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Association between air pollution and CSF sTREM2 in cognitively normal older adults: The CABLE study

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Abstract

Objectives: Ambient air pollution aggravates the process of Alzheimer's disease (AD) pathology. Currently, the exact inflammatory mechanisms underlying these links from clinical research remain largely unclear. **Methods**: This study included 1,131 cognitively intact individuals from the Chinese Alzheimer's Biomarker and LifestylE database with data provided on cerebrospinal fluid (CSF) AD biomarkers (amyloid beta-peptide 42 [Aβ42], total tau [t-tau], and phosphorylated tau [p-tau]), neuroinflammatory (CSF sTREM2), and systemic inflammatory markers (high sensitivity C-reactive protein and peripheral immune cells). The 2-year averaged levels of ambient fine particulate matter with diameter <2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) were estimated at each participant's residence. Multiple-adjusted models were approached to detect associations of air pollution with inflammatory markers and AD-related proteins. **Results**: Ambient 2-year averaged exposure of $PM_{2.5}$ was associated with changes of neuroinflammatory markers, that is, CSF sTREM2 ($\beta = -0.116$, $p = 0.0002$). Similar results were found for O_3 exposure among the elderly ($\beta = -0.111$, $p = 0.0280$) or urban population ($\beta = -0.090$, $p = 0.0144$). No significant evidence supported NO_2 related to CSF sTREM2. For potentially causal associations with accumulated AD pathologies, the total effects of $PM_{2.5}$ on CSF amyloid-related protein (CSF Aβ42 and p-tau/Aβ42) were partly mediated by CSF sTREM2, with proportions of 14.22% and 47.15%, respectively. Additional analyses found inverse associations between peripheral inflammatory markers with $PM_{2.5}$ and NO_2, but a positive correlation with O_3. **Interpretation**: These findings demonstrated a strong link between $PM_{2.5}$ exposure and microglial dysfunction. Furthermore, CSF sTREM2 as a key mediator modulated the influences of $PM_{2.5}$ exposure on AD amyloid pathologies.

Introduction

The Lancet Commission 2017 on dementia prevention, intervention, and care has added air pollution to the list of potentially modifiable risk factors for dementia.[1] Accumulating longitudinal studies demonstrate a causal link between air pollution and cognitive decline[2] or incident dementia.[3] Rodent models revealed that air pollutants inhalation accelerated the accumulations of Alzheimer's disease (AD) pathology, including amyloid accumulation[4] and hyperphosphorylation of tau.[5] Inflammation and oxidative stress are identified as basic and common mechanisms promoting the progress of neurodegenerative diseases.[6,7] A post-mortem survey showed a significant increase in neuroinflammatory markers in individuals with high air pollutant exposure.[8] A new murine study reports that ozone (O_3) dysregulates microglia protein expression and exacerbates amyloid pathology in the peri-plaque microenvironment, leading to increased dystrophic synapses and increased amyloid beta-peptide (Aβ) plaque load.[9] Although available experimental articles[10] have given a hint about the association between air pollution and neuroinflammation, the underlying mechanism is still unclear especially based on clinical research. Therefore, further validation is warranted, especially compelling empirical support based on the evidence from human epidemiologic studies.

The triggering receptor expressed on myeloid cell 2 (TREM2) expressed by microglia is an innate immune receptor. The soluble TREM2 (sTREM2) is released as a result of the ectodomain shedding of the transmembrane TREM2 receptor, which serves as a surrogate measure of microglial activity and neuroinflammation.[11,12] Emerging evidence implicates that neuroinflammation and microglial activation play prominent roles in the pathogenesis of AD.[13,14] According to the "Neuroinflammation hypothesis," inhaled air pollution may activate microglia through both direct and indirect pathways, subsequently causing the release of neurotoxic cytokines and reactive oxygen species (ROS).[15] Air pollution may generate detrimental effects on accelerating neurodegenerative processes by activating microglia and elevating neuroinflammation. Therefore, as a marker reflecting microglial activation and neuroinflammation, the application of sTREM2 may help monitor the neuroinflammatory burden of air pollution exposure. Nevertheless, it remains to be ascertained whether CSF sTREM2 plays a role in the air pollution-induced AD pathologies.

AD as a systemic multifactorial disease involves dynamic peripheral and central immune responses. A growing number of studies have shown that patients with AD are accompanied by alterations in the peripheral immune system.[16,17] Therefore, we aimed to: (1) explore the relationship between air pollution and neuroinflammation represented by CSF sTREM2; (2) investigate the associations of air pollution exposure with systemic inflammatory markers, including high sensitivity C-reactive protein (hsCRP) and peripheral immune cells; (3) ascertain whether neuroinflammation or systemic inflammation has an effect on AD pathologies response to air pollution.

