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Ambient Air Pollution and the Severity of Alzheimer Disease Neuropathology

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IMPORTANCE Exposure to fine particulate matter air pollution ($PM_{2.5}$) may increase risk for dementia. It is unknown whether this association is mediated by dementia-related neuropathologic change found at autopsy.

OBJECTIVE To examine associations between $PM_{2.5}$ exposure, dementia severity, and dementia-associated neuropathologic change.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data associated with autopsy cases collected from 1999 to 2022 at the Center for Neurodegenerative Disease Research Brain Bank at the University of Pennsylvania. Data were analyzed from January to June 2025. Participants included 602 cases with common forms of dementia and/or movement disorders and older controls after excluding 429 cases with missing data on neuropathologic measures, demographic factors, *APOE* genotype, or residential address.

EXPOSURES One-year mean $PM_{2.5}$ concentration prior to death or prior to last Clinical Dementia Rating Sum of Boxes (CDR-SB) assessment was estimated using a spatiotemporal prediction model at residential addresses.

MAIN OUTCOMES AND MEASURES Dementia severity was measured by CDR-SB scores. Ten dementia-associated neuropathologic measures representing Alzheimer disease, Lewy body disease, limbic-predominant age-related transactive response DNA-binding protein (TDP)-43 encephalopathy, and cerebrovascular disease were graded or staged. Linear, logistic, and structural equation models were used to examine the associations between $PM_{2.5}$, CDR-SB, and neuropathologic measures, adjusting for demographic factors and *APOE* ε4 allele status.

RESULTS In a total of 602 autopsy cases (median [IQR] age at death, 78 [71-85] years; 328 male [54.5%] and 274 female [45.5%]), higher $PM_{2.5}$ exposure prior to death was associated with increased odds of more severe Alzheimer disease neuropathologic change (ADNC) (odds ratio, 1.19; 95% CI, 1.11-1.28). In a subset of 287 cases with CDR-SB records (median [IQR] age at death, 79 [72-86] years; 154 [53.7%] male and 133 female [46.3%]), higher $PM_{2.5}$ exposure prior to CDR-SB assessment was associated with greater cognitive and functional impairment (β = 0.48; 95% CI, 0.22-0.74). Lastly, 63% of the association between higher $PM_{2.5}$ exposure and greater cognitive and functional impairment was statistically mediated by ADNC (β = 0.30; 95% CI, 0.04-0.53).

CONCLUSIONS AND RELEVANCE In this study, $PM_{2.5}$ exposure was associated with increased dementia severity and increased ADNC. Population-based studies are needed to better understand this relationship.

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Supplemental content

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Air pollution has been suggested to be an environmental risk factor for dementia.[1-3] Studies have shown that exposure to air pollution, or more specifically, fine particulate air pollution ($PM_{2.5}$) matter with aerodynamic diameter less than 2.5 µm, is associated with an increased incidence of dementia,[4] impaired cognitive function,[5,6] and accelerated cognitive decline.[7] Disease-modifying therapies that target the underlying neuropathology of Alzheimer disease (AD) show partial clinical benefit, but substantial economic and logistical barriers preclude widespread implementation and serious adverse effects occur in some instances.[8,9] Given the social inequities with regard to air pollution exposure around the globe, better understanding of the association between air pollution exposure and risk for different subtypes of dementia may provide evidence that curbing $PM_{2.5}$ levels has the potential to benefit health outcomes and prevent dementia risk at the population level.

Despite growing evidence of the adverse effect of $PM_{2.5}$ on cognition,[10,11] the underlying biological mechanisms for this association are largely unknown. $PM_{2.5}$ exposure has been associated with brain volume loss,[12] brain atrophy,[13-15] worsening of cerebrospinal fluid amyloid-β42 biomarker levels,[16,17] increased amyloid positron emission tomography positivity,[18] and accelerated epigenetic aging,[19] raising the possibility that $PM_{2.5}$ might contribute to dementia risk by enhancing AD neurodegenerative disease pathways.[20-22] Postmortem autopsy examination remains the gold standard for the neuropathologic diagnosis of AD and related dementias. However, only 2 postmortem studies have investigated the association between $PM_{2.5}$ exposure and AD neuropathology, but not other neurodegenerative disease pathology,[23,24] and the tripartite association between $PM_{2.5}$, neurodegenerative disease pathology, and cognitive and functional outcomes has not been studied.

