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Long-Term Exposure to PM10 and *in vivo* Alzheimer's Disease Pathologies

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Abstract.
Background: Previous studies indicated an association between Alzheimer's disease (AD) dementia and air particulate matter (PM) with aerodynamic diameter <10 μm (PM10), as well as smaller PM. Limited information, however, is available for the neuropathological links underlying such association.
Objective: This study aimed to investigate the relationship between long-term PM10 exposure and *in vivo* pathologies of AD using multimodal neuroimaging.
Methods: The study population consisted of 309 older adults without dementia (191 cognitively normal and 118 mild cognitive impairment individuals), who lived in Republic of Korea. Participants underwent comprehensive clinical assessments, ^{11}C-Pittsburg compound B (PiB) positron emission tomography (PET), and magnetic resonance imaging scans. A subset of 78 participants also underwent ^{18}F-AV-1451 tau PET evaluation. The mean concentration of PM with aerodynamic diameter <10 μm over the past 5 years ($PM10_{mean}$) collected from air pollution surveillance stations were matched to each participant's residence.
Results: In this non-demented study population, of which 62% were cognitively normal and 38% were in mild cognitive impairment state, exposure to the highest tertile of $PM10_{mean}$ was associated with increased risk of amyloid-β (Aβ) positivity (odds ratio 2.19, 95% confidence interval 1.13 to 4.26) even after controlling all potential confounders. In contrast, there was no significant associations between $PM10_{mean}$ exposure and tau accumulation. AD signature cortical thickness and white matter hyperintensity volume were also not associated with $PM10_{mean}$ exposure.
Conclusion: The findings suggest that long-term exposure to PM10 may contribute to pathological Aβ deposition.

Keywords: Amyloid-β, cognitively normal, mild cognitive impairment, neurodegeneration, PM10, tau

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INTRODUCTION

There is a great deal of evidence that air particulate matter (PM) is associated with adverse health effects, thereby exerting various negative impacts on public health [1–4]. Accumulating evidence also suggests that PM may be neurotoxic and have an adverse effect on the central nervous system (CNS) [5, 6].

PM can be categorized based on the aerodynamic diameter size: 1) less than 10 μm (PM10), 2) less than 2.5 μm (PM2.5), or 3) less than 0.1 μm (PM0.1) [4]. In regard of the influence of PM on Alzheimer's disease (AD), many human studies demonstrated that PM2.5 was associated with increased risk of AD dementia or cognitive impairment [7–19]. Although not frequently studied compared to PM2.5, PM10 was also reported to be related with AD dementia [20] and amnestic type mild cognitive impairment (MCI), a high-risk state of AD dementia [19].

PM can affect CNS through both direct and indirect pathways [6, 21]. PM2.5 or smaller particles may directly transmit through the olfactory bulb or through the systemic circulation into the brain and trigger CNS damage *via* direct pathway [22–24]. In contrast, nasal epithelial transmission or mechanical inhalation of PM10, as well as PM2.5, may produce systemic inflammation and the released inflammatory cytokines may damage the CNS through indirect pathway [25–28]. Therefore, all size fractions of PM should be considered as possible neurotoxins or risk factors for AD-related brain changes or cognitive decline [19, 29].

In regard of neuropathological links underlying the association between PM and AD, a postmortem brain study demonstrated that individuals living in severely polluted areas were more likely to have neuroinflammation and amyloid-β 42 ($A\beta_{42}$) accumulation in brain compared to those living in control areas [30]. Preclinical studies using animal models [7, 31–33] also showed that exposure to PM2.5 induced AD-related brain pathologies. However, little information is available regarding the influence of chronic PM10 exposure on AD-related neuropathological changes.

In this context, we investigated the associations of long-term exposure to PM10 with cerebral Aβ and tau deposition on positron emission tomography (PET) as well as AD-type regional neurodegeneration and white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) in non-demented older adults.

MATERIALS AND METHODS

Study population

The study population consisted of 309 older adults without dementia [191 cognitively normal (CN) subjects and 118 with MCI] who were recruited from the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), an ongoing prospective cohort study that began in 2014 [34].

