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Association Between Ambient Air Pollution and Amyloid Positron Emission Tomography Positivity in Older Adults With Cognitive Impairment

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IMPORTANCE Amyloid-β (Aβ) deposition is a feature of Alzheimer disease (AD) and may be promoted by exogenous factors, such as ambient air quality.

OBJECTIVE To examine the association between the likelihood of amyloid positron emission tomography (PET) scan positivity and ambient air quality in individuals with cognitive impairment.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study used data from the Imaging Dementia—Evidence for Amyloid Scanning Study, which included more than 18 000 US participants with cognitive impairment who received an amyloid PET scan with 1 of 3 Aβ tracers (fluorine 18 [^{18}F]–labeled florbetapir, ^{18}F-labeled florbetaben, or ^{18}F-labeled flutemetamol) between February 16, 2016, and January 10, 2018. A sample of older adults with mild cognitive impairment (MCI) or dementia was selected.

EXPOSURES Air pollution was estimated at the patient residence using predicted fine particulate matter ($PM_{2.5}$) and ground-level ozone (O_3) concentrations from the Environmental Protection Agency Downscaler model. Air quality was estimated at 2002 to 2003 (early, or approximately 14 [range, 13-15] years before amyloid PET scan) and 2015 to 2016 (late, or approximately 1 [range, 0-2] years before amyloid PET scan).

MAIN OUTCOMES AND MEASURES Primary outcome measure was the association between air pollution and the likelihood of amyloid PET scan positivity, which was measured as odds ratios (ORs) and marginal effects, adjusting for demographic, lifestyle, and socioeconomic factors and medical comorbidities, including respiratory, cardiovascular, cerebrovascular, psychiatric, and neurological conditions.

RESULTS The data set included 18 178 patients, of which 10 991 (60.5%) had MCI and 7187 (39.5%) had dementia (mean [SD] age, 75.8 [6.3] years; 9333 women [51.3%]). Living in areas with higher estimated biennial $PM_{2.5}$ concentrations in 2002 to 2003 was associated with a higher likelihood of amyloid PET scan positivity (adjusted OR, 1.10; 95% CI, 1.05-1.15; *z* score = 3.93; false discovery rate [FDR]–corrected $P < .001$; per 4-μg/m^3 increments). Results were similar for 2015 to 2016 data (OR, 1.15; 95% CI, 1.05-1.26, *z* score = 3.14; FDR-corrected $P = .003$). An average marginal effect (AME) of +0.5% (SE = 0.1%; *z* score, 3.93; 95% CI, 0.3%-0.7%; FDR-corrected $P < .001$) probability of amyloid PET scan positivity for each 1-μg/m^3 increase in $PM_{2.5}$ was observed for 2002 to 2003, whereas an AME of +0.8% (SE = 0.2%; *z* score = 3.15; 95% CI, 0.3%-1.2%; FDR-corrected $P = .002$) probability was observed for 2015 to 2016. Post hoc analyses showed no effect modification by sex (2002-2003: interaction term β = 1.01 [95% CI, 0.99-1.04; *z* score = 1.13; FDR-corrected $P = .56$]; 2015-2016: β = 1.02 [95% CI, 0.98-1.07; *z* score = 0.91; FDR-corrected $P = .56$]) or clinical stage (2002-2003: interaction term β = 1.01 [95% CI, 0.99-1.03; *z* score = 0.77; FDR-corrected $P = .58$]; 2015-2016: β = 1.03; 95% CI, 0.99-1.08; *z* score = 1.46; FDR-corrected $P = .47$]). Exposure to higher O_3 concentrations was not associated with amyloid PET scan positivity in both time windows.

CONCLUSIONS AND RELEVANCE This study found that higher $PM_{2.5}$ concentrations appeared to be associated with brain Aβ plaques. These findings suggest the need to consider airborne toxic pollutants associated with Aβ pathology in public health policy decisions and to inform individual lifetime risk of developing AD and dementia.

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Supplemental content

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Alzheimer disease (AD) is the most common cause of dementia worldwide[1] and is characterized neuropathologically by extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tau tangles.[2] Sporadic AD has been proposed to have a complex etiology resulting from gene-environment interplay.[2-4] In this framework, exogenous risk factors, such as air pollution, may modulate the lifetime risk of AD.[4] Ambient air pollution is a mixture of different particles and gases, with fine particulate matter ($PM_{2.5}$, or PM with aerodynamic diameter <2.5 μm) and ground-level ozone (O_3) being commonly used to monitor air quality.[5] Defined as an inhalable combination of invisible solid and liquid droplets suspended in the air, $PM_{2.5}$ can be directly emitted (eg, from construction sites or wildfires) and can also result from chemical reactions involving other pollutants.[6] Defined as a colorless harmful gas at ground level, O_3 is a component of smog and results from chemical reactions involving emitted molecules, such as volatile organic compounds, with heat and sunlight.[7]

Both $PM_{2.5}$ and O_3 have a role in the global burden of disease and mortality[5,8] and have been associated with an increased risk of cognitive decline, clinically diagnosed AD, and all-cause dementia in epidemiological studies.[9-15] The Lancet Commission 2020 update on dementia prevention, intervention, and care recently recognized exposure to air pollution as a modifiable risk factor for late-life cognitive decline.[16] Findings from animal studies support the notion that exposure to polluted air can result in increased Aβ production and deposition in both wild-type mice or rats and transgenic AD models, with the latter also showing fibrillar Aβ plaques.[17-23] Human studies that assessed neuropathologic or cerebrospinal fluid levels of Aβ1-42 have found that children, young adults, and middle-aged adults who lived in more polluted areas were more likely to harbor signs of modified Aβ processing and, in some instances, pathologic amyloid deposition.[24-29] However, these studies have several limitations, including small sample sizes, a focus on urban areas, and scant data on older populations who are at higher risk of AD.