To address this knowledge gap, we studied the associations between $PM_{2.5}$ exposure, neuropathologic change, and cognitive and functional impairment in a large, well-characterized autopsy cohort. Using high spatial resolution estimates of $PM_{2.5}$ obtained from a validated prediction model,[25] we determined whether $PM_{2.5}$ exposure prior to death was associated with differences in the burden of the most common dementia-related neuropathologies, including AD neuropathologic change (ADNC), Lewy body disease (LBD), limbic-predominant age-related transactive response DNA-binding protein (TDP)-43 encephalopathy neuropathologic change (LATE-NC), and cerebrovascular disease.[26,27] Next, we evaluated the association between $PM_{2.5}$ exposure, dementia severity measured by Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score, and dementia-related neuropathologic changes in our autopsy cohort. For this purpose, we explored whether $PM_{2.5}$ exposure prior to CDR-SB assessment was associated with worse CDR-SB scores and whether this association was mediated by neuropathologic change observed at autopsy.

Key Points

Question What are the associations between air pollution, neuropathology, and dementia?

Findings In this study of 602 autopsy-confirmed individuals, exposure to higher levels of fine particulate matter air pollution ($PM_{2.5}$) was associated with more advanced Alzheimer disease neuropathologic change (ADNC) and more advanced clinical measures of dementia. The association between $PM_{2.5}$ exposure and clinical dementia severity appeared to be statistically mediated by ADNC.

Meaning Higher $PM_{2.5}$ exposure may exacerbate Alzheimer disease neuropathologic change and cognitive dysfunction in the setting of dementia; population-based autopsy studies are further needed to generalize these findings.

Methods

Written informed consent was obtained from participants of neurodegenerative research programs with approval from the University of Pennsylvania Institutional Review Board, in addition to informed consent at time of death from next of kin prior to autopsy. This cohort study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Study Participants

We obtained data associated with autopsy cases from the Integrated Neurodegenerative Disease (INDD) database at the Center for Neurodegeneration Disease Research at the University of Pennsylvania.[28] Cases were recruited mainly through the Penn Alzheimer Disease Research Center, which focuses on dementia of the Alzheimer type (as opposed to vascular or other dementias), and the Penn Parkinson Disease and Movement Disorder Center, which includes a research cohort focusing on cognitive dysfunction in the setting of LBD, including dementia with Lewy bodies and Parkinson disease dementia. Details on the study cohort are provided in the eMethods and eFigure 1 in Supplement 1. In brief, we restricted our autopsy cases to individuals older than 40 years with common neuropathological forms of dementia from 1999 through 2022. We excluded 429 cases due to missing data on neuropathology (n = 9 [2.1%]), *APOE* ε4 allele status (n = 3 [0.7%]), self-reported race (n = 12 [2.8%]), years of education (n = 226 [52.8%]), and/or residential address (n = 179 [41.7%]), resulting in a full cohort of 602 cases.

Air Pollution Exposure Assessment

We used estimates of annual $PM_{2.5}$ exposure at a 0.01° × 0.01° (approximately 1.1 km × 1.1 km) grid-cell resolution from 1998 to 2022, from a publicly available prediction model (V5.GL.04; Washington University, St Louis).[25] We then spatially matched each case's geocoded residential address before death to grid cells to obtain 1-year mean $PM_{2.5}$ concentration either prior to death or prior to last CDR-SB assessment proximate to death as the primary exposure (eMethods in Supplement 1).

Neuropathological Assessment

Ten neuropathologic measures representing 4 proteinopathies (tau, β-amyloid, α-synuclein, and TDP-43) and 3 cerebrovascular lesions (infarcts, amyloid angiopathy, and arteriolosclerosis) were obtained from the INDD database and used to assess neuropathologic outcomes as follows: Thal amyloid phase, Braak stage, Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score, level of ADNC,[29] absence/presence of LBD,[30] LATE-NC stage,[27] absence/presence of large infarcts anywhere in the brain based on gross and microscopic examination, absence/presence of moderate to high occipital cerebral amyloid angiopathy burden, absence/presence of moderate to high arteriolosclerosis in occipital white matter, and likelihood that cerebrovascular pathology contributed to cognitive impairment (vascular cognitive impairment neuropathology guidelines [VCING]).[31] All assessments were based on consensus criteria.[27,29-31] Further details are described in the eMethods in Supplement 1.

Clinical Assessment

The INDD records on clinician-reported CDR-SB scores were used as the clinical outcome. The CDR-SB assessment is a comprehensive measure of dementia severity across 6 cognitive and functional domains, including memory, orientation, judgment, community affairs, home hobbies, and personal care, and is scored ranging from 0 to 18, with higher scores indicating more severe dementia.[32]

Statistical Analysis

Analyses were performed with R version 4.2.3 (The R Project). All statistical tests were 2-sided. Diagnostic and assumption tests were performed for fitted models, if appropriate (eMethods in Supplement 1).