Participants were 65 years old or older, and were recruited between April 2014 and November 2016. The data from the baseline visit were utilized in this study. The inclusion criteria for the CN group were: 1) age between 65 and 90 years (inclusive); 2) no diagnosis of MCI or dementia; and 3) global Clinical Dementia Rating (CDR) score of 0 [35]. Inclusion criteria for participants with MCI were as follows: 1) memory complaints confirmed by a reliable informant; 2) objective memory impairments; 3) preserved global cognition; 4) independence in functional activities; and 5) no diagnosis of dementia. With regard to criterion (2), the age-, education-, and sex-adjusted z-scores for at least one of four episodic memory tests were <–1.0. The four memory tests were the Word List Memory, Word List Recall, Word List Recognition, and Constructional Recall tests, which are included in the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) neuropsychological battery [36]. All MCI participants had a CDR score of 0.5. The exclusion criteria were as follows: 1) presence of a major psychiatric illness, including alcohol-related disorders; 2) significant neurological or medical conditions or comorbidities that could affect mental function; 3) contraindications for MRI (e.g., pacemaker or claustrophobia); 4) illiteracy; 5) the presence of significant visual/hearing difficulties and/or severe communication or behavioral problems that would make clinical examinations or brain scans difficult; 6) taking an investigational drug; and 7) pregnant or breastfeeding. Additional information regarding the recruitment procedure of the KBASE cohort was presented previously [34]. The study protocol was approved by the Institutional Review Boards of Seoul National University Hospital and SNU-SMG Boramae Center (Seoul, Republic of Korea) and conducted in accordance with the recommendations of the current version of the Declaration of Helsinki. All study participants and/or their caregivers provided written informed consent.

Clinical, neuropsychological, and laboratory assessments

All participants underwent comprehensive clinical and neuropsychological assessments according to a standardized clinical assessment protocol incorporating the CERAD-K clinical assessment [37]. The protocol included various assessment tools for evaluation of clinical diagnosis, severity, activities of daily living, depression status, current or past medical comorbidities, use of medications, smoking status, socioeconomic status (SES), and a large amount of information on lifestyle factors. To acquire accurate information, reliable informants were interviewed and medical records were reviewed. KBASE neuropsychological assessments were performed according to the standardized protocol, which incorporated the CERAD-K neuropsychological battery [36]. The participants also underwent laboratory assessments including apolipoprotein E (*APOE*) genotyping.

Air particulate matter exposure

The exposure variable of this study was the mean concentration of PM with aerodynamic diameter <10 μm (PM10) over the past 5 years from the baseline assessment ($PM10_{mean}$). During the study period, the raw PM10 concentration data were measured continuously from 276 air pollution monitoring stations distributed across Republic of Korea using the β-ray absorption method on an hourly basis (24 times a day and 7 days a week). From the raw data, the annual mean for each station was calculated by the Statistics Division of the Korean Ministry of Environment, and were distributed publicly through the Air Korea website (http://www.airkorea.or.kr). Individual participants were matched with their nearest station according to their residential address. To protect the privacy of the participants, only the streets, not building numbers or house numbers of the participants' addresses, were collected. For this reason, the midpoint of each residential street was matched with the nearest monitoring station, and the distance between the two points were also measured. Three participants who lived more than 10 kilometers (km) away from the nearest monitoring station were excluded from the study (the distances were 22.9, 38.9, and 40.2 km). The usage of the residential address was separately reviewed and approved by the Institutional Review Board of Seoul National University Hospital (Seoul, Republic of Korea). The $PM10_{mean}$ was calculated for each participant from the annual mean values. Finally, referring to previous reports that suggested non-linear relationship between PM exposure and CNS toxicity [20, 38], $PM10_{mean}$ was stratified into the three tertile groups: the lowest tertile (34.8 to 44.8 $\mu g/m^3$), the medium tertile (45.0 to 47.8 $\mu g/m^3$), and the highest tertile (48.0 to 67.0 $\mu g/m^3$) groups. The tertile groups of $PM10_{mean}$ were used as a final exposure variable.

Neuroimaging measures

All subjects ($n = 309$) underwent simultaneous three-dimensional ^{11}C Pittsburg compound B (PiB)-PET and T1-weighted MRI using a 3.0T Biograph mMR (PET-MR) scanner (Siemens) and a subset of subjects ($n = 78$) underwent ^{18}F-AV-1451 PET scans (Siemens) using a Biograph True point 40 PET/CT scanner (Siemens) according to the manufacturer's guidelines. While ^{11}C PiB-PET and brain MRI were performed during the baseline visit, ^{18}F-AV-1451 PET imaging was performed after an average of 2.6 (standard deviation 0.3) years from the baseline visit. The details of ^{11}C PiB-PET, ^{18}F-AV-1451 PET, and MRI acquisition and preprocessing are reported elsewhere [34, 39].