Providing large-scale in vivo biomarker evidence that exposure to air pollution is associated with brain Aβ pathology in humans could inform public health policy and further the understanding of how environmental risk factors interact with AD pathology. In this cross-sectional study, we performed a secondary analysis of the data obtained for the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study,[30] which included more than 18 000 US participants with cognitive impairment who underwent a positron emission tomography (PET) scan to assess brain Aβ accumulation (amyloid PET scan). Previous PET-to-autopsy studies have shown that visual readings of antemortem amyloid PET scans can reliably predict postmortem amyloid burden, and this technique is therefore considered the criterion standard for measuring fibrillar Aβ deposits in living people.[31-37] We leveraged the large, geographically distributed IDEAS Study cohort to examine the associations between the likelihood of amyloid PET scan positivity and ambient air quality, as measured in data provided by the Downscaler model (which combines pollutant concentrations, photochemical properties, and atmospheric data) of the US Environmental Protection Agency (EPA). To account for potential short- and long-term associations with amyloid deposition, we modeled 2 different exposure time windows: 2002 to 2003 (early, or approximately 14 [range, 13-15] years before the amyloid PET scan, or the earliest availability of EPA data) and 2015 to 2016 (late, or approximately 1 [range, 0-2] years before the amyloid PET scan). We hypothesized that IDEAS Study participants who lived in areas with higher concentrations of airborne pollutants would be more likely to have positive amyloid PET scan results.

Key Points

Question Does living in areas with greater air pollution increase the likelihood of positive amyloid positron emission tomography (PET) scan results in older adults with cognitive impairment in the US?

Findings In this cross-sectional study of 18 178 individuals with cognitive impairment, people living in areas with worse air quality were more likely to have positive amyloid positron emission tomography scan results; specifically, higher $PM_{2.5}$ concentrations appeared to be associated with brain amyloid-β plaques, a signature characteristic of Alzheimer disease. This association was dose dependent and statistically significant after adjusting for demographic, lifestyle, and socioeconomic factors as well as medical comorbidities.

Meaning Findings of this study suggest that exposure to air pollution is associated with amyloid-β pathology in older adults with cognitive impairment; such information should be considered in public health policy decisions and should inform lifetime risk of Alzheimer disease and dementia.

Methods

This cross-sectional secondary analysis of deidentified data was exempted from review by the University of California, San Francisco Institutional Review Board. The IDEAS Study was managed by the American College of Radiology under a central institutional review board (Advarra, formerly Schulman Associates), and a number of sites required local institutional review board approval. Written informed consent for patient participation in the IDEAS Study was obtained by the dementia specialist from patients or their legally authorized representatives.[30]

Data Collection and Preparation

The IDEAS Study enrolled Medicare beneficiaries aged 65 years or older who met appropriate use criteria for amyloid PET scan.[38] These patients had mild cognitive impairment (MCI) or dementia of an uncertain etiology, defined after a comprehensive evaluation by a dementia specialist. A detailed description of the study design and aims has been published previously.[30] All participants received an amyloid PET scan with 1 of 3 US Food and Drug Administration–approved radiopharmaceutical Aβ tracers (fluorine 18 [^{18}F]-labeled florbetapir, ^{18}F-labeled florbetaben, or ^{18}F-labeled flutemetamol, all of

which were validated against postmortem data[31-33]) between February 16, 2016, and January 10, 2018. Amyloid PET scans were rated as positive or negative by certified imaging specialists at each imaging site using tracer-specific criteria.

In the present study, clinical data were collected from the IDEAS Study. Data for the participants (n = 18 293) were provided by the IDEAS Study data core at Brown University. These data included case registration forms (completed by site staff) that specified patient demographic characteristics and residential zip codes; pre-PET case report forms (supplement in Rabinovici et al[30]) completed by the referring dementia specialists that recorded the clinical stage (ie, MCI or dementia) and diagnosis (ie, suspected cause of cognitive impairment), medical history, and family history of dementia or AD; and imaging case report forms completed by the imaging specialists that recorded PET scan interpretation (positive or negative for Aβ). Details on race/ethnicity classification in the IDEAS Study are provided elsewhere,[30] and such data are used in this study only to describe the cohort and as a nuisance covariate.

Air Quality Data

A complete description of the Downscaler model is provided on the EPA website and in other published studies.[39,40] Briefly, the Downscaler model uses a bayesian space-time framework to merge atmospheric model data, which include chemical and physical processes, with point air pollution measurements (ie, 24-hour mean $PM_{2.5}$ and 8-hour maximum O_3) collected by local EPA monitors. By merging air quality monitoring and atmospheric modeling, the Downscaler data provide a gridded output of predicted daily mean $PM_{2.5}$ and maximum O_3 concentrations at US Census tract-level centroids (per 2010 US Census tract geography). We calculated the means of $PM_{2.5}$ and O_3 data for the time windows 2002 to 2003 and 2015 to 2016 and assigned them to each participant by residential zip code (eMethods in the Supplement).

Statistical Analysis

Statistical analyses and plotting were performed with R, version 4.0.0 (R Foundation for Statistical Computing). Analyses were conducted from September 23, 2019, to August 8, 2020.