For the full autopsy cohort, logistic regression was used to estimate the association between 1-year mean $PM_{2.5}$ exposure before death and the odds of ordered categorical neuropathologic outcomes that included Thal amyloid phase, Braak stage, CERAD score, ADNC level, LATE-NC stage, and VCING likelihood level, and the odds of dichotomous neuropathologic outcomes that included the presence/absence of LBD, large infarcts, occipital lobe cerebral amyloid angiopathy, and occipital white matter arteriolosclerosis. All models were adjusted for sex, age at death, *APOE* ε4 allele status, race, and years of education.

For the subset of cases where their last CDR-SB score was evaluated within 5 years of death (Clinical Dementia Rating [CDR] cohort), we estimated the association between 1-year mean $PM_{2.5}$ exposure before last CDR assessment and last CDR-SB score prior to death representing dementia severity at death using linear regression and neuropathologic measures using the same statistical models and neuropathologic outcomes described for the full autopsy cohort. All models included the same covariates used for the full autopsy cohort.

For the subset of cases where multiple CDR-SB records were available (longitudinal CDR cohort), we used a linear mixed-effects model to estimate the association between 1-year mean $PM_{2.5}$ concentration before each CDR assessment and longitudinal change in CDR-SB scores, with an interaction term between $PM_{2.5}$ exposure and interval years from initial CDR-SB assessment to each follow-up assessment as the main effect using case-specific intercepts and slopes as random factors. Covariates were the same as those described for other cohorts.

To explore the adjusted tripartite association between $PM_{2.5}$ exposure, CDR-SB score, and neuropathologic change, we performed a mediation analysis with structural equation modeling (SEM) using the R lavaan package.[33] In the SEM, we estimated direct and indirect effects of 1-year mean $PM_{2.5}$ exposure before last CDR-SB assessment on last CDR-SB score prior to death, accounting for ADNC as a potential endogenous mediator, using a bias-corrected accelerated bootstrap confidence interval method with 2000 simulations.

Post Hoc Analyses

In a secondary analysis exploring effect modification, we added an interaction term for *APOE* ε4 allele status in main regression models. In a series of sensitivity analyses, we determined the effect of uncertainty in the $PM_{2.5}$ prediction model (eMethods in Supplement 1). Furthermore, we applied additional exposure time windows corresponding to 2-year, 3-year, and 4-year mean $PM_{2.5}$ exposures before death or before last CDR assessment prior to death, included an additional covariate of area-level socioeconomic status (eMethods in Supplement 1), and also applied different estimated $PM_{2.5}$ values from another well-validated prediction model (eMethods in Supplement 1).

Results

Cohort Characteristics

Demographic, clinical, and genetic features of the cohort are provided in **Table 1**. Within the full autopsy cohort of 602 cases, 328 were male (54.5%) and 274 were female (45.5%), the median (IQR) age at death was 78 (71-85) years, most of the participants were White (94.4%) and non-Hispanic or Latino (99%), and 53.2% carried at least 1 ε4 allele of the *APOE*, which is the strongest genetic risk factor for sporadic AD. Overall, the cohort was highly educated with a median (IQR) of 16 (12-18) years of education, with a moderate level of dementia corresponding to a median (IQR) CDR-SB score of 12 (5-17) at last assessment. The most common clinical diagnoses were AD (47.3%) and Parkinson disease with dementia (14.1%).

Neuropathological features of the cohort are presented in **Table 2**. More than one-half of the cohort exhibited severe AD neuropathologic measures, including Thal amyloid phase 4/5 (71.3%), Braak stage V/VI (63.8%), CERAD score 3 (64.3%), and high overall ADNC (62.3%). A total of 38.2% exhibited transitional/limbic or diffuse/neocortical LBD and 34.4% exhibited LATE-NC. Notably, very few cases exhibited large infarcts (5.3%), moderate to severe occipital lobe cerebral amyloid angiopathy (31.1%), moderate to severe occipital white matter arteriolosclerosis burden (16.8%), or overall high likelihood that cerebrovascular pathology contributed to cognitive impairment (2.7%).