To estimate the cerebral Aβ burden, a global cortical region of interest (ROI) consisting of the frontal, lateral parietal, posterior cingulate-precuneus, and lateral temporal regions was defined to characterize the global PiB retention level. A global PiB retention value, i.e., the standardized uptake value ratio (SUVR), was calculated by dividing the mean value for all voxels within the ROI by the mean cerebellar uptake value in the same image [40]. Each participant was classified as Aβ-positive if the global SUVR value was >1.21 [41]. Considering the bimodal distribution of our PiB data, only Aβ positivity was used as an outcome variable.

To estimate cerebral tau burden, we created ^{18}F-AV-1451 PET SUVR images normalized by the mean inferior cerebellar gray matter uptake, and defined an *a priori* ROI of AD signature regions of tau accumulation, which is a size-weighted average of partial volume-corrected uptake in entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal ROIs, based on a previous report [42]. AV-1541 SUVR of the abovementioned ROI was used as an outcome variable.

To measure the AD-specific regional neurodegeneration, the AD-signature cortical thickness (AD-CT) was calculated for each participant. AD-CT (cm) was defined as the mean cortical thickness value of AD-signature regions, including the middle temporal,

entorhinal, inferior temporal, and fusiform gyrus, as described previously [43].

To determine the volume (cm^3) of WMH, we utilized the previously reported validated automatic procedure [44], with two modifications. An optimal threshold of 70 was applied, compared to the threshold of 65 used in the original paper, as it was more suitable for our data. As a preparative preliminary analysis of the data, randomly selected 20% of the total scans were processed using various thresholds (e.g., 60, 65, 70, and 75). The derived/processed WMH mask images were overlaid on the junction map [44], and the boundaries of the WMH were visually reviewed by an experienced image analyst (DY). Comparisons between the WMH masks using four different thresholds were performed visually, in addition to reviewing of the extracted voxels intensity histograms. The threshold of 70 yielded the best mask that most closely aligned with the boundaries. The mask from the threshold of 65, which was used in the original paper, often included the voxels close to the boundaries but that are not clearly identified as WMH. This may be due to the differences of the scanner properties or the reconstruction protocol. In addition, we did not use diffusion-weighted imaging in the current automated procedure because individuals with acute cerebral infarction were not enrolled in our study. Using the final WMH candidate images, WMH volumes were extracted based on lobar ROIs in the native space of each subject [45].

Statistical analysis

One-way analysis of variance and linear-by-linear association were used to compare variables among tertile groups of $PM10_{mean}$. To test the associations between tertile groups of $PM10_{mean}$ and neuroimaging parameters, multivariate linear or logistic regression analyses were performed as appropriate. Three models were defined. The first model did not include any covariates, the second model included age and sex as covariates, and the third model included all potential covariates, including age, sex, education level, annual income, vascular risk score, smoking status, *APOE* ε4 positivity, and cognitive status, i.e., CN or MCI. Education level was the total number of years of formal education, and annual income was categorized into three groups: below the minimum cost of living (MCL), above the MCL but below twice the MCL, more than twice the MCL. The MCL was determined according to the administrative rules published by the Ministry of Health and Welfare, Republic of Korea, in November 2012. The MCL was 572,168 Korean Won for a single-person household, with addition of 286,840 Korean Won for each additional housemate. Smoking status was categorized into three groups: current smoker, former smoker, never smoked.

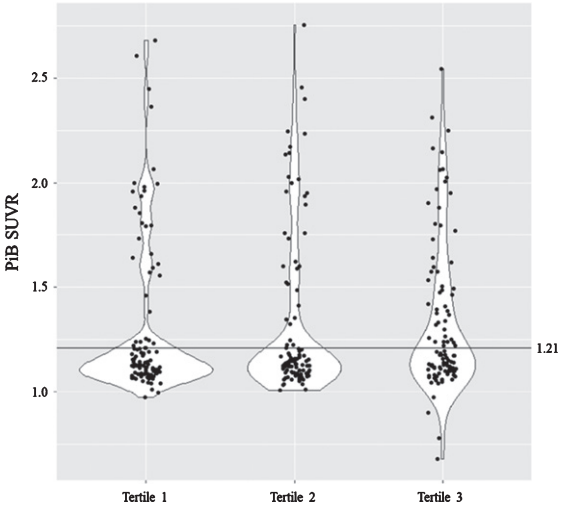

Fig. 1. Violin plots displaying individual distributions of global PiB SUVR among $PM10_{mean}$ tertile groups and the thresholds for amyloid-β positivity PiB, Pittsburgh Compound B; SUVR, standardized uptake value ratio; $PM10_{mean}$, 5-year mean concentration of particulate matter with aerodynamic diameter <10 μm.