Pearson coefficients were calculated to estimate correlations between air quality data measured at different time windows. Logistic regression models were used to estimate changes in the odds of amyloid PET scan positivity associated with pollutant concentrations. Analyses were conducted with and without adjustment for covariates relevant for Aβ pathology and/or associated with exposure to air pollution, including demographic characteristics; clinical stage and diagnosis; pre-PET physician confidence in AD pathology causing cognitive symptoms; use of AD drugs; relevant medical history, including reported presence of cardiovascular, respiratory, cerebrovascular, psychiatric, and neurological conditions; smoking status; family history; and median household income, which was assigned based on zip code using US survey data (a complete list of covariates and details are provided in the eMethods in the Supplement). Odds ratios (ORs) were converted to represent 4-μg/m^3 increases in $PM_{2.5}$ concentration and 5 ppb (parts per billion) increases in O_3 (respective 2002-2003 interquartile ranges). Global performance was assessed with C statistic. Statistical significance was set at 2-sided $P < .05$ using the false discovery rate (FDR) method for multiple comparisons. Significant fully adjusted models were replicated using quartiles data to assess possible nonlinear associations (eTable 1 and eFigure 1 in the Supplement).

In an effect modification post hoc analysis, separate adjusted logistic regression models were conducted to add interaction terms for either sex (male vs female) or clinical stage (MCI vs dementia stage). Marginal effects were estimated to assess increases in the probability of a positive amyloid PET scan associated with changes in exposure to pollutants, keeping all of the other covariates fixed.[41,42] Marginal effects provide an easier and more quantitative interpretation of the associations and are less sensitive to model specifications than ORs.[41,42] In an additional sensitivity analysis, we assessed whether the associations between pollutant concentrations and likelihood of a positive amyloid PET scan were maintained after accounting for study locations by performing mixed-effects logistic regression models, fitting a random intercept by US Census tracts. The eMethods in the Supplement provide additional details on the statistical approach and analysis used in this study.

Results

The selected data set included 18 178 IDEAS Study participants with available demographic, amyloid PET scan status, and residential zip code data. Of these participants, 10 991 (60.5%) had MCI, 7187 (39.5%) had dementia, and 256 (1.4%) had missing values for at least 1 of 3 covariates and were excluded from adjusted models. These participants had a mean (SD) age of 75.8 (6.3) years (9333 women [51.3%] and 8845 men [48.7%]). Demographic characteristics, clinical information, and geographical distributions are presented in **Table 1** and **Figure 1**. The eMethods and eFigure 2 in the Supplement show additional details and the prevalence of amyloid PET scan positivity stratified by the National Oceanic and Atmospheric Administration Climatic Zones.

Ambient Air Quality

We analyzed data for 5713 unique residential zip codes belonging to 5609 US Census tracts. Air quality improved from the 2002 to 2003 time window to the 2015 to 2016 time window (**Figure 2**), especially for $PM_{2.5}$ (mean [SD] difference, −4.11 [1.67] μg/m^3; range, −10.44 to +1.43) compared with O_3 (mean [SD] difference, −0.63 [2.41] ppb; range, −7.42 to +9.18). The 2002 to 2003 $PM_{2.5}$ and O_3 concentrations correlated with their respective 2015 to 2016 data ($r = 0.84$; FDR-corrected $P < .001$; $r = 0.87$; FDR-corrected $P < .001$). Concentrations of $PM_{2.5}$ and O_3 were not statistically significantly correlated in 2002 to 2003 ($r = 0.02$; FDR-corrected $P = .17$) and had a correlation in 2015 to 2016 ($r = 0.19$; FDR-corrected $P < .001$) (eFigures 3-6 in the Supplement).

Table 1. Demographic Characteristics and Clinical Summary

Characteristic	Total	MCI	Dementia
Sample size, No.	18 178	10 991	7187
Age, mean (SD), y	75.8 (6.3)	75.2 (6.1)	76.6 (6.6)
Modified MMSE, mean (SD)[a]	24.5 (4.8)	26.6 (3.0)	21.3 (5.4)
Confidence in AD pathology, mean (SD)[b]	6.2 (1.6)	5.9 (1.6)	6.5 (1.5)
Sex, No. (%)			
Male	8845 (48.7)	5499 (50.0)	3346 (46.6)
Female	9333 (51.3)	5492 (49.9)	3841 (53.4)
Race, No. (%)			
White	15 780 (86.8)	9787 (89.1)	5993 (83.4)
Other	2398 (13.2)	1204 (11.0)	1194 (16.6)
Highest educational level, No. (%)			
<High school	1286 (7.1)	435 (4.0)	851 (11.8)
High school diploma	4790 (26.4)	2523 (23.0)	2267 (31.5)
College degree	8463 (46.6)	5534 (50.4)	2929 (40.8)
Postgraduate degree	3639 (20.0)	2499 (22.7)	1140 (15.9)
Use of AD drugs, No. (%)			
Cholinesterase inhibitors	6636 (36.5)	3123 (28.4)	3513 (48.9)
Memantine hydrochloride	3402 (18.7)	1362 (12.4)	2040 (28.4)
Any	7801 (42.9)	3694 (33.6)	4107 (57.1)
Both	2237 (12.3)	791 (7.2)	1446 (20.1)
Presence of relevant medical history, No. (%)			
No	3123 (17.2)	1907 (17.4)	1216 (16.9)
Yes	15 055 (82.8)	9084 (82.7)	5971 (83.1)
History of cardiovascular conditions or risk factors, No. (%)			
No	5983 (32.9)	3699 (33.7)	2284 (31.8)
Yes	12 195 (67.1)	7292 (66.4)	4903 (68.2)
History of respiratory condition, No. (%)			
No	17 560 (96.6)	10 611 (96.5)	6949 (96.7)
Yes	618 (3.4)	380 (3.5)	238 (3.3)
History of psychiatric condition, No. (%)			
No	14 747 (81.1)	8849 (80.5)	5898 (82.1)
Yes	3431 (18.9)	2142 (19.5)	1289 (17.9)
History of cerebrovascular condition, No. (%)			
No	15 496 (85.3)	9511 (86.5)	5985 (83.3)
Yes	2682 (14.8)	1480 (13.5)	1202 (16.7)
History of neurological condition, No. (%)			
No	16 297 (89.7)	9894 (90.0)	6403 (89.1)
Yes	1881 (10.4)	1097 (10.0)	784 (10.9)
Amyloid PET scan status, No. (%)			
Positive	11 094 (61.0)	6081 (55.3)	5013 (69.8)
Negative	7084 (39.0)	4910 (44.7)	2174 (30.3)

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination (score range: 0-30, with lower scores indicating worse global cognition); PET, positron emission tomography.