Table 1. Demographic and Clinical Characteristics of Study Participants

Characteristic	No. (%)
No. of participants	602
Sex	
Female	274 (45.5)
Male	328 (54.5)
Age at death, y, median (IQR)	78 (71-85)
Self-reported race	
African American	27 (4.5)
Asian	2 (0.3)
Multiracial	5 (0.8)
White	568 (94.4)
Ethnicity[a]	
Hispanic or Latino	6 (1.0)
Not Hispanic or Latino	589 (99.0)
APOE ε4 allele status	
APOE ε4 positive	320 (53.2)
ε2/ε4	11 (1.8)
ε3/ε4	228 (37.9)
ε4/ε4	81 (13.5)
APOE ε4 negative	282 (46.8)
ε2/ε2	2 (0.3)
ε2/ε3	39 (6.5)
ε3/ε3	241 (40.0)
Education, y, median (IQR)	16 (12-18)
CDR-SB at last assessment within 5 y of death, median (IQR)[b]	12 (5-17)
Age at last CDR-SB assessment, y, median (IQR)[b]	78 (71-85)
Interval between last CDR-SB assessment and death, y, median (IQR)[b]	1 (1-3)
Annual change in CDR-SB, y, median (IQR)[c]	1.4 (0.4-2.2)
Interval between initial and last CDR-SB assessment, y, median (IQR)[c]	4 (2-7)
Primary clinical diagnosis	
Behavioral variant frontotemporal dementia	16 (2.7)
Corticobasal syndrome	26 (4.3)
Dementia, uncertain etiology	7 (1.2)
Dementia with Lewy bodies	51 (8.5)
Frontotemporal dementia, not otherwise specified	16 (2.7)
Hydrocephalus	1 (0.2)
Limbic-predominant age-related TDP-43 encephalopathy	1 (0.2)
Logopenic primary progressive aphasia	14 (2.3)
Mild cognitive impairment	12 (2.0)
Neurologically normal	28 (4.7)
Parkinson disease with dementia	85 (14.1)
Parkinson disease without dementia	37 (6.1)
Possible/probable Alzheimer disease	285 (47.3)
Posterior cortical atrophy	6 (1.0)
Progressive nonfluent aphasia	4 (0.7)
Progressive supranuclear palsy	1 (0.2)
Semantic variant primary progressive aphasia	4 (0.7)
Vascular dementia	8 (1.3)

Abbreviations: CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; TDP-43, transactive response DNA-binding protein 43.

[a] A total of 7 participants (1.2%) had missing data.

[b] Scores on the CDR-SB at last assessment prior to death range from 0 to 18, with higher scores indicating greater cognitive and functional impairment. A total of 287 participants were included after excluding 315 (52.3%) cases with missing data on CDR-SB scores within 5 years of death.

[c] Annual change in CDR-SB score was assessed for a period between initial to last Clinical Dementia Rating assessment, with higher values indicating faster cognitive and functional impairment. A total of 261 participants were included after excluding 341 (56.6%) cases who did not have multiple annual records on CDR-SB scores.

Table 2. Neuropathologic Characteristics of Study Participants

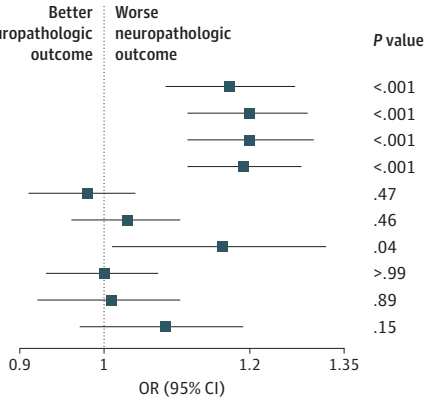
Characteristic[a]	No. (%)
No. of participants	602
Thal amyloid phase	
0	41 (6.8)
1/2	63 (10.5)
3	69 (11.5)
4/5	429 (71.3)
Braak NFT stage	
0	14 (2.3)
I/II	101 (16.8)
III/IV	103 (17.1)
V/VI	384 (63.8)
CERAD score	
0	99 (16.4)
1	42 (7.0)
2	74 (12.3)
3	387 (64.3)
ADNC level	
No	40 (6.6)
Low	101 (16.8)
Intermediate	86 (14.3)
High	375 (62.3)
Lewy pathology	
No	209 (37.4)
Brainstem predominant	54 (9.0)
Transitional or limbic predominant	106 (17.6)
Diffuse or neocortical predominant	124 (20.6)
Amygdala	109 (18.1)
LATE	
No	395 (65.6)
LATE-NC stage 1	35 (5.8)
LATE-NC stage 2	147 (24.4)
LATE-NC stage 3	25 (4.2)
Large infarct	
No	570 (94.7)
Yes	32 (5.3)
Cerebral amyloid angiopathy burden in occipital lobe	
Absent to mild	415 (68.9)
Moderate to severe	187 (31.1)
Arteriolosclerosis burden in occipital white matter	
Absent to mild	501 (83.2)
Moderate to severe	101 (16.8)
VCING level	
Low	535 (88.9)
Intermediate	51 (8.5)
High	16 (2.7)

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; CERAD, Consortium to Establish a Registry for Alzheimer Disease; LATE-NC, limbic-predominant age-related transactive response DNA-binding protein (TDP)-43 encephalopathy; NFT, neurofibrillary tangle; VCING, vascular cognitive impairment neuropathology guidelines.