To additionally investigate whether there were any interactions between tertile groups of $PM10_{mean}$ and *APOE* ε4 positivity on neuroimaging parameters referring to the previous epidemiological studies [16], we added an interaction term, i.e., tertile groups of $PM10_{mean} \times$*APOE* ε4 positivity, in the regression models. For sensitivity analyses, the associations of quartiled $PM10_{mean}$ with imaging parameters were tested with identical statistical methods. Interaction and sensitivity analyses were performed only for statistically significant associations. All statistical analyses were performed using IBM SPSS Statistics 24 (IBM Corp., Armonk, N.Y., USA), and the drawing of violin plot in Fig. 1 was done using R 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Subject characteristics

Table 1 shows the clinical and demographic characteristics of the participants by tertile groups of $PM10_{mean}$. There were no significant differences

Table 1
Characteristics of participants by $PM10_{mean}$ tertile groups

Variables	Tertile 1	Tertile 2	Tertile 3	χ^2 or F	p
n	104	102	103		
$PM10_{mean}$ ($\mu g/m^3$)	34.8 to 44.8	45.0 to 47.8	48.0 to 67.0		
Age	75.2 ± 6.0	73.6 ± 5.4	74.1 ± 4.8	2.22	0.111
Sex, female (%)	50 (48.1)	69 (67.6)	58 (56.3)	1.45	0.229
Years of education	10.6 ± 5.1	10.2 ± 4.7	11.3 ± 4.9	1.12	0.329
Annual income				2.63	0.105
<MCL	13 (12.5)	6 (5.9)	13 (12.6)		
≥MCL, <2 × MCL	53 (51.0)	50 (49.0)	37 (35.9)		
≥2 × MCL	38 (36.5)	46 (45.1)	53 (51.5)		
Smoking status				0.57	0.451
Never	69 (66.4)	82 (80.4)	70 (68.0)		
Past smoker	30 (28.8)	17 (16.7)	32 (31.1)		
Current smoker	5 (4.8)	3 (2.9)	1 (1.0)		
Vascular risk score	20.7 ± 17.3	19.1 ± 17.1	20.1 ± 15.2	0.23	0.795
Diagnosis, MCI (%)	38 (36.5)	45 (44.1)	35 (34.0)	0.14	0.708
CDR-SB	0.54 ± 0.81	0.61 ± 0.75	0.52 ± 0.84	0.32	0.727
MMSE	25.1 ± 3.5	24.6 ± 3.3	25.3 ± 3.2	1.11	0.332
APOE ε4 positive, *n* (%)	23 (22.1)	24 (23.5)	30 (29.1)	1.35	0.245
Distance from monitoring station (km)	2.02 ± 1.73	1.93 ± 1.09	2.36 ± 2.05	1.19	0.153
PiB positive, *n* (%)	31 (29.8)	33 (32.4)	47 (45.6)	5.60	0.018
PiB SUVR	1.31 ± 0.37	1.33 ± 0.39	1.33 ± 0.36	0.15	0.858
AV-1451 SUVR[a]	1.67 ± 0.76	1.52 ± 0.44	1.52 ± 0.67	0.45	0.641
AD-CT (cm)	2.74 ± 0.24	2.77 ± 0.22	2.77 ± 0.18	0.82	0.442
WMH volume (cm^3)	6.42 ± 5.20	6.46 ± 5.36	6.14 ± 5.29	0.10	0.906

Data for continuous variables are presented as means ± standard deviation and were analyzed by one-way ANOVA with F values presented in the table. Categorical variables are presented as n (%) and were analyzed by linear-by-linear association test with χ^2 values presented in the table. [a]Number of subjects = 78 (Tertile 1, 26; Tertile 2, 20; Tertile 3, 32), performed after an average of 2.6 (standard deviation 0.3) years from the baseline visit. $PM10_{mean}$, 5-year mean concentration of particulate matter with aerodynamic diameter <10 μm; MCL, minimum cost of living; MCI, mild cognitive impairment; CDR-SB, Clinical Dementia Rating sum of box score; MMSE, Mini-Mental State Examination; *APOE*, apolipoprotein E; PiB, Pittsburgh Compound B; SUVR, standardized uptake value ratio; AD-CT, Alzheimer's disease signature cortical thickness; WMH, white matter hyperintensity.

in demographic or clinical variables among tertile groups of $PM10_{mean}$. Also, there were no statistically significant differences between participants who underwent ^{18}F-AV-1451 PET and those who did not in terms of demographic or clinical variables.