[a] The modified MMSE score includes converted Montreal Cognitive Assessment scores for study participants who had Montreal Cognitive Assessment but not MMSE data (see the eMethods in the Supplement for details on clinical and medical history variables). Modified MMSE scores were missing for 49 persons (11 in the MCI group and 38 in the dementia group).

[b] The score range for confidence in AD pathology was 1 to 10, with higher scores indicating higher confidence that AD pathology is present and a factor in cognitive symptoms. One person in the MCI group was missing confidence in AD pathology data.

Exposure to Pollutants and Amyloid PET Scan Positivity

Living in areas with higher concentrations of $PM_{2.5}$ was associated with an increase in the odds of amyloid PET scan positivity, with and without controlling for covariates. In adjusted models when considering 2002 to 2003 data, the odds of a positive amyloid PET scan were increased by a factor of 1.10 (OR, 1.10; 95% CI, 1.05-1.15; z score = 3.93; FDR-corrected $P < .001$) for each 4-μg/m^3 increase of estimated biennial $PM_{2.5}$; the findings using 2015 to 2016 data were similar (OR, 1.15; 95% CI, 1.05-1.26; z score = 3.14; FDR-corrected $P = .003$). Considering 2002 to 2003 quartiles' $PM_{2.5}$ data, the most pronounced increased likelihood of amyloid PET scan positivity was observed in quartile 4 (locations with predicted $PM_{2.5}$>14.44 μg/m^3) compared with quartile 1 (reference group). For the 2015 to 2016 time window, the most pronounced increase in likelihood was observed in quartile 3 (locations with predicted $PM_{2.5}$ between 8.34 and 9.37 μg/m^3) compared with quartile 1 (reference group). The C index for the fully adjusted models was 0.69 for both 2002 to 2003 and 2015 to 2016, with both continuous and quartiles data (eTable 2 in the Supplement). Exposure to higher O_3 concentrations was not associated with amyloid PET scan positivity for either 2002 to 2003

(OR, 1.03; 95% CI, 0.99-1.06; *z* score = 1.59; FDR-corrected *P* = .15; per increase of 5 ppb) or 2015 to 2016 (OR, 1.02; 95% CI, 0.98-1.06; *z* score = 0.84; FDR-corrected *P* = .40). A complete description of the findings is found in **Figure 3** and **Table 2**.

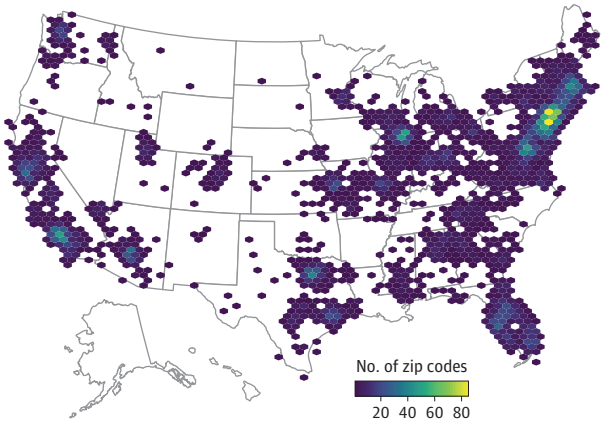
Effect Modification Analysis

The association between $PM_{2.5}$ and amyloid PET scan positivity was not stronger in female than in male participants in either time window (2002-2003: interaction term β = 1.01 [95% CI, 0.99-1.04; *z* score = 1.13; FDR-corrected *P* = .56]; 2015-2016: β = 1.02 [95% CI, 0.98-1.07; *z* score = 0.91; FDR-corrected *P* = .56]). No difference was observed in the strength of association between participants with MCI vs participants with dementia (2002-2003: interaction term β = 1.01 [95% CI, 0.99-1.03; *z* score = 0.77; FDR-corrected *P* = .58]; 2015-2016: β = 1.03; 95% CI, 0.99-1.08; *z* score = 1.46; FDR-corrected *P* = .47]). eTable 3 in the Supplement has details and replication with quartiles data.