Methods

Study population

All enrolled participants were gathered from the Chinese Alzheimer's Biomarker and Lifestyle (CABLE) database, an ongoing large-scale cohort study since 2017, which was designed to ascertain the genetic and environmental modifiers that may impact the onset of AD, thereby providing evidence for early diagnosis and prevention of AD.[18,19] Participants were recruited from Qingdao Municipal Hospital, Shandong, China and all were Han Chinese, aged between 40 to 90 years old. Individuals were excluded if diagnosed with (1) major neurological disorders (e.g., central nervous system [CNS] infection, epilepsy, multiple sclerosis, and head trauma); (2) serious systemic disease that may disturb CSF AD biomarkers, such as malignant tumors; (3) major psychological disorders; (4) family history of genetic diseases. All individuals received biochemical testing, blood and CSF sample collections, as well as clinical and neuropsychological assessments. The general cognitive function was estimated by the adapted China-Modified Mini-Mental State Examination (CM-MMSE). Demographic information and medical histories were obtained through comprehensive questionnaires and electronic medical records systems. The research protocol was approved by the institutional Ethics Committee of Qingdao Municipal Hospital and written informed consents were obtained from all participants or their guardians following the Declaration of Helsinki.

A total of 1,131 cognitively normal participants from CABLE with available air pollution estimation and complete information about age, gender, educational years, and *Apolipoprotein-ε4* (*APOE-ε4*) carrier status were included in the present study. Next, participants were excluded separately if they did not have either data of CSF sTREM2, hsCRP, and immune cells or the data outside the standard deviation of four times. Quality control additionally excluded sTREM2 measurements with an inter-batch coefficient of variation values greater than 15% and the concentrations of hsCRP greater than 10 mg/L. Because concentrations of hsCRP above 10 mg/L might be attributable to acute infection or trauma.[20] Finally, 1,031, 307, and 735 individuals were involved in analyses of sTREM2, hsCRP, and immune cells, respectively.

Air pollution exposure assessment

A satellite-based high spatial and temporal resolution model[21] was used for predicting $PM_{2.5}$ levels. According to previous modeling studies,[22] the real-time measurements of $PM_{2.5}$ from ground-based monitors and satellite aerosol optical depth (AOD) values were used as the independent variable and basic predictor variable. Additional variables were also considered as predictors, for example, temperature, population density, cloudiness, relative humidity, wind speed, precipitation, and elevation.[23] Besides, the non-AOD model was adapted to integrate predicted values when AOD information was lacking. Annual average estimates of O_3[24] and nitrogen dioxide (NO_2)[25] were obtained from the 2019 Global Burden of Disease (GBD) exposure products, the methodology for which has been reported in previous GBD documents (Supplementary method).

The annual averaged estimates of the $PM_{2.5}$, O_3, and NO_2 were allocated to each participant based on geocoding of residential address. The concentrations of 2-year average air exposure were calculated and adopted as basic variables for subsequent analyses to ensure an appropriate temporal relationship between air pollutants and indicators of inflammation.

CSF collection and measurement

Fasting lumbar cerebrospinal fluid samples were collected and processed within 2 h immediately after the standard lumbar puncture. The measurements of CSF sTREM2 were performed using an ELISA kit (Human TREM2 SimpleStep ELISA Kit; Abcam, No.Ab224881). The concentrations of CSF AD core biomarkers protein including Aβ42, total phosphorylated tau (p-tau), and tau (t-tau) were detected by the enzyme-linked immunosorbent assay (ELISA) kit (Innotest-AMYLOID (1–42), PHOSPHO-TAU (181p), and hTAU-Ag; Fujirebio, Ghent, Belgium). The above ELISA assays were conducted by professional technicians who were blinded to clinical information. Samples and standards were measured in duplicate and statistically analyzed using the same methods. In addition, the inter-batch coefficients of variation were < 15% for all AD core biomarkers protein.

The ratios of p-tau/Aβ42 and t-tau/Aβ42 were calculated for subsequent analyses because they were better predictors than alone to reflect cerebral amyloid deposition.[26]

Blood collection and measurement

Fasting blood samples from the CABLE participants were obtained within 24 h after hospital admission. The hsCRP level was estimated through an automated analytical platform (Beckman Coulter AU5800: Beckman Coulter Inc. Brea, CA, USA) of which the lower detective limit was 0.01 mg/L. In accordance with prior literature, the hsCRP was binarized as normal (hsCRP <3 mg/L) and "low-grade" inflammation (3 to 10 mg/L) in subsequent analyses.[20]

Peripheral immune cell counts, encompassing the counts of white blood cell (WBC), neutrophil (NEUT), and lymphocyte (LY), were examined using flow cytometry and acquired from a fully automated hematology analyzer (Kobe Sysmex, Japan). In addition, the neutrophil to lymphocyte ratio (NLR) was also calculated for subsequent analyses.