Air particulate matter concentration and neuroimaging parameters

Linear-by-linear association test showed that the rate of Aβ positivity was significantly higher in the highest tertile group of $PM10_{mean}$ (45.6%) than in the lowest (29.8%) and medium (32.4%) tertile groups, while one-way analysis of variance showed that global PiB retention was not different among tertile groups of $PM10_{mean}$ (Table 1 and Fig. 1). Multivariate logistic regression analyses also revealed that Aβ positivity was significantly associated with tertile groups of $PM10_{mean}$ in all three models (Table 2 and Fig. 2). Regardless of covariates, the highest tertile of $PM10_{mean}$ exposure was associated with increased risk of Aβ positivity compared to the lowest tertile (reference). On the other hand, both analyses of variance and multiple linear regression analyses demonstrated that tertile groups of $PM10_{mean}$ were not associated with cerebral tau deposition, AD-CT, and WMH volume (Tables 1 and 2).

Interaction and sensitivity analyses

There were no interactions between tertile groups of $PM10_{mean}$ and *APOE* ε4 positivity on Aβ positivity (Table 3).

Sensitivity analysis using quartile groups of $PM10_{mean}$ yielded similar results for the association between $PM10_{mean}$ and Aβ positivity. Regardless of covariates, the highest quartile of $PM10_{mean}$ exposure was associated with increased risk of Aβ positivity (Table 4).

DISCUSSION

To summarize the results of this study, long-term exposure to the highest tertile of PM10 was associated with increased risk of Aβ positivity in older adults

Table 2
Associations of $PM10_{mean}$ tertile groups with neuroimaging parameters

Model	Tertile 1	Tertile 2	Tertile 3
PiB positivity			
Model 1	Reference	OR = 1.13 (0.62 to 2.03) $p = 0.693$	OR = 1.98 (1.12 to 3.50) $p = 0.020$
Model 2	Reference	OR = 1.18 (0.64 to 2.15) $p = 0.596$	OR = 2.05 (1.15 to 3.66) $p = 0.015$
Model 3	Reference	OR = 1.05 (0.53 to 2.05) $p = 0.899$	OR = 2.19 (1.13 to 4.26) $p = 0.020$
AV-1451 SUVR[a]			
Model 1	Reference	B = –0.151 (–0.539 to 0.237) $p = 0.440$	B = –0.147 (–0.492 to 0.197) $p = 0.397$
Model 2	Reference	B = –0.142 (–0.541 to 0.257) $p = 0.481$	B = –0.143 (–0.493 to 0.207) $p = 0.418$
Model 3	Reference	B = –0.153 (–0.516 to 0.209) $p = 0.402$	B = –0.134 (–0.448 to 0.181) $p = 0.400$
AD-CT (cm)			
Model 1	Reference	B = 0.033 (–0.027 to 0.092) $p = 0.281$	B = 0.034 (–0.025 to 0.094) $p = 0.258$
Model 2	Reference	B = 0.003 (–0.052 to 0.057) $p = 0.924$	B = 0.017 (–0.037 to 0.071) $p = 0.542$
Model 3	Reference	B = 0.008 (–0.043 to 0.059) $p = 0.753$	B = 0.023 (–0.028 to 0.075) $p = 0.375$
WMH volume (cm^3)			
Model 1	Reference	B = 0.041 (–1.508 to 1.591) $p = 0.958$	B = –0.279 (–1.802 to 1.245) $p = 0.719$
Model 2	Reference	B = 0.623 (–0.861 to 2.106) $p = 0.409$	B = –0.053 (–1.390 to 1.496) $p = 0.942$
Model 3	Reference	B = 0.491 (–1.023 to 2.006) $p = 0.523$	B = 0.082 (–1.393 to 1.557) $p = 0.913$

The results of multivariate logistic or linear regression analyses are presented with OR or B coefficient values, 95% CI, and *p*-values. Model 1 did not include any covariates, model 2 included age and sex as covariates, and model 3 included all potential covariates, including age, sex, education level, annual income, vascular risk score, smoking status, *APOE* ε4 positivity, and cognitive status. [a]Number of subjects = 78 (Tertile 1, 26; Tertile 2, 20; Tertile 3, 32), performed after an average of 2.6 (standard deviation 0.3) years from the baseline visit. $PM10_{mean}$, 5-year mean concentration of particulate matter with aerodynamic diameter <10 μm; OR, odds ratio; SUVR, standardized uptake value ratio; AD-CT, Alzheimer's disease signature cortical thickness; WMH, white matter hyperintensity; CI, confidence interval; *APOE*, apolipoprotein E.

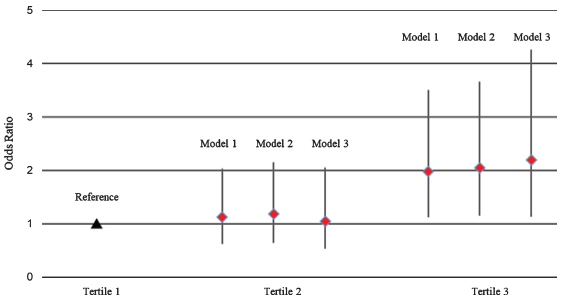

Fig. 2. Associations of $PM10_{mean}$ tertile groups with amyloid-β positivity. The results of multivariate logistic regression are depicted with OR values and 95% CI. Model 1 did not include any covariates, model 2 included age and sex as covariates, and model 3 included all potential covariates, including age, sex, education level, annual income, vascular risk score, smoking status, *APOE* ε4 positivity, and cognitive status. $PM10_{mean}$, 5-year mean concentration of particulate matter with aerodynamic diameter <10 μm; OR, odds ratio; CI, confidence interval; *APOE*, apolipoprotein E.

without dementia. However, there was no significant association between PM10 exposure and tau accumulation. Also, AD-type regional neurodegeneration, or white matter changes were not associated with PM10. To the best of our knowledge, this is the first study to investigate the association between chronic PM10 exposure and *in vivo* cerebral Aβ and tau deposition in humans.

Several previous studies suggested a possible association between PM10 and AD. An epidemiological study conducted in Taiwan indicated that long-term exposure to PM10 was associated with higher prevalence of AD dementia [20]. Similarly, another epidemiological study performed in Germany reported significant association between PM10 exposure and prevalence of amnestic type MCI, a high-risk state of AD dementia [19]. The specific association between chronic PM10 exposure and Aβ

Table 3
Interaction analysis of tertile groups of $PM10_{mean}$ and *APOE* ε4 positivity on Aβ positivity

	OR (95% CI)	Wald	*p*
Tertile 1	Reference		
Tertile 2	1.03 (0.46 to 2.31)	0.01	0.937
Tertile 3	2.36 (1.08 to 5.16)	4.68	0.031
APOE ε4 positivity	4.76 (1.60 to 14.18)	7.83	0.005
Tertile 1 × *APOE* ε4 positivity	Reference		
Tertile 2 × *APOE* ε4 positivity	1.04 (0.24 to 4.57)	<0.01	0.960
Tertile 3 × *APOE* ε4 positivity	0.76 (0.18 to 3.32)	0.13	0.764

The results of multivariate logistic regression analyses including interaction terms are presented with OR, 95% CI, Wald, and *p*-values. As for the covariates, all potential covariates, including age, sex, education level, annual income, vascular risk score, smoking status, *APOE* ε4 positivity, and cognitive status were adjusted as appropriate. $PM10_{mean}$, 5 year mean of concentration of particulate matter with aerodynamic diameter of <10 μm; *APOE*, apolipoprotein E; OR, odds ratio; CI, confidence interval.

Table 4
Results of sensitivity analyses showing the association of quartile groups of $PM10_{mean}$ with amyloid-β positivity

Model	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Model 1	Reference	OR 1.46 (0.74 to 2.88) $p = 0.276$	OR 1.23 (0.62 to 2.44) $p = 0.562$	OR 2.05 (1.06 to 3.97) $p = 0.034$
Model 2	Reference	OR 1.52 (0.76 to 3.02) $p = 0.234$	OR 1.35 (0.66 to 2.73) $p = 0.411$	OR 2.15 (1.10 to 4.19) $p = 0.025$
Model 3	Reference	OR 1.81 (0.83 to 3.97) $p = 0.137$	OR 1.32 (0.60 to 2.90) $p = 0.486$	OR 2.60 (1.20 to 5.66) $p = 0.016$

The results of multivariate logistic regression analyses are presented with OR values, 95% CI and *p*-values. As for the covariates, model 1 did not include any covariates. Model 2 included age and sex, and model 3 included all potential covariates, including age, sex, education level, annual income, vascular risk score, smoking status, *APOE* ε4 positivity, and cognitive status. $PM10_{mean}$, 5-year mean of concentration of particulate matter with aerodynamic diameter of <10 μm; OR, odds ratio; CI, confidence interval; *APOE*, apolipoprotein E.

positivity observed in the present study was consistent with these previous reports and presented the first evidence for a pathological link between chronic PM10 exposure and AD.

The results of this study indicated a nonlinear dose–response relationship between PM10 exposure and pathological Aβ deposition. The risk of Aβ positivity was increased only in the highest tertile (>48.0 $\mu g/m^3$) group, but not in the medium tertile group. Similar results were reported in an epidemiological study performed in Taiwan. Wu et al. reported increased risk of AD dementia only in the highest tertile (PM10 > 49.2 $\mu g/m^3$) group (odds ratio (OR) 4.17, 95% confidence interval (CI) 2.31 to 7.54), but not in the medium tertile group (OR 1.68, 95% CI 0.94 to 3.00) [20]. The thresholds for increased risk were similar between the two studies. This nonlinear dose–response relationship between PM10 and brain health has also been suggested by mortality studies. Daniels et al. reported that although cardiovascular and respiratory deaths were linearly associated with PM10 without a threshold, deaths due to other causes, including CNS diseases, were more fitted to a threshold model [38]. The results of the present study suggested a threshold level of PM10, i.e., 48.0 $\mu g/m^3$, below which the concentration should be maintained to prevent the accumulation of pathological cerebral Aβ and, eventually, to minimize the PM10-related risks for AD dementia. Several studies performed in countries where PM10 concentration is relatively well regulated indicated a linear association between PM10 concentration and cognition [18, 29]. The relationship between PM10 and cognition or brain change may be linear in the range of PM10 concentration below the threshold.

Despite the significant association between $PM10_{mean}$ tertile group and Aβ positivity, there was no association between $PM10_{mean}$ tertile group and global PiB SUVR in this study. This discrepancy may be explained by the characteristic bimodal distribution of cerebral Aβ retention values, especially in the cognitively healthy population [46]. Figure 1 demonstrates such bimodal distribution of global PiB SUVR values for each PM10 tertile group and the threshold for cerebral Aβ positivity, and the discrepancy can be better explained by the figure. Given the characteristics of the bimodal distribution, logistic regression analyses with dichotomous variables for

Aβ positivity may be more suitable for elucidating the relationship between PM10 tertile group and cerebral Aβ pathology.

Although a previous study reported on the moderation effects of *APOE* ε4 positivity on the association between PM10 and cognitive function [16], the current results from the interaction analysis indicated that *APOE* ε4 positivity did not moderate the association between PM10 and cerebral Aβ deposition. This difference may be related to the study participants' stages of AD progression; while Aβ deposition begins at the earliest stage of AD development, cognitive decline manifests at the later stage of the disease progression. *APOE* ε4 may moderate the influence of PM10 on the clinical manifestations of cognitive impairment but not the effect of earlier Aβ deposition.

In contrast to Aβ deposition, tau burden was not associated with PM10 tertile groups, which may be explained by the time course of the pathogenesis of AD. While Aβ deposition is initiated at least a decade before the symptom onset and almost saturate before the symptoms manifest [47–49], tau deposition occurs just before or close to manifestation of cognitive declines [50–52] and the early tau deposition is located only in the very restricted regions with small amount [53]. Given that only non-demented (50 CN and 28 MCI) individuals were included in the current analysis on tauopathy and the limited sensitivity and off-target bindings of currently used tau PET modality [54, 55], the degree or variation of tau deposition may be subtle to yield significant association with PM10.