Exposure to $PM_{2.5}$ and Predicted Probability of Amyloid PET Scan Positivity

Marginal effects analyses showed an estimated average marginal effect (AME) of +0.5% (SE = 0.1%; *z* score = 3.93; 95% CI, 0.3%-0.7%; FDR-corrected *P* < .001) probability of amyloid PET scan positivity for each 1-μg/m^3 increase in $PM_{2.5}$ for 2002 to 2003 data and an AME of +0.8% (SE = 0.2%; *z* score = 3.15; 95% CI, 0.3%-1.2%; FDR-corrected *P* = .002) probability for 2015 to 2016. According to the 2002 to 2003 data, living in areas in quartile 2 was associated with an AME of +4% (SE = 1%; *z* score = 4.24; 95% CI, 2%-6%; FDR-corrected *P* < .001) predicted probability, quartile 3 was associated with an AME of +4% (SE = 1%; *z* score = 3.75; 95% CI, 2%-6%; FDR-corrected *P* < .001) predicted probability, and quartile 4 was associated with an AME of +5% (SE = 1%; *z* score = 5.08; 95% CI, 3%-7%; FDR-corrected *P* < .001) predicted probability of amyloid PET scan positivity. According to the 2015 to 2016 data, living in areas assigned to quartile 3 was associated with an AME of +3% (SE = 1%; *z* score = 3.15; 95% CI, 1%-5%; FDR-corrected *P* = .005) probability and quartile 4 was associated with an AME of +3% (SE = 1%; *z* score = 2.78; 95% CI, 1%-5%; FDR-corrected *P* = .008) probability (Figure 3 and eTable 4 in the Supplement). Overall, dose-response associations were statistically significant and of similar magnitude (based on overlapping CIs) within each time window. Marginal effects were also re-estimated according to sex (male 2002-2003: AME, 0.4% [SE = 0.2%; *z* score = 2.08; 95% CI, 0%-0.7%; FDR-corrected *P* = .06]; 2015-2016: AME, 0.6% [SE = 0.3%; *z* score = 1.62; 95% CI, -0.1% to 1.2%; FDR-corrected *P* = .12]; female 2002-2003: AME, 0.6% [SE = 0.2%; *z* score = 3.63; 95% CI, 0.3%-1%; FDR-corrected *P* = .001]; 2015-2016: AME, 1% [SE = 0.3%; *z* score = 2.89; 95% CI, 0.3%-1.6%; FDR-corrected *P* = .008]) or clinical stage (dementia 2002-2003: AME, 0.4% [SE = 0.2%; *z* score = 1.69; 95% CI, -0.1% to 0.8%; FDR-corrected *P* = .12]; 2015-2016: AME, 0.3% [SE = 0.4%; *z* score = 0.74; 95% CI, -0.5% to 1.1%; FDR-corrected *P* = .46]; MCI 2002-2003: AME, 0.6% [SE = 0.2%; *z* score = 3.69; 95% CI, 0.3%-0.9%; FDR-corrected *P* = .001]; 2015-2016: AME, 1% [SE = 0.3%; *z* score = 3.41; 95% CI, 0.4%-1.6%; FDR-corrected *P* = .002]) for both time windows from fully adjusted models with interaction terms (eTable 5 and eFigures 7 and 8 in the Supplement).

Figure 1. Geographical Distribution of Imaging Dementia—Evidence for Amyloid Scanning Study Participants



Participants were mapped by the centroid of the residential zip codes. To maintain confidentiality, a perturbation approach was adopted by adding random noise (jittering) to residential zip code coordinates, displacing them within a 50 by 50-km grid.

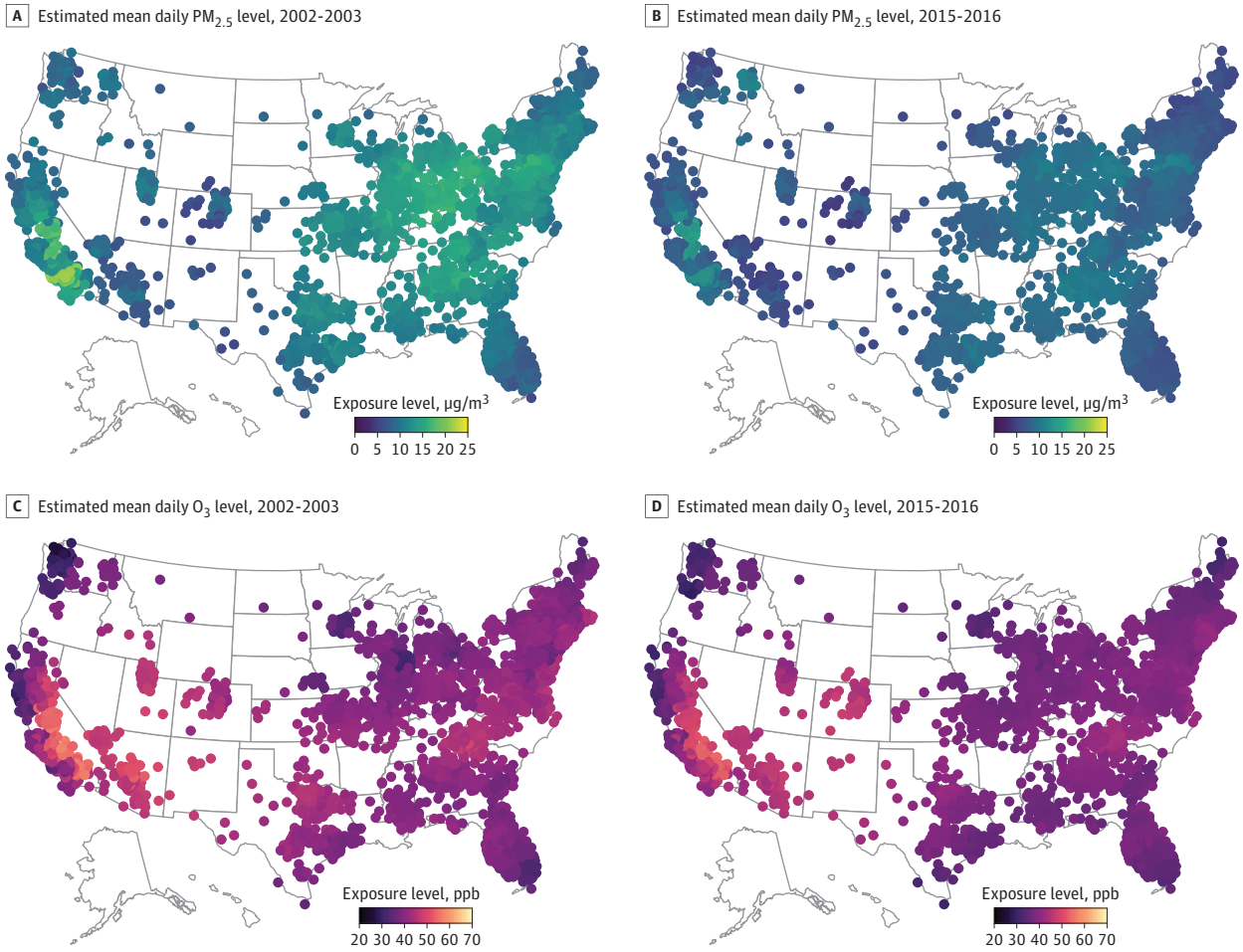
Significance of Results Across Study Locations

The association between exposure to $PM_{2.5}$ and amyloid PET scan positivity remained statistically significant after adjusting for US Census tract random effects, supporting the robustness of the association. Mixed-effects analysis showed statistically significant associations with amyloid PET scan positivity for both 2002 to 2003 (OR, 1.27; 95% CI, 1.08-1.48; *z* score = 2.94; FDR-corrected *P* = .006) and 2015 to 2016 (OR, 1.18; 95% CI, 1.01-1.37; *z* score = 2.14; FDR-corrected *P* = .04). Given the presence of US Census tracts with a single participant, which may have affected the estimation of random effects, we performed mixed-effects analyses that included only US Census tracts with at least 2 or 5 participants, replicating the findings (eTable 6 in the Supplement).

Discussion

We hypothesized that exposure to airborne pollutants would be associated with amyloid PET scan positivity based on previous cell, animal, epidemiological, and small human biomarker and neuropathologic studies.[17-22,24-28,43] We found that older adults with cognitive impairment and who resided in areas with higher concentrations of $PM_{2.5}$ were more likely to have a positive amyloid PET scan. The associations were statistically significant after adjusting for individualized covariates and showed similar dose-response associations across the whole sample. These findings suggest that brain Aβ accumulation could be 1 of the biological pathways in the increased incidence of dementia and cognitive decline associated with exposure to air pollution.[9-15]

Figure 2. Estimated Levels of Fine Particulate Matter ($PM_{2.5}$) and Ground-Level Ozone (O_3)



Mean daily $PM_{2.5}$ and mean daily 8-hour maximum O_3 levels among participants across geographical locations were estimated for both 2002 to 2003 and 2015 to 2016 using the Downscaler model. Data are provided for both exposure time windows and expressed in micrograms per cubic meter ($\mu g/m^3$) for $PM_{2.5}$ and in parts per billion (ppb) for O_3. To maintain confidentiality, a perturbation approach was adopted by adding random noise (jittering) to residential zip code coordinates, displacing them within a 50-by-50 km grid.

Epidemiological Studies of Exposure to Airborne Pollutants and Likelihood of Dementia and AD Clinical Diagnosis

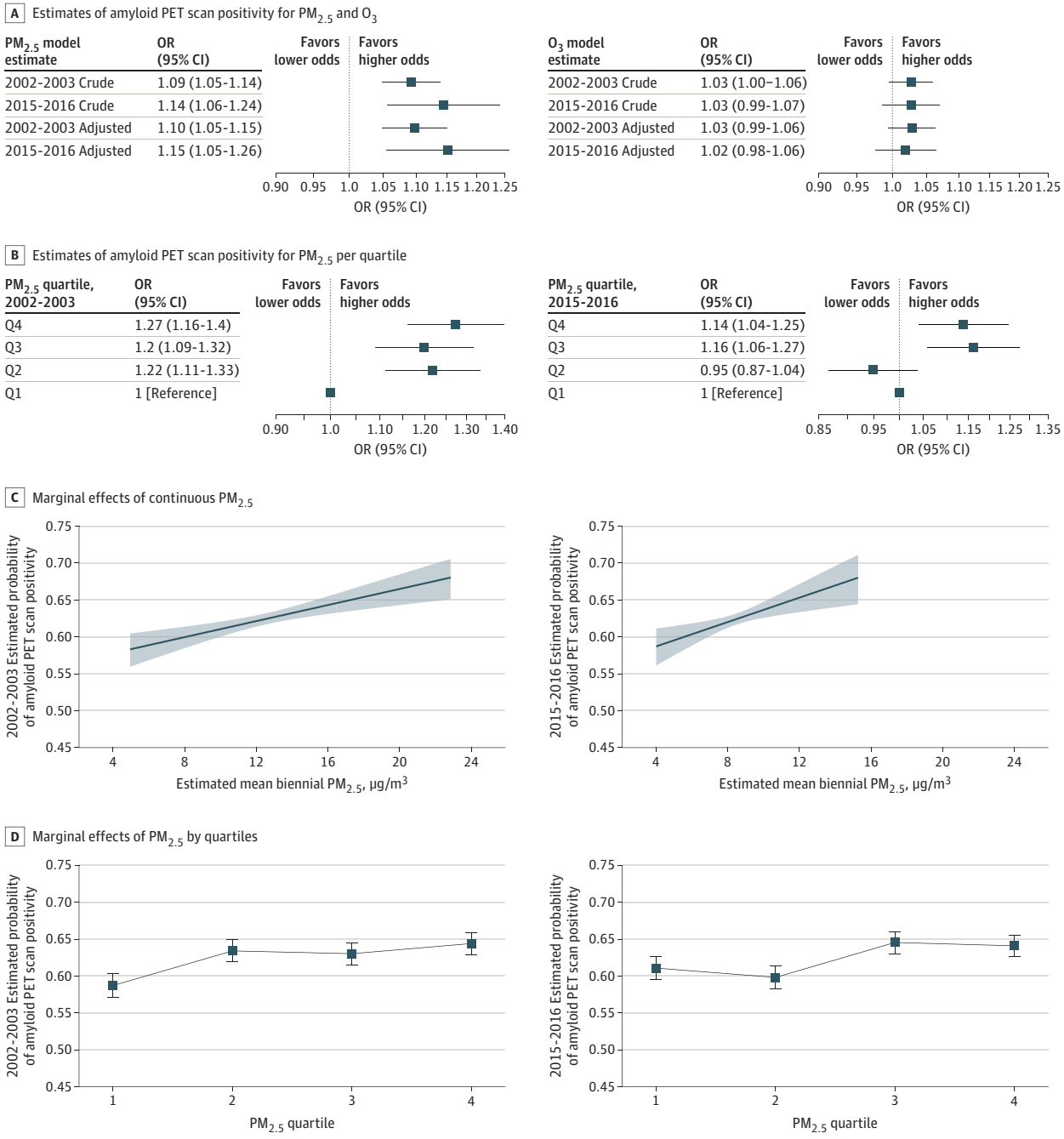
Previous epidemiological studies provide evidence of an association between exposure to ambient air pollution (including but not limited to $PM_{2.5}$) and cognitive decline, all-cause dementia, and clinically diagnosed AD.[9-15] One study in approximately 9.8 million Medicare beneficiaries across 50 northeastern cities found that long-term exposure to $PM_{2.5}$ was associated with shorter time to first neurological hospitalization for dementia, AD, or Parkinson disease.[44] Similar results were observed in 2 other large-scale independent studies that included 1.1 million Medicare beneficiaries and 2.1 million Ontario residents, showing that greater long-term exposure to $PM_{2.5}$ increased the likelihood of dementia diagnosis[45] and dementia incidence.[46] We believe that the present study adds novel findings to the literature by studying a cohort of individuals with cognitive impairment at different clinical stages and by considering the presence of brain Aβ pathology measured by PET, rather than clinical diagnosis, as the outcome.

We did not find evidence of a statistically significant association between predicted O_3 and likelihood of amyloid PET scan positivity. Previous data on the associations between exposure to O_3 and incidence of AD were inconsistent.[47-51] When identified, associations have been mild in magnitude[48] and reported primarily in individuals with normal cognition[50] and in regions with much higher O_3 concentrations compared with levels in the present study.[49] It is plausible that $PM_{2.5}$ and O_3 would manifest different profiles and mechanisms of toxic effect given that these pollutants have distinct chemical and physical properties.[11,52,53] Inhaled gaseous pollutants, such as O_3, are less likely to reach the central nervous system and may trigger neurotoxic effects through indirect pathways,[9] such as microglial activation and priming through O_3-induced peripheral circulating proinflammatory factors.[54]

Airborne Toxic Pollutants and Amyloid Pathology

Previous animal studies have provided evidence of an association between airborne pollutants and increased Aβ

Figure 3. Associations Between Exposure to Fine Particulate Matter ($PM_{2.5}$) and Ground-Level Ozone (O_3) and Amyloid Positron Emission Tomography (PET) Scan Positivity



A, Odds ratios (ORs) are expressed as changes compared with increases of 4 µg/m^3 for $PM_{2.5}$ and 5 parts per billion (ppb) for O_3 (ie, the observed respective interquartile ranges in 2002 to 2003). B, Adjusted OR estimations in the full sample with $PM_{2.5}$ considered as quartile (Q) data. Error bars show 95% CIs. Marginal effects plots are shown for continuous (C) and quartiles (D) data. C, Solid lines indicate linear fit, and the shaded area indicates 95% CIs. D, Quartile 1 is the lowest (least polluted) quartile, and quartile 4 is the highest (most polluted) quartile.

pathology.[17-19,21,22,43] Murine studies tested the association of long-term exposure to pollutants (such as $PM_{2.5}$, total PM, and diesel exhaust particles) with wild-type animals, showing increases in Aβ1-40,[19] Aβ immunoreactivity (4G8 antibody),[19] and elevated cerebral and cerebellar Aβ1-42,[18,22] with similar associations found in dogs.[43] Neurotoxic effects of exposure to air pollution on amyloidogenic processing have similarly been reported in monogenic familial AD animal models.[17,20,21,23] Such associations have been observed with different air pollutants, including PM[17,20,21] and diesel engine exhaust,[23] and in animals carrying the human *APOE* (OMIM 107741) ε4 allele,[17] the strongest genetic risk factor for sporadic AD.[55] Proamyloi-

Table 2. Logistic Regression Results

Model	Group	No.	Time window					
			2002-2003			2015-2016		
			OR (95% CI)	*z* Score	*P* value[a]	OR (95% CI)	*z* Score	*P* value[a]
$PM_{2.5}$								
Crude	Full	18 178	1.09 (1.05-1.14)	4.16	<.001	1.14 (1.06-1.24)	3.27	.003
Adjusted	Full	17 922	1.10 (1.05-1.15)	3.93	<.001	1.15 (1.05-1.26)	3.14	.003
Quartile-adjusted	Full—quartile 4	17 922	1.27 (1.16-1.4)	5.08	<.001	1.14 (1.04-1.25)	2.78	.006
	Full—quartile 3		1.2 (1.09-1.32)	3.75	<.001	1.16 (1.06-1.27)	3.14	.003
	Full—quartile 2		1.22 (1.11-1.33)	4.24	<.001	0.95 (0.87-1.04)	−1.14	.25
	Full—quartile 1		1 [Reference]	NA	NA	1 [Reference]	NA	NA
O_3[b]								
Crude	Full	18 178	1.03 (1.00-1.06)	1.68	.15	1.03 (0.99-1.07)	1.26	.24
Adjusted	Full	17 922	1.03 (0.99-1.06)	1.59	.15	1.02 (0.98-1.06)	0.84	.40

Abbreviations: NA, not applicable; O_3, ground-level ozone; OR, odds ratio; $PM_{2.5}$, fine particulate matter.

[a] The reported *P* values are false discovery rate corrected for multiple comparisons (see Methods in the main text).

[b] O_3 quartile analyses were not performed given the nonsignificance of the crude and adjusted estimates for both time windows. Unit increases for the interpretation of the ORs were transformed to changes compared with increases of 4 μg/m^3 for $PM_{2.5}$ and 5 parts per billion for O_3 (respective interquartile ranges in 2002 to 2003).

dogenic amyloid precursor protein processing and increased Aβ peptide load were also observed in vitro after PM treatment on neuroblastoma N2a cells expressing Swedish mutant amyloid precursor protein (N2a-APPswe).[17,20] Consistent with our findings, a study investigating the association of cyclic O_3 exposure in a familial AD animal model reported negative (ie, evidence for no association) results.[56]

Convergent results have been provided by human studies showing that children and young or middle-aged adults living in highly polluted areas exhibit abnormal amyloid processing, including increased intracellular Aβ1-42 and diffuse plaques at autopsy as well as lower cerebrospinal fluid Aβ1-42.[24-28] These abnormalities may precede neuritic plaques, which are more closely associated with clinical manifestations.[57-59] The lack of evidence of increased neuritic plaques could be attributed to the fairly young age of the studied cohorts. Consistent with data from animal models, the neurotoxic effect of air pollution seems to be most pronounced in *APOE ε4* allele carriers.[17,26,60-62] Complementary evidence comes from a recent neuroimaging study indicating that exposure to $PM_{2.5}$ has an unfavorable association with episodic memory performance, an association mediated by volume loss in AD brain regions.[63] The present study adds to the current literature by demonstrating an association between worse air quality and amyloid PET scan positivity, the criterion standard antemortem marker of neuritic plaques,[31-33,37] in participants with cognitive impairment.

Putative Biological Mechanisms

Neuroinflammation and oxidative stress have been identified as the most likely biological mechanisms in the adverse brain health effects of ambient air pollution,[9,11,15,20,52] with microglia as the possible main cellular mediators of neurotoxic effects.[9,52] In vivo and in vitro microglia studies show a proliferative, activated morphological phenotype and enhanced secretion of reactive oxygen species and proinflammatory cytokines, such as interleukin-1β and tumor necrosis factor-α, in response to air pollutants.[9,15] Microglia activation may become chronic when the exposure to pathogens or brain injury is prolonged,[64] which is likely in cases of long-term exposure to air pollutants.[52] Reactive microgliosis may be triggered both locally by pollutants reaching the brain and systemically by peripheral immune mediators,[15,52] eventually leading to impaired phagocytosis and increased Aβ accumulation.[65]

Strengths and Limitations

This study has several strengths. First, the large and geographically dispersed sample size allowed us to test the associations between ambient air pollution and presence of Aβ plaque pathology, controlling for potential individualized confounding factors. The geographic dispersion of participants in the IDEAS Study largely reflected the population density in the US and included locations covering the full range of air quality detected in the US in the respective years.[66] Second, the outcome measure was amyloid PET scan positivity, which is a biologically specific measure of Aβ plaques observed at autopsy.[31-37] Third, we used Downscaler predicted data to estimate air quality, which reduced the error in the measurement of associations between air pollution and health outcomes.[67] Fourth, marginal effects analyses showed a dose-dependent association between exposure to $PM_{2.5}$ concentration and predicted probability of amyloid PET scan positivity for both $PM_{2.5}$ continuous and quartiles data, which strengthened the plausibility of the observed association. Fifth, mixed-effects analyses showed that the associations remained after accounting for US Census tracts random effects.

This study has limitations. First, this study was a retrospective secondary analysis of a clinical trial that was not designed to address the associations between air pollution and amyloid PET scan positivity in the general population, limiting the generalizability of these findings. In particular, the

IDEAS Study did not recruit individuals with normal cognition, limiting the observed associations to older adults with cognitive impairment who presented to memory clinics. These factors could lead to selection bias. We also cannot exclude the possibility of bias from competing survival, whereby individuals with severe medical comorbidities also associated with exposure to air pollution would have been excluded. Second, we cannot exclude residual confounding from factors that were not adequately adjusted for in the models. Third, exposure to air pollution was estimated at recorded participant residences given that information regarding indoor and occupational exposures was not available.[12,68] Fourth, data on the geographical mobility of the participants were not available. However, the US Census Bureau Current Population Survey Geographical Mobility 2016 to 2017 data indicated that only 4% of older (aged >65) individuals moved in the previous year, with most relocations (57%) being within county.[69] Furthermore, migration rates in older adults in the US were found to be stable or declining over time.[70] The $PM_{2.5}$ and O_3 pollutants are more spatially homogeneous than other airborne pollutants, such as nitrogen dioxide,[12] mitigating the potential impact of local migration. Fifth, $PM_{2.5}$ can be composed of different particles or droplets from different sources, which may have different toxic effects.[71,72]

Conclusions

In this cross-sectional study, we observed an association between air pollution and Aβ pathology in older adults with cognitive impairment who were enrolled in the IDEAS Study, a finding with strong biological plausibility based on bench-to-bedside evidence. Specifically, higher $PM_{2.5}$ concentrations appeared to be associated with brain Aβ plaques, a signature of Alzheimer disease. Adverse effects of airborne toxic pollutants associated with Aβ pathology should be considered in public health policy decisions and should inform individual lifetime risk of developing AD and dementia.[16]

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