APOE-ε4 genotyping

The QIAamp DNA Blood Mini Kit was used to extract DNA from blood samples. Isolated DNA was stored in enzyme-free EP tubes at −80 °C until *APOE-ε4* genotyping was performed. Genotypes were determined by restriction fragment length polymorphism technology based on the specific loci of rs7412 and rs429358. *APOE-ε4* status was the allelic load of the *APOE-ε4* allele ($APOE\text{-}\varepsilon4^{-/-} = 0$, $APOE\text{-}\varepsilon4^{+/-} = 1$, or $APOE\text{-}\varepsilon4^{+/+} = 2$). In addition, the *APOE-ε4* non-carriers referred to individuals without the *APOE-ε4* gene, and individuals with *APOE-ε4* allele (1 or 2) were identified as *APOE-ε4* carriers.

Covariates

Fundamental covariates contained gender (female or male), age (continuous), *APOE-ε4* status (0, 1, or 2), and educational level (continuous). In addition, socioeconomic status, lifestyle characteristics, clinical comorbidities, and AD core pathologies were identified as potential confounders. Lifestyles and socioeconomic characteristics were assessed by comprehensive questionnaires, including regular physical activity (yes or no), body mass index (BMI, continuous), current or former smokers (yes or no), current or former drinkers (yes or no), and the current occupational status (yes or no). Comorbidities information was determined according to the diagnoses or medical history recorded in the electronic medical record (EMR) systems, including the history of stroke, diabetes, coronary heart disease, and hypertension. In subgroups analyses, a cut-off of 65 years was set to define the mid- or late-life stage,[27] and individuals with a BMI≥25 kg/m^2 were classified as obese.[28]

Statistical analyses

In the description of epidemiological characteristics, categorical variables were presented as numbers (percentages); continuous variables were expressed as mean (standard deviation, SD) when normally distributed (Kolmogorov–Smirnov test >0.05) or median (interquartile range, IQR) if non-normally distributed. Data on CSF sTREM2 and peripheral immune cell counts were transformed based on Box-Cox approach via the "car" package in R software to achieve an approximately normal distribution. To facilitate comparisons between modalities, all air pollutants, CSF sTREM2, immune cell and CSF AD biomarkers were standardized by z-scale.

First, single-pollutant models as the main models were applied to assess the effects of air pollution ($PM_{2.5}$, O_3, and NO_2) on neuroinflammation and systemic inflammation with gender, age, educational level, and *APOE-ε4* status as covariates. To investigate the associations between air pollution exposure and neuroinflammation, multivariable linear regression was conducted with CSF sTREM2 as the dependent variable. As for the systemic inflammation, we performed multivariate logistic regression to clarify the relationships of air pollution exposure with hsCRP, and linear regression to estimate the correlations between air pollution and peripheral immune cell (WBC, NEUT, LY, and NLR) counts. Next, multi-pollutants models (three air pollutants simultaneously involved) were applied for further adjustment of the two other air pollutants, in consideration of the complex coexistence of various components of air pollutants.

Sensitivity analyses were carried out in the following three ways to consolidate the statistical results: (1)

additional adjustments for socioeconomic and lifestyle characteristics, clinical comorbidities, and CSF Aβ42 and p-tau were sequentially added to the main model; (2) repeating primary results using averaged exposure of different years (3-year, 4-year, and 5-year); (3) excluding the data outside the means±4SD interval of air pollutants. To investigate whether some covariates could confound the correlations between air pollution and neuroinflammation, we conducted a series of subgroup analyses stratified by gender, age, *APOE-ε4* carrier status, obesity, residence, smoking status, and physical activity as well as occupational status.

Furthermore, mediation analyses according to the method proposed by Baron and Kenny[29] were implemented to explore whether neuroinflammation and systemic inflammation mediated the relationships of air pollution with AD pathologies. Mediation effects were established if the following requirements were simultaneously reached: (1) air pollution was significantly associated with inflammation markers (sTREM2, hsCRP, and immune cells counts); (2) air pollution was associated with CSF AD biomarkers significantly; (3) inflammation markers were associated with CSF AD biomarkers significantly; and (4) the associations of air pollution with CSF AD biomarkers were attenuated when inflammation markers were added in a regression model. Moreover, the attenuation or indirect effect was determined via 10,000 bootstrapped resamples ("mediate" package in R software). The above analyses were corrected for gender, age, educational level, and *APOE-ε4* status.

The R software version 3.5.1 and IBM SPSS Statistics 23 were applied to perform statistical analyses and figure preparation. A two-tailed *p*-value <0.05 was considered statistically significant.

Results

Study population

The epidemiological characteristics of included participants in CABLE were summarized in Table 1. A total of 1,131 normal cognitive individuals (CM-MMSE score median, 28; IQR, 27–30) were involved in the study, with a median educational year of 9 (IQR, 9–12). In brief, the mean age of the study population was 62.47 (SD, 10.34) years, the percentage of females was 41.1%, and the proportion of *APOE-ε4* carriers was 15.2%.

Air pollutants

Spearman correlation coefficients were calculated for the associations between three air pollutants. The results showed that NO_2 was weakly ($r = -0.17$) negatively correlated with $PM_{2.5}$ and moderately ($r = -0.48$) negatively correlