%)	577 (53.4%)
1 allele	241 (21.7%)	231 (21.4%)
2 alleles	23 (2.1%)	21 (1.9%)
Missing	258 (23.2%)	251 (23.2%)
Air pollution concentration		
1-y ambient $PM_{2.5}$ ($\mu g/m^3$)		
Mean (SD)	9.52 (0.764)	9.56 (0.707)
Median (min, max)	9.52 (5.63, 13.2)	9.54 (7.38, 13.2)
IQR	0.845	0.825
3-y ambient $PM_{2.5}$ ($\mu g/m^3$)		
Mean (SD)	9.85 (0.832)	9.90 (0.772)
Median (min, max)	9.96 (5.99, 12.0)	9.98 (7.16, 12.0)
IQR	1.10	1.07
5-y ambient $PM_{2.5}$ ($\mu g/m^3$)		
Mean (SD)	9.96 (0.735)	10.0 (0.682)
Median (min, max)	10.1 (6.41, 12.0)	10.1 (7.60, 12.0)
IQR	0.945	0.936
1-y traffic $PM_{2.5}$ ($\mu g/m^3$)		
Mean (SD)	1.15 (0.464)	1.15 (0.464)
Median (min, max)	1.10 (0.155, 5.06)	1.10 (0.155, 5.06)
IQR	0.523	0.523
Missing *n* (%)	33 (3.0%)	—
3-y traffic $PM_{2.5}$ ($\mu g/m^3$)		
Mean (SD)	1.26 (0.455)	1.26 (0.455)
Median (min, max)	1.23 (0.175, 5.56)	1.23 (0.175, 5.56)
IQR	0.479	0.479
Missing *n* (%)	33 (3.0%)	—
5-y traffic $PM_{2.5}$ ($\mu g/m^3$)		
Mean (SD)	1.25 (0.432)	1.25 (0.432)
Median (min, max)	1.21 (0.168, 5.38)	1.21 (0.168, 5.38)
IQR	0.447	0.447
Missing *n* (%)	33 (3.0%)	—

Note: —, no data; APOE-ε4, apolipoprotein E4; BMI, body mass index; EHBS, Emory Healthy Brain Study; IQR, interquartile range; max, maximum; min, minimum; $PM_{2.5}$, fine particulate matter; SD, standard deviation.
[a]Self-reported race was categorized into 13 groups, and participants were able to choose one or more races from a five-item list: White/Caucasian, Black/African American, Asian, American Indian/Alaska Native, Hawaiian/Other Pacific Islander. For statistical analyses, race was grouped into three categories: White/Caucasian, Black/African American, and Other. Ethnicity was categorized as a binary Hispanic origin variable.
[b]Education was self-reported and included less than high school, high school/GED, some college, associate's degree, bachelor's degree, master's degree, and a professional degree (e.g., PhD). For statistical analyses, education was grouped into three categories representing educational attainment: master's degree or higher, college degree, or less than a college degree.
[c]Area Deprivation Index was derived from factor analysis and validated to the Census Block Group neighborhood level with factors for the theoretical domains of income, education, employment, and housing quality; higher scores indicate higher levels of "disadvantage."
[d]Urbanicity was derived from the Rural and Urban Commuting Area (RUCA) code (1–10) with Rural if >1 and Urban if equal to 1.

Effect Modification Analyses

We tested for effect modification by several well-established risk factors for AD, adding an interaction term between $PM_{2.5}$ and each risk factor in individual regression models. These risk factors included whether a participant had at least one APOE-ε4 allele, family history of AD (indicated by parent or first sibling diagnosis), gender, age, and ADI. Despite a hypothesized additive genetic effect of the ε4 allele, statistical interaction was assessed dichotomously due to the small number of homozygous ε4 carriers (2.1%; Table 1). Family history of AD (no/yes), gender (male/female), and ADI ($<50/\geq 50$) were also added as dichotomous variables whereas interaction with age was assessed continuously. Using the models with interaction, we then tested for effect modification with the *interplot* R package and $n = 100,000$ simulations.

For all statistical analysis, we used R Statistical Software (version 4.2.2; R Core Development Team) and the significance level $\alpha = 0.05$.

Results

Study Population

After excluding EHBS participants with missing demographic data ($n = 46$), the analytic sample included 1,113 individuals (Table 1). Participants lived primarily around the Atlanta metropolitan area, spanning 489 census blocks in the state of Georgia (detailed neighborhood characteristics are summarized in Table S2). The average age of our sample participants was 61.7 y (SD = 6.73), 69.9% were females, 84.7% identified as White/Caucasian, 10.9% identified as Black/African American, and 2.9% identified as Hispanic. The average BMI was 25.5 kg/m^2 (SD = 3.55). Our sample was highly educated with 86.7% having received an associate's degree or higher. The ADI was right

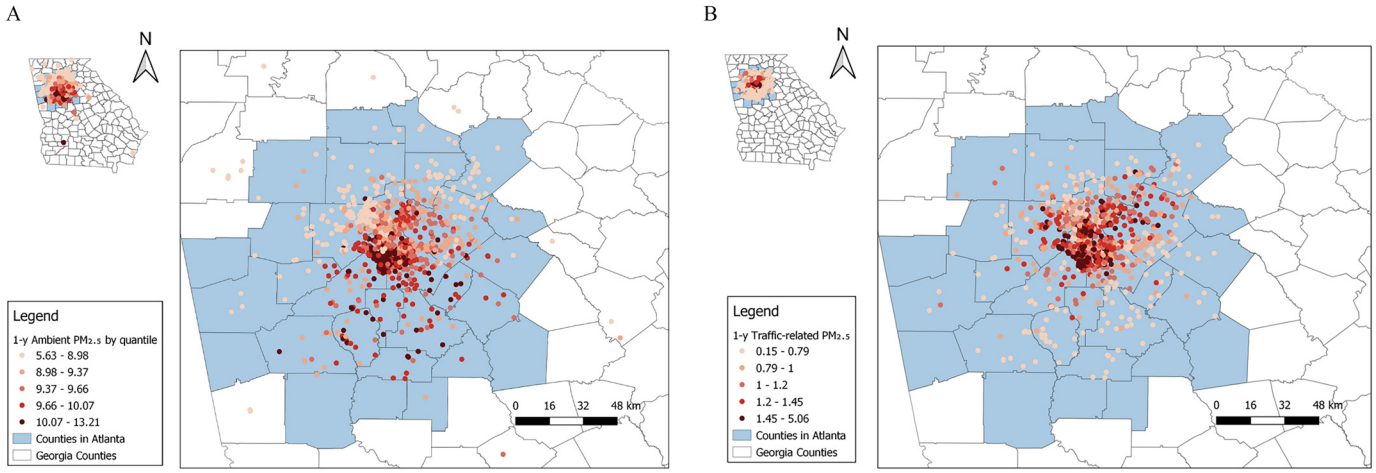

Figure 1. Map of the geographic distribution of our study population and their residential $PM_{2.5}$ exposure concentrations in the year prior to specimen collection. Each dot represents an EHBS participant. (A) Annual ambient residential $PM_{2.5}$ (in $\mu g/m^3$) exposure by quintile ($n = 1{,}113$). (B) Annual traffic-related residential $PM_{2.5}$ exposure (in $\mu g/m^3$) by quintile ($n = 1{,}080$). Note: EHBS, Emory Healthy Brain Study; $PM_{2.5}$, fine particulate matter.

skewed with a median of 25, indicating half of the sample lived in areas with 25 percentage points lower deprivation than the national average. In addition, most of our participants lived in a major commuting area where 95% of residences were classified as urban.

There was spatial variability in ambient $PM_{2.5}$ levels in our study area, with the highest quintile of exposure (10.1–13.21 $\mu g/m^3$) localized to the south of the city of Atlanta and lowest quintile of exposure (5.63–8.98 $\mu g/m^3$) localized to communities north of Atlanta, such as Marietta and Roswell (Figure 1; Table 1). Traffic-related $PM_{2.5}$ exposure levels ($n = 1{,}080$) had lower concentrations (because we only estimated the traffic-related component of $PM_{2.5}$) but higher variability with annual average exposures of 1.15 $\mu g/m^3$ (SD = 0.46) in comparison with annual average ambient exposures of 9.52 $\mu g/m^3$ (SD = 0.76). Traffic-related $PM_{2.5}$ estimates had a maximum of 5.10 $\mu g/m^3$, and these levels were observed in the city of Atlanta. Annual ambient and traffic-related $PM_{2.5}$ exposure concentrations were weakly correlated (Pearson correlation = 0.36). More details on the distribution of and relation between ambient and traffic-related $PM_{2.5}$ exposure concentrations are provided in the supplemental material (Figures S3–S6). For context, National Ambient Air Quality Standards (NAAQS) for $PM_{2.5}$ defined by the US Environmental Protection Agency (US EPA) include annual averages of 12.0 $\mu g/m^3$.[35]

We observed a wide spread of concentrations for CSF $A\beta_{42}$ in the study population (median $A\beta_{42}$ level = 1,210, IQR = 692.3). $A\beta_{42}$ concentrations did not show a major departure from normality, except for the highest level, which had a very high frequency, indicating normal $A\beta_{42}$ concentrations in most participants, but tTau and pTau distributions were skewed (Table 2; Figure S7–8). After log transformation, tau concentrations were approximately normally distributed (Table S3; Figure S9–10). Approximately 36% of participants had $A\beta_{42}$ concentrations less than or equal to 1,030 pg/mL, which corresponds, on average, to a positive reading for AD as indicated by Elecsys AD CSF portfolio positive (+) cutoffs. We observed AD positive readings for tTau and pTau cutoffs in 6% of the study population. Based on the $pTau/A\beta_{42}$ ratio AD (+) cutoff, we detected amyloid positivity in 10.6% of participants. Details on the distributions of AD CSF biomarker concentrations and the frequency of biomarker-positivity detected among participants are provided in Table 2.

$PM_{2.5}$ and AD CSF Biomarkers

In line with our hypothesis, higher levels of 1- and 3-y ambient $PM_{2.5}$ exposures were associated with lower $A\beta_{42}$ CSF concentrations at baseline after adjusting for potential confounding variables (Figure 2A). Specifically, an IQR (0.845 $\mu g/m^3$) increase in the 1- or 3-y ambient $PM_{2.5}$ exposure was associated with a −0.09 (95% CI: −0.15, −0.02) and −0.07 (95% CI: −0.13, −0.005) lower $A\beta_{42}$ CSF *z*-score, respectively, after confounder adjustment. The associations of 5-y ambient $PM_{2.5}$ (Figure 2A) and traffic-related $PM_{2.5}$ (Figure 2F) and $A\beta_{42}$ CSF were similar (Table S4). Inverse associations were observed between ambient $PM_{2.5}$ and tTau and pTau (Figure 2B and

Table 2. Baseline AD CSF biomarker outcomes at enrollment between 2016 and 2020 for EHBS participants.

AD CSF concentrations and (+) cutoff	Total ($n = 1{,}113$)	Traffic-related $PM_{2.5}$ subset ($n = 1{,}080$)
$A\beta_{42}$ (pg/mL)		
Mean (SD)	1,200 (382)	1,200 (382)
Median (min, max)	1,210 (200, 1,700)	1,210 (200, 1,700)
IQR	692.3	687.0
tTau (pg/mL)		
Mean (SD)	187 (70.9)	186 (71.3)
Median (min, max)	174 (80.0, 799)	174 (80.0, 799)
IQR	79.6	79.7
pTau (pg/mL)		
Mean (SD)	16.7 (7.16)	16.7 (7.19)
Median (min, max)	15.2 (8.00, 83.8)	15.2 (8.00, 83.8)
IQR	7.63	7.64
$tTau/A\beta_{42}$ (pg/mL)		
Mean (SD)	0.171 (0.107)	0.170 (0.107)
Median (min, max)	0.141 (0.0818, 1.72)	0.141 (0.0818, 1.72)
$pTau/A\beta_{42}$ (pg/mL)		
Mean (SD)	0.0154 (0.0116)	0.0154 (0.0116)
Median (min, max)	0.0123 (0.00692, 0.200)	0.0123 (0.00692, 0.200)
$A\beta_{42}$ (+) ≤1,030 pg/mL	402 (36.1%)	392 (36.3%)
tTau (+) >300 pg/mL	68 (6.1%)	67 (6.2%)
pTau (+) >27 pg/mL	65 (5.8%)	62 (5.7%)
$tTau/A\beta_{42}$ (+) >0.28 pg/mL	87 (7.8%)	82 (7.6%)
$pTau/A\beta_{42}$ (+) >0.023 pg/mL	118 (10.6%)	112 (10.4%)

Note: $A\beta_{42}$, beta-amyloid 42; AD, Alzheimer's disease; CSF, cerebrospinal fluid; EHBS, Emory Healthy Brain Study; IQR, interquartile range; max, maximum; min, minimum; mL, milliliter; PET, positron emission tomography; pTau, phosphorylated Tau; (+), positive; SD, standard deviation; tTau, total Tau.

[a]Biomarker measurements based on Elecsys AD CSF assays and clinically validated cutoffs.

[b]Ratios achieve 90% concordance with amyloid PET.

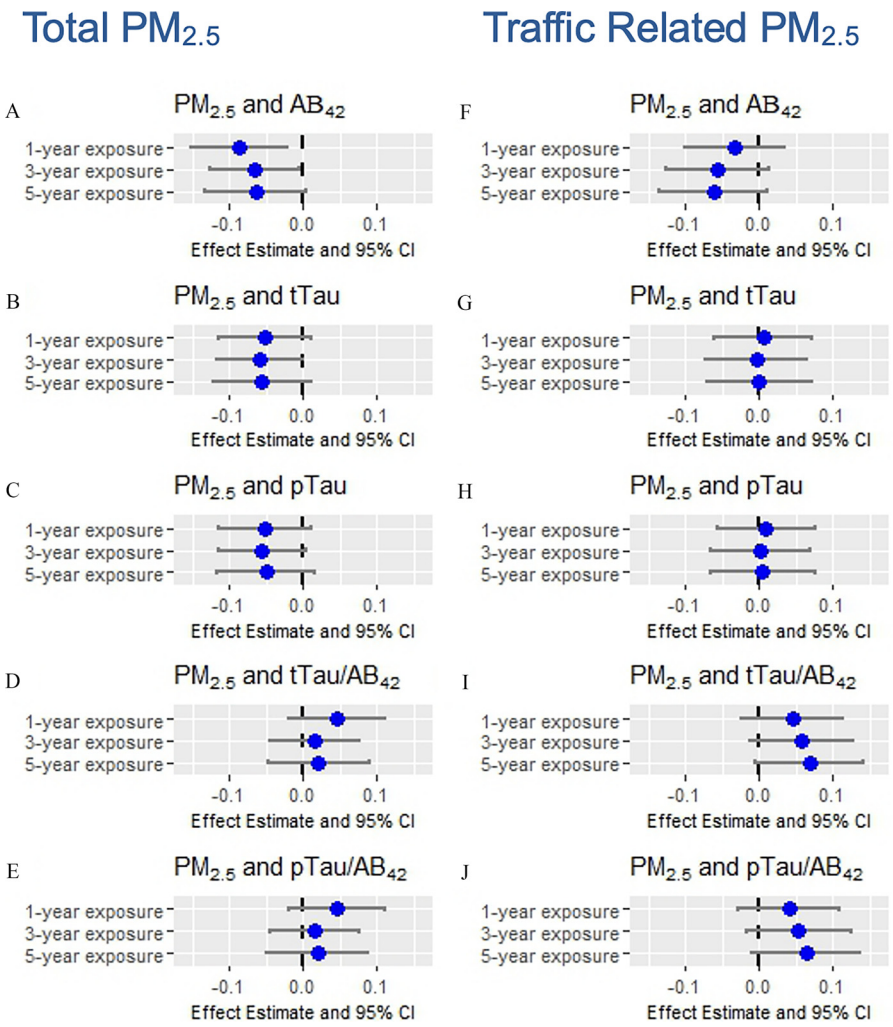

Figure 2. Associations between residential $PM_{2.5}$ exposure and AD CSF biomarker concentrations. Effect Estimate (±95% CI) of 1, 3, and 5-y ambient (A–E) ($n = 1{,}113$) and traffic-related (F–J) ($n = 1{,}080$) $PM_{2.5}$ exposure on AD CSF biomarker concentrations (in pg/mL) ($A\beta_{42}$, tTau, pTau, tTau/$A\beta_{42}$, and pTau/$A\beta_{42}$). All estimates are standardized and adjusted for gender, age, N-SES, race, ethnicity, educational attainment, and BMI. The dashed line indicates the significance threshold: 0 for linear regression. Numeric data can be found in Table S4. Note: $A\beta_{42}$, beta-amyloid 42; AD, Alzheimer's disease; BMI, body mass index; CI, confidence interval; CSF, cerebrospinal fluid; N-SES, neighborhood socioeconomic status; $PM_{2.5}$, fine particulate matter; pTau, phosphorylated Tau; tTau, total Tau.

2C), which contrasts with our hypothesis (only statistically significant for 3-y ambient $PM_{2.5}$ exposure and tTau concentrations). However, associations with tTau and pTau were null for traffic-related $PM_{2.5}$ exposures (Figure 2G and 2H). Associations with tTau/$A\beta_{42}$ and pTau/$A\beta_{42}$ were consistent with our hypothesis (Figure 2I–2J) for ambient and traffic-related $PM_{2.5}$ exposure.

Associations between ambient residential $PM_{2.5}$ and each biomarker were consistent with our main models, even after restricting to participants with available traffic-related $PM_{2.5}$ data (Table S5; Figure S11A–E) and after additionally adjusting for the year of specimen collection for each participant (Table S6; Figure S12) or urbanicity (Table S7; Figure S13). After controlling for residential urbanicity, the negative associations between 3-y ambient $PM_{2.5}$ and tTau concentrations were no longer significant (Table S7; Figure S13).

AD CSF Biomarker Positive Cutoff Outcomes

To evaluate the robustness of our finding, we also included biomarker positivity outcomes and found that higher residential ambient $PM_{2.5}$ exposures were associated with increased prevalence of an AD positive (+) $A\beta_{42}$ portfolio reading at baseline, with associations observed for an IQR (0.845 $\mu g/m^3$) increase in 1-y (OR = 1.23; 95% CI: 1.07, 1.42), 3-y (OR = 1.20; 95% CI: 1.04, 1.37), and 5-y (OR = 1.21; 95% CI: 1.04, 1.40) average ambient $PM_{2.5}$ exposure (Table S8, Figure S14A). The associations between traffic-related $PM_{2.5}$ exposures and an AD positive (+) $A\beta_{42}$ portfolio reading at enrollment were similar but weaker (Table S8; Figure S14F) and significant for pTau/$A\beta_{42}$ (3 y and 5 y average exposures; Table S8; Figure S14J). We observed null associations between ambient (Table S8; Figure S14B–C) and traffic-related (Table S8; Figure S14G–H) $PM_{2.5}$ exposures and AD positive (+) tTau or pTau cutoffs.

The associations between ambient $PM_{2.5}$ and AD positive (+) $A\beta_{42}$ portfolio reading remained, even after restricting our sample size to only those located in the Atlanta metropolitan area (Table S9, Figure S11F–J), which is the subsample for which traffic-related $PM_{2.5}$ exposures estimates were available (sample size reduced from $n_{ambient} = 1{,}113$ to $n_{traffic} = 1{,}080$).

Effect Modification by Other Common Risk Factors for AD

The association of annual average ambient $PM_{2.5}$ exposure and concentrations of $A\beta_{42}$ CSF was not significantly modified by APOE-ε4 carriership ($p = 0.59$), AD family history ($p = 0.37$), ADI ($p = 0.62$) or gender ($p = 0.67$) (Table S10; Figure 3A–D).

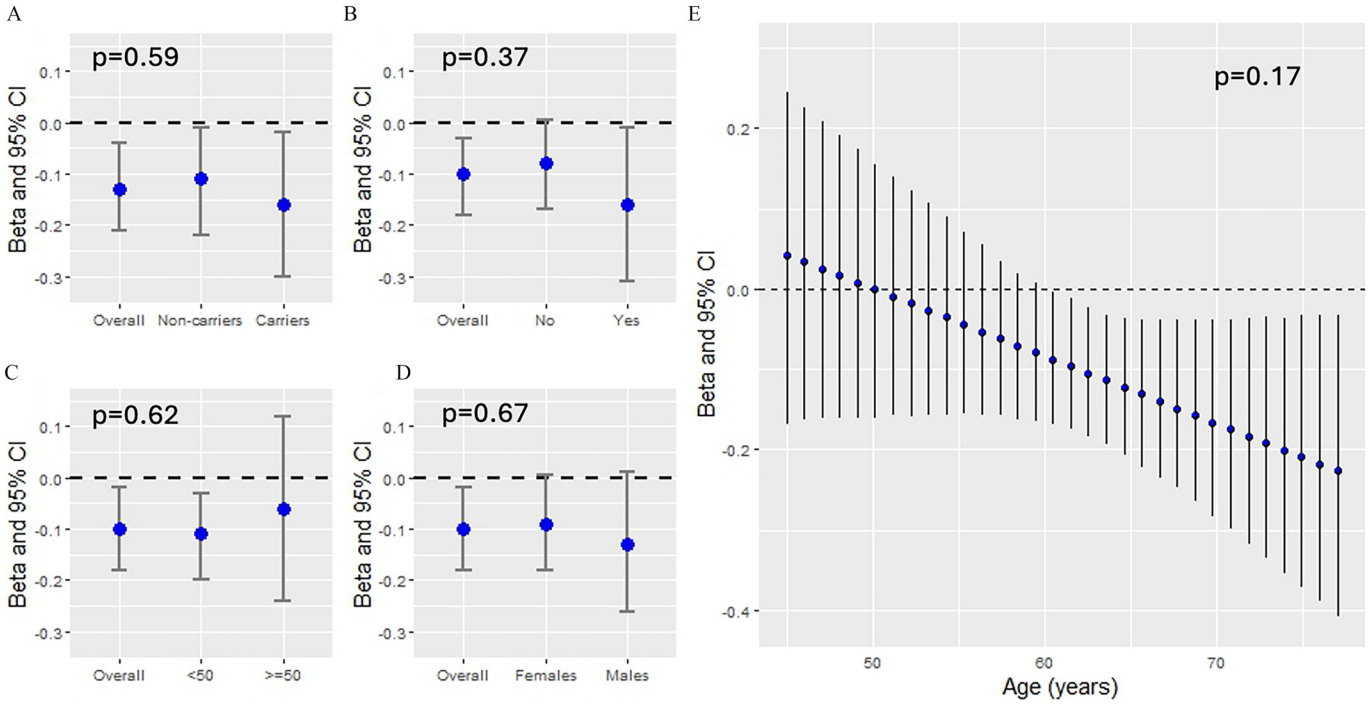

Figure 3. Effect modification by other common risk factors for AD. Effect ($\pm$95% CI) of yearly ambient $PM_{2.5}$ exposure on $A\beta_{42}$ CSF concentrations (in pg/mL) by (A) APOE-ε4 allele carriership, (B) AD family history, (C) ADI, (D) gender, and (E) age. Presented as overall and stratified effects for dichotomous variables and as continuous for age, with interaction *p*-values depicted on each graph. The dashed line indicates the significance threshold: 0 for linear regression. The overall effect in Figure 3A ($n = 855$) differs slightly from Figure 3B–D ($n = 1{,}113$) due to the decreased sample size after including only participants with APOE genotype data. Numeric data can be found in Table S10. Note: $A\beta_{42}$, beta-amyloid 42; ADI, Area Deprivation Index APOE-ε4, apolipoprotein E4; CI, confidence interval; CSF, cerebrospinal fluid; $PM_{2.5}$, fine particulate matter with aerodynamic diameter $\leq$2.5 μm.

Similarly, the association of annual average ambient $PM_{2.5}$ exposure and AD positive (+) $A\beta_{42}$ portfolio reading was not significantly modified by APOE-ε4 carriership ($p = 0.80$), AD family history ($p = 0.27$), ADI ($p = 0.12$), or gender ($p = 0.72$) (Table S11; Figure S15A–D). Effect modification by age was also not significant ($p = 0.17$), but we observed an increasing negative effect of $PM_{2.5}$ on $A\beta_{42}$ CSF levels with increasing age, and we observed statistically significant associations between $PM_{2.5}$ and $A\beta_{42}$ CSF levels starting around 60 y of age (Table S10; Figure 3E); a similar pattern was revealed when looking at the stratified effects of $PM_{2.5}$ on AD positive (+) $A\beta_{42}$ portfolio reading by age (interaction $p = 0.34$) (Table S11; Figure S15E).

Discussion

In the present study, we examined the impacts of both ambient $PM_{2.5}$ exposure and traffic-related $PM_{2.5}$, a major source of ambient $PM_{2.5}$ in urban environments, on CSF biomarkers of AD in 1,113 cognitively healthy individuals. Our findings show associations between long-term ambient $PM_{2.5}$ concentrations and decreased $A\beta_{42}$ AD CSF biomarker concentrations (significant for 1- and 3-y average exposures), as well as increased likelihood of an $A\beta_{42}$ AD (+) positive portfolio reading (significant for 1-, 3- and 5-y average exposures). Decreased $A\beta_{42}$ CSF reflect the deposition of amyloid plaques in the brain, indicative of the disease phenotypes associated with AD. $PM_{2.5}$ pTau/$A\beta_{42}$ (+) $PM_{2.5}$. We found mainly null associations between ambient or traffic-related $PM_{2.5}$ exposures and pTau or tTau continuous concentrations or their ratios with $A\beta_{42}$; however, the directions of effect for pTau/$A\beta_{42}$ and tTau/$A\beta_{42}$ continuous ratio outcomes were consistent with AD-related amyloid pathology. Further, although not statistically significant, the strength of the association between annual ambient $PM_{2.5}$ exposure and $A\beta_{42}$ AD CSF concentrations differed by age and was particularly pronounced for individuals older than 60 y of age.

The observed associations between $PM_{2.5}$ exposure and the $A\beta_{42}$ AD CSF biomarker as well as pTau/$A\beta_{42}$ positive portfolio readings, which are equally predictive of amyloid PET status ($\pm$) as Aβ ratio outcomes,[36] among cognitively healthy older adults is consistent with evidence from existing literature. Signs of AD can be detected in the early stages of the AD continuum,[18] and decreases in CSF concentrations of $A\beta_{42}$ (a marker of amyloidosis) and elevation in Tau species (phosphorylated and total Tau) are well established as pathogenic biomarkers in AD diagnosis.[37] To date, there have been few studies estimating the effects of $PM_{2.5}$ exposure on certified biomarkers of AD in healthy, aging populations. One study found a similar relationship between air pollution exposure and $A\beta_{42}$, although they used a CSF $A\beta_{42/40}$ ratio to reflect Aβ pathology rather than the individual biomarker measurements.[16] Their estimates were similarly negative but did not reach significance, likely owing to the relatively small sample size ($n = 147$).[16] Another study[15] found a statistically significant total effect of ambient $PM_{2.5}$ on $A\beta_{42}$ CSF as well as pTau/$A\beta_{42}$ concentrations among $n = 1{,}131$ cognitively healthy older individuals, which was further mediated by a CSF biomarker of neuroinflammation, sTREM2.[15]

We found null associations between 1-, 3-, and 5-y average traffic-related $PM_{2.5}$ exposures and tTau as well as pTau concentrations at enrollment. Unexpectedly, however, associations between ambient $PM_{2.5}$ and tTau as well as pTau concentrations were negative, corresponding to less AD-related neurofibrillary tangle formation and neuronal damage with higher ambient $PM_{2.5}$ exposure. The negative associations between ambient $PM_{2.5}$ and Tau biomarkers diminished when taking AD CSF cutoffs or urbanicity into account, suggesting that the negative association with the continuous tTau levels was potentially a false positive finding. Other studies examining the associations between air pollution

and CSF biomarkers of AD in cognitively healthy adults also found null associations between $PM_{2.5}$ and pTau as well as tTau CSF concentrations.[15,16]

Stronger associations were detected between ambient $PM_{2.5}$ and AD CSF biomarkers in comparison with traffic-related $PM_{2.5}$ exposure. Ambient $PM_{2.5}$ contains emissions from traffic, industry, domestic fuel burning, and natural sources including soil dust and sea salt, as well as unspecific sources of human origin.[38] On the other hand, traffic-related $PM_{2.5}$ is a source of ambient $PM_{2.5}$ that includes emissions of organic and inorganic gaseous PM precursors from the combustion of fuels and lubricants.[38] Because both sources contain organic and often toxic particles, we expected to see relationships between both sources of $PM_{2.5}$ and AD CSF biomarkers, and the associations between traffic-related $PM_{2.5}$ and AD CSF biomarkers were similar to associations with ambient $PM_{2.5}$. In this study, the spatial resolution for the traffic exposure assessment was 200-250 m, which may be too coarse to capture the rapid decay of many primary pollutants from traffic. Primary traffic-related air pollutants, including primary $PM_{2.5}$ from traffic, generally decrease to background levels within 150 m of roadways.[39] As such, our traffic exposure assessment may not fully capture differences in primary traffic-related $PM_{2.5}$ exposures among participants. Given that exposure misclassification can bias effect estimates toward the null, this could explain the inconsistency of effect between models with traffic-related vs. ambient $PM_{2.5}$ exposure. In addition, more research needs to be done to determine which $PM_{2.5}$ mixtures are particularly harmful to the central nervous system.

Although we did not find effect modifications by APOE-ε4 carriership or other common risk factors for AD, the association between ambient $PM_{2.5}$ exposure and $A\beta_{42}$ CSF became stronger with increasing age. These results could suggest that AD CSF biomarkers might not be sensitive enough to detect AD-related changes in participants <60 y of age, but more research in the population will clarify the most clinically relevant age for biomarker measurement. Previous research suggests that biomarker patterns of $A\beta_{42}$ consistent with stage 1 AD (amyloid pathology only) are first detectable during early middle age (45–54 y of age), whereas increases in tTau and pTau are typically not apparent until later (≥55 y of age).[40] However, this previous study used an unstandardized assay, the INNOTEST ELISA, which often yields systematic variability in comparison with the Elecsys assay. Another potential explanation for the stronger associations among participants older than 60 y of age could be the higher accumulative $PM_{2.5}$ exposure over the lifetime among older individuals. In line with this hypothesis, one study examining the relationship between $PM_{2.5}$ exposure and AD prevalence found a stronger effect of $PM_{2.5}$ on AD prevalence among those at or above 70 y of age.[3] Similarly, the lack of a positive relationship between ambient $PM_{2.5}$ exposure and Tau biomarker concentrations could be explained by our study population's relatively young age in comparison with when AD-related Tau pathology begins to manifest, suggesting that AD-related Tau pathology is not detectable with AD CSF biomarkers until late age (e.g., >75 y). In support, Elecsys AD CSF portfolio cutoffs only classified 6% of study participants as AD positive (+) based on pTau and tTau concentrations, whereas >35% of participants were AD positive (+), based on $A\beta_{42}$ levels.