[a] All pathological measures were assessed using consensus criteria.

Figure 1. Fine Particulate Matter Air Pollution ($PM_{2.5}$) Exposure and Dementia-Related Neuropathologies in the Full Autopsy Cohort

Outcome	OR (95% CI)	P value
Thal amyloid phase	1.17 (1.08-1.27)	<.001
Braak stage	1.20 (1.11-1.29)	<.001
CERAD score	1.20 (1.11-1.30)	<.001
ADNC level	1.19 (1.11-1.28)	<.001
LBD stage	0.98 (0.91-1.04)	.47
LATE-NC stage	1.03 (0.96-1.10)	.46
Large infarct	1.16 (1.01-1.32)	.04
Cerebral amyloid angiopathy	1.00 (0.93-1.07)	>.99
Arteriolosclerosis	1.01 (0.92-1.10)	.89
VCING level	1.08 (0.97-1.19)	.15



Odds ratios (ORs) and 95% CIs are reported for each neuropathologic outcome corresponding to every 1-µg/m^3 increase in 1-year mean $PM_{2.5}$ exposure before death from a series of ordinal logistic regression models with ordinal Thal amyloid phase, ordinal Braak stage, ordinal Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score, ordinal Alzheimer disease neuropathologic change (ADNC) level, ordinal limbic-predominant age-related transactive response DNA-binding protein (TDP)-43 encephalopathy neuropathologic change (LATE-NC) stage, and ordinal vascular cognitive impairment neuropathology guidelines (VCING) score as outcome variables, and binary logistic regression models with dichotomously treated Lewy body disease (LBD) stage, presence of large infarcts, presence of occipital cerebral amyloid angiopathy, and presence of arteriolosclerosis as outcome variables in the full autopsy cohort (n = 602). All models were controlled for sex, age at death, race, *APOE* ε4 status, and years of education. ORs and 95% CIs greater than 1 indicate worse neuropathologic outcomes. *P* values less than .05 were considered statistically significant.

Air Pollution and Neuropathologic Change in Autopsy Cases

The cases were geographically distributed across 11 states (California, Colorado, Connecticut, Delaware, Maryland, New Jersey, New York, Ohio, Pennsylvania, Virginia, and West Virginia) with most cases from Pennsylvania (72.9%) (eFigure 2 in Supplement 1). The median (IQR) 1-year mean $PM_{2.5}$ concentration prior to death was 9.4 (8.1-12.4) µg/m^3.

In adjusted models, higher $PM_{2.5}$ exposure was associated with increased odds of more severe AD neuropathology (**Figure 1**; eTable 1 in Supplement 1). Specifically, for every 1 µg/m^3-increase in 1-year mean $PM_{2.5}$ exposure before death, there were 17%, 20%, 20%, and 19% increases in the odds of higher Thal amyloid phase (odds ratio [OR], 1.17; 95% CI, 1.08-1.27; *P* < .001), Braak stage (OR, 1.20; 95% CI, 1.11-1.29; *P* < .001), CERAD score (OR, 1.20; 95% CI, 1.11-1.30; *P* < .001), and overall level of ADNC (OR, 1.19; 95% CI, 1.11-1.28; *P* < .001), respectively. Furthermore, for every 1 µg/m^3-increase in 1-year mean $PM_{2.5}$ exposure, there was a 16% increase in the odds of having large infarcts (OR, 1.16; 95% CI, 1.01-1.32; *P* = .04). In contrast, higher $PM_{2.5}$ was not associated with increased odds of LBD stage (OR, 0.98; 95% CI, 0.91-1.04; *P* = .47), LATE-NC stage (OR, 1.03; 95% CI, 0.96-1.10; *P* = .46), and other cerebrovascular lesions, including occipital lobe cerebral amyloid angiopathy burden (OR, 1.00; 95% CI, 0.93-1.07; *P* > .99), occipital white matter arteriolosclerosis burden (OR, 1.01; 95% CI, 0.92-1.10; *P* = .89), and overall VCING level (OR, 1.08; 95% CI, 0.97-1.19; *P* = .15).

Air Pollution, Neuropathologic Change, and Dementia in the Subset of Autopsy Cases With CDR-SB Scores

To explore the association between $PM_{2.5}$ exposure, neuropathologic change, and clinical dementia severity, the study cohort was restricted to 287 autopsy cases with CDR-SB scores within 5 years of death. The median (IQR) age at death was 79 (72-86) years and 154 were male (53.7%). Overall, this CDR cohort was not different from the full cohort in terms of demographic and neuropathologic characteristics (eTables 2 and 3 in Supplement 1).

Table 3. Fine Particulate Matter Air Pollution ($PM_{2.5}$) Exposure and Clinical Dementia Rating Sum of Boxes (CDR-SB)

Variable[a]	β (95% CI)[b]	*P* value[c]
$PM_{2.5}$	0.48 (0.22 to 0.74)	<.001
Sex, male	−0.72 (−2.13 to 0.68)	.31
Age at CDR	−0.08 (−0.14 to −0.02)	.01
APOE ε4 positive	2.94 (1.57 to 4.31)	<.001
Race, White	−1.71 (−4.53 to 1.10)	.23
Education	−0.31 (−0.54 to −0.08)	.009

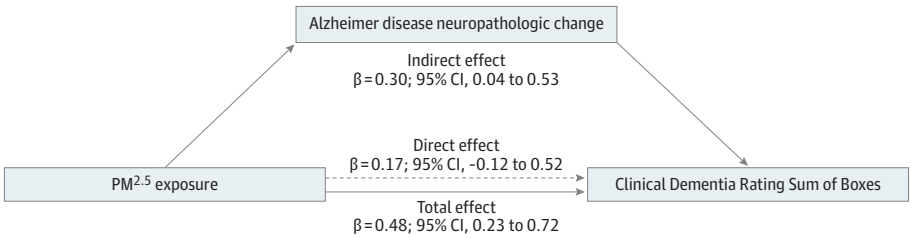
[a] Associations were evaluated by a linear regression model in which the outcome variable was CDR-SB score at last assessment with higher values indicating greater cognitive and functional impairment, the exposure variable was 1-year mean $PM_{2.5}$ exposure before death, and covariates were sex, age at last CDR-SB assessment, *APOE* ε4 allele status, race, and years of education.

[b] Estimated effects (β) and 95% CIs are shown as adjusted CDR-SB score at last assessment per 1-µg/m^3 increase in 1-year mean $PM_{2.5}$ exposure before last CDR-SB assessment, with positive values indicating greater cognitive and functional impairment. The CDR cohort of 287 cases who had their last CDR evaluation within 5 years of death was analyzed.

[c] *P* values less than .05 were considered statistically significant.

In adjusted models, each 1 µg/m^3-increase in 1-year mean $PM_{2.5}$ concentration before last CDR-SB assessment prior to death was associated with a 0.48-point increase in the last CDR-SB score (β = 0.48; 95% CI, 0.22-0.74; *P* < .001; **Table 3**), indicating greater cognitive and functional impairment. Although the requirement for CDR-SB clinical assessment resulted in a smaller cohort, the ORs for AD neuropathologic outcomes were similar to those observed in the full-autopsy cohort

Figure 2. Alzheimer Disease Neuropathologic Change Mediates the Association Between Fine Particulate Matter Air Pollution ($PM_{2.5}$) Exposure and Clinical Dementia Rating Sum of Boxes (CDR-SB)



A path diagram of the structural equation modeling shows associations among $PM_{2.5}$ exposure, Alzheimer disease neuropathologic change (ADNC), and CDR-SB with 1-year mean $PM_{2.5}$ exposure before last Clinical Dementia Rating (CDR) assessment prior to death as the exposure variable, ordinal ADNC level as the potential mediator, and CDR-SB at last assessment prior to death as the outcome variable in the CDR cohort (n = 287) after adjusting for sex, age at CDR, race, years of education, and *APOE* ε4 status as confounding variables. In this model, the indirect effect is the effect of $PM_{2.5}$ exposure on CDR-SB through ADNC and the direct effect is the effect of $PM_{2.5}$ exposure on CDR-SB that is independent from ADNC. β estimates of indirect, direct, and total effects with 95% CIs were calculated with structural equation modeling using a bias-corrected and accelerated bootstrap confidence interval method with 2000 simulations. Positive values indicate greater cognitive and functional impairment. This model exhibited good fit indices as follows: comparative fit index, 0.98; root mean square error of approximation, 0.02; Tucker-Lewis index, >0.99).

with an overall increase in the odds of more severe AD neuropathology (Thal amyloid phase, OR, 1.23; 95% CI, 1.09-1.40; P = .001; Braak stage, OR, 1.25; 95% CI, 1.12-1.41; P < .001; CERAD score, OR, 1.26; 95% CI, 1.13-1.42; P < .001; ADNC level, OR, 1.25; 95% CI, 1.12-1.40; P < .001; eFigure 3 and eTable 4 in Supplement 1).

In an adjusted longitudinal model with 261 cases who had multiple CDR-SB records, every 1 μg/m^3-increase in 1-year mean exposure to $PM_{2.5}$ before each CDR assessment was associated with a 0.07-point increase in annual change of CDR-SB score (β = 0.07; 95% CI, 0.04-0.09; P < .001; eTable 5 in Supplement 1), indicative of faster cognitive and functional decline.

Furthermore, the study team examined whether the adjusted association between higher $PM_{2.5}$ exposure and more severe dementia indicated by higher CDR-SB was mediated by ADNC (**Figure 2**). Using SEM mediation analysis, the estimated total effect of 1-year mean $PM_{2.5}$ concentration before last CDR-SB was 0.48 (β = 0.48; 95% CI, 0.23-0.72) and the estimated indirect effect through increasing the odds of higher ADNC levels was 0.30 (β = 0.30; 95% CI, 0.04-0.53), where 63% of the estimated association between $PM_{2.5}$ exposure and dementia severity was mediated by ADNC.

Diagnostic and assumption tests confirmed both linearity and no spatial autocorrelation for the observed associations in regression models (eTable 6 in Supplement 1) and the SEM model exhibited good model fit indices (Figure 2).

Post Hoc Analyses

Secondary analyses revealed that *APOE* ε4 allele status was not an effect modifier for both neuropathologic (eTables 7 and 9 in Supplement 1) and cognitive outcomes (eTable 8 in Supplement 1). Sensitivity analyses confirmed the robustness of the association between higher $PM_{2.5}$ and worse AD neuropathologic outcomes in the face of uncertainty in predicted $PM_{2.5}$ values (eFigure 4 in Supplement 1). Furthermore, the observed associations remained when applying longer exposure time frames (eFigures 5 and 6 and eTables 10 and 11 in Supplement 1), another well-validated $PM_{2.5}$ prediction model (eTable 12 in Supplement 1), and an additional covariate of median household income as a measure of socioeconomic status (eTables 13 through 17 in Supplement 1).

Discussion

In this relatively large autopsy series, we found that higher $PM_{2.5}$ concentrations were strongly associated with more severe amyloid and tau pathologies, culminating in more advanced overall ADNC. In addition, exposure to higher $PM_{2.5}$ levels was also associated with significantly greater and faster cognitive and functional impairment. These associations were not modified by *APOE* ε4 allele status. Lastly, the impact of $PM_{2.5}$ on dementia severity was largely mediated by an increase in ADNC. This suggests that $PM_{2.5}$ may directly affect brain vulnerability where increased ADNC appears to mediate $PM_{2.5}$-induced cognitive dysfunction.

The association between $PM_{2.5}$ exposure and neurodegenerative pathology is largely unknown. Two prior studies examining the effects of $PM_{2.5}$ on AD pathology have been reported, one of which demonstrated an association between $PM_{2.5}$ exposure and higher CERAD score but no other AD pathology based on a study of an Alzheimer's Disease Research Center autopsy cohort.[24] In contrast, no significant effect of $PM_{2.5}$ exposure and amyloid, tau, or overall ADNC was observed in another study of a community-based autopsy cohort study.[23] In contrast with these previous studies, we observed that $PM_{2.5}$ exposure before death was significantly associated with an overall increased OR for more severe AD neuropathology, including higher Thal amyloid phase, Braak stage, CERAD score, and ADNC level. Inconsistencies between studies may be related to differences in autopsy cohort characteristics and exposure measurements. While the study of the community-based cohort is likely to have more heterogenous causes of cognitive dysfunction,[23] our cohort consisted mainly of symptomatic dementia cases that were enriched for AD dementia, perhaps allowing for more homoge-

neity and, therefore, statistical power to detect AD specific effects. In addition, when compared with the prior study of the research-based autopsy cohort,[16] our study included a relatively large sample size and estimated total $PM_{2.5}$ derived from different emission sources, perhaps enhancing the statistical power to detect associations between $PM_{2.5}$ and neuropathologic outcomes.