Unlike a previous neuroimaging study using brain MRI showed that PM10 exposure is associated with neurodegeneration changes [56], the results showed that the AD-CT and WMH volume were not associated with PM10 tertile groups. There are several possible reasons for this discrepancy. First, the discrepancy may be explained by differences in PM10 level between the study settings; the study by Power and colleagues indicated a significant association in a setting where the PM10 concentration was 16–31 $\mu g/m^3$ [56], which was far below that of the present study, i.e., 34–67 $\mu g/m^3$. PM10 exposure may have a dose–response relationship with brain atrophy or white matter vascular changes below a certain level, but have a ceiling effect above this level. All or most of our subjects may have been exposed to PM10 levels above this level and, therefore, did not show any apparent correlation between PM10 increase and brain changes on MRI. Second, another possible explanation for the discrepancy may be related to the proportion of smokers in the study population; the proportion of participants who were never smokers was much higher in the present study (70%) compared to the previous study (52%). As smoking is another source of PM10 [57], and is a well-known risk factor for AD [58, 59], it is reasonable to speculate that smoking and PM10 may have harmful effects on brain health in an additive or synergistic manner. Therefore, the higher proportions of smokers in previous studies may have synergistically exacerbated the neurotoxic effect of PM10 on brain MRI measures. Additional interaction analysis, however, showed that there was no moderation effect of smoking status (never smoker versus past or current smoker) on the association between PM10 and brain MRI measures (Supplementary Table 1). Third, subjects with a history of severe cardiovascular or cerebrovascular disease or with cerebral infarcts and hemorrhages detected on brain MRI were excluded from the present study [34]. As PM10 is a well-known risk factor for both cardiovascular and cerebrovascular diseases [60–63], the exclusion of such subjects with severe cardiovascular or cerebrovascular disease may have weakened the association between PM10 and WMH. Finally, our study targeted only ROIs showing AD-specific neurodegeneration, while previous studies used various ROIs including regions unrelated to AD. Similar to our findings, some previous studies focusing on AD-specific regions, such as hippocampal volume [56] and AD-signature region volume [56], did not find significant associations between PM10 and atrophy. However, additional explorative analyses did not show any association between PM10 with brain volumetric measures used in the previous study, i.e., deep gray volume [56] (Supplementary Table 2), suggesting that the other possibilities mentioned above should also be considered.

This study had several limitations. First, individuals with serious medical or psychiatric comorbidities were excluded from our cohort. Therefore, caution is required regarding generalizability of the results. Physically or mentally ill patients may be more vulnerable to the influence of PM or air pollution. Second, as the data on PM2.5 for the study participants were only available after 2015, we could not incorporate these data in our analyses. However, as PM2.5 is a subset of PM10 and annual mean PM2.5/PM10 ratio was reported to be steady in various studies [15, 64–69], PM10 used in this study may also reflect the variations of PM2.5. The PM2.5/PM10 ratio in Republic of Korea was reported

to be around 0.45–0.55 [65, 66]. Nevertheless, future studies incorporating PM2.5 data would be helpful to gain better understanding for the effects of PM on AD-related brain pathology. In addition, other types of air pollutants, such as ozone, nitrogen or sulfur compounds, which could covary with the PM concentration and thereby confound the association between PM and brain pathologies, also need to be considered in future analyses. Third, as information on residential address was gathered once, at the baseline visit, there may have been misclassifications of the PM10 exposure level. However, the results of the Korea Housing Survey 2017 (http://stat.molit.go.kr) from the Ministry of Land, Infrastructure and Transport, Republic of Korea, showed that older Korean adults live in one place for an average of 15.5 years. This would reduce concerns regarding the proportion of misclassification during the 5-year study period. Fourth, exposure for 5 years may not be long enough to reveal the association between PM10 and brain health. Recent studies focusing on lifelong exposure or younger populations suggested that the adverse effects of PM may begin at an earlier stage of life than expected [53, 70–72]. In addition, occupational hazards and environmental disasters before late-life can also expose PM to individuals. Therefore, further studies including longer and earlier periods of exposure are still needed. Finally, as the tau burden was measured after an average of 2.6 years from the baseline visit, there was a temporal gap between PM10 exposure and the measurement of tau. However, the neuropsychological profiles at baseline assessment were similar to those nearest Tau PET acquisition (Supplementary Table 3). As tau burden is closely correlated with cognitive function [73, 74], tau burden at baseline was likely to be similar to that actually measured by tau PET.

The findings suggest that long-term exposure to PM10 may contribute to pathological Aβ deposition. The results also provided additional scientific evidence to prompt global and regional health authorities or governments to intensify their efforts, to reduce the adverse effects of PM on brain health and dementia.

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SUPPLEMENTARY MATERIAL

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