There are several strengths to be noted, such as the exposure assessment, which included two sources of $PM_{2.5}$, ambient and traffic-related, which were estimated at a high spatial resolution of up to 200 m; our outcome assessment, which relied on a recommended assay for AD CSF biomarker measurement[17] and for which we observed consistent associations using continuous biomarker concentrations as well as AD positivity cutoffs; our inclusion of several well-known confounders and methods to reduce confounding by neighborhood-level characteristics; and our relatively large sample size ($n = 1{,}113$) of CSF measurements from cognitively healthy older adults free of chronic illness. The level of depth in our outcome assessment, underscored by the inclusion of a substantial sample size with CSF measurements, a highly invasive and challenging-to-obtain biological fluid, provides a rare and valuable opportunity to understand potential associations between fine PM and neurological biomarkers of AD. The use of Elecsys AD CSF biomarkers not only presents several notable strengths in AD diagnosis and research but also offers the potential for early detection of AD pathology, enabling interventions at earlier stages of the disease. Their specificity in targeting AD-associated proteins ensures a focused and disease-specific diagnostic approach. In addition, Elecsys AD CSF biomarkers play a crucial role in advancing AD research by providing objective and quantitative measurements, facilitating a deeper understanding of disease mechanisms and aiding in the evaluation of treatment efficacy in clinical trials. However, collecting CSF poses a challenge, because it is an invasive procedure with associated risks and potential patient reluctance, but the EHBS has enabled the analysis of AD CSF biomarker data from more than 1,000 healthy aging adults, highlighting the novelty of this study.

In addition to its strengths, our study has several limitations. Given that AD progresses over the course of several years or decades, we evaluated the associations with 3- and 5-y average $PM_{2.5}$ concentrations prior to enrollment in addition to the 1-y averages. It is expected to see long-term/cumulative exposures, e.g., up to a decade or lifetime exposures, to have a stronger effect than shorter periods of high exposure concentrations. However, given that exposure was assigned based on the baseline residence, we were not able to investigate longer exposure windows. Therefore, our study might not cover the most relevant exposure window for AD risk. Furthermore, some participants could have relocated in the years prior to the study, and therefore, the 3- and 5-y estimates may be affected by exposure misclassification due to the introduction of measurement error. Such exposure misclassification is a potential explanation for the weaker associations between the 3- and 5-y $PM_{2.5}$ exposures and $A\beta_{42}$ CSF concentrations in comparison with the 1-y exposure concentrations. Furthermore, the lagged exposures used in this study (3- and 5-y) may not evaluate the proper windows in relation to the biomarker outcomes, meaning the choice of time window did not capture the temporal relationship between the $PM_{2.5}$ exposure and AD CSF biomarkers. Our study only used cross-sectional CSF measurements; longitudinal repeated measures analyses may provide a better understanding of the long-term effect of air pollution on CSF biomarker trajectories of AD. Further, our sample was not representative of the Atlanta metropolitan area, the target population, because it was mainly high SES and White, which limits both the generalizability and transportability of our estimates. Finally, although we looked at two different sources of $PM_{2.5}$, we did not examine the relationship between AD pathology and specific components of $PM_{2.5}$. Future studies should consider the components of $PM_{2.5}$ because they are dynamic between ambient and traffic-related sources with different toxicity[41] and could reveal important and undiscovered relationships between exposure and disease pathogenesis.

In conclusion, our results suggest that, even at levels below current primary and secondary standards defined by the US EPA for $PM_{2.5}$, exposure to ambient and traffic-related $PM_{2.5}$ increases the risk of future AD development. In addition, our results add to the growing body of evidence that suggests that air pollution directly contributes to neurodegeneration by accelerating $A\beta_{42}$ accumulation in the brain.[2,42]

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