Our study builds on prior studies in that cognitive and functional data were included for a subset of individuals to evaluate the impact of $PM_{2.5}$ exposure on dementia severity at death in relation to neuropathologic changes. Considering the temporal ordering between exposure and outcomes variables, when evaluating dementia severity, we applied 1-year mean $PM_{2.5}$ concentrations before last CDR-SB assessment proximate to death. In doing so, our findings are consistent with prior population-based cohort studies, which have demonstrated an association between $PM_{2.5}$ exposure and worse cognitive outcomes.[5,13] Furthermore, the association of $PM_{2.5}$ exposure with AD pathology, but not other pathologies, suggests that there may be some specificity with regards to the effects of $PM_{2.5}$ exposure on central nervous system pathology. This is consistent with antemortem human studies, which tend to show that $PM_{2.5}$ exposure is associated with increased AD biomarkers, including structural magnetic resonance imaging changes, cerebrospinal fluid measures,[16] and amyloid positron emission tomography outcomes.[18,34-36] Notably, we found that the association between $PM_{2.5}$ exposure and cognitive and functional dysfunction was largely mediated by increased ADNC. This supports the hypothesis that $PM_{2.5}$ exposure is deleterious for brain maintenance pathways, resulting in worsening of ADNC.[37,38]

Strengths and Limitations

One strength of this study is the comprehensive study of a large autopsy series with well-defined demographical, clinical, and neuropathological profiles based on consensus criteria. Furthermore, we demonstrated the robustness of our findings with several sensitivity analyses accounting for $PM_{2.5}$ exposure uncertainty estimates, different exposure time frames, and area-level socioeconomic status.

Despite these strengths, we note the following limitations. First, our clinical research-oriented autopsy cohort is skewed demographically. Indeed, the vast majority of participants were White, non-Hispanic or Latino, highly educated with a higher than a college degree, and/or from less disadvantaged neighborhoods. This biased, unrepresentative sample may limit the generalizability of our findings. Moreover, compared with a population-based study cohort where a diverse spectrum of cognitive and neuropathologic conditions are found,[39] our autopsy cohort included a large proportion of cases through research programs that were enriched for AD dementia and that did not enroll individuals with vascular dementia, which may induce selection bias. Due to the rarity of cerebrovascular pathology in our cohort, we likely underestimated the true associations between $PM_{2.5}$ and cerebrovascular disease, which have been strongly supported by epidemiologic studies.[40,41] Moreover, our study included a small number of cases when compared with most epidemiologic studies, precluding a more robust examination of relationships among variables with strong statistical power. Thus, studies of large population-based autopsy cohorts are required to extrapolate these findings to the general population.

Second, we excluded many cases with missing values due to incomplete assessment. While overall characteristics did not differ between the full vs CDR cohorts, there was a small difference in the mean age at death for those excluded from this study. However, the mean difference of only 1 or 2 years is unlikely to be clinically or biologically meaningful. In addition, $PM_{2.5}$ exposure is associated with increased mortality, and so there is a potential for survivorship bias in this study. Methods, such as inverse probability weighting, may be considered to correct for selection bias, such as the impact of conditioning on death and consent to autopsy.

Third, $PM_{2.5}$ was measured only at each case's last residential address. Moving to a new address was not common in our cohort, with less than 1% of individuals changing their address within the last year of life. However, longitudinal $PM_{2.5}$ exposure values including the use of more accurate $PM_{2.5}$ self-monitors would add more precision to future studies.

Lastly, we have not comprehensively evaluated other potential confounding factors, such as physical and leisure activity, smoking and alcohol history, medical treatment history, neighborhood greenness, differences between urban and rural exposures (as this cohort was 100% urban), and other air pollutants, such as nitrogen dioxide or ozone that may affect downstream neuropathologic change and cognition. Furthermore, due to the nature of an observational cohort study, we were not able to uncover the mechanisms underlying our findings, which may require experimental and/or interventional studies to uncover. Considering these limitations, replication in large population-based cohorts and mechanistic studies are warranted.

Conclusions

This autopsy cohort study reinforces the finding that $PM_{2.5}$ exposure appears to negatively affect cognitive function and suggests that this association may be mediated by ADNC. Our findings suggest that $PM_{2.5}$ exposure may exacerbate AD pathogenesis. Population-based autopsy studies are further needed to replicate our findings and better understand relationships among $PM_{2.5}$ exposure, cognition, and neuropathology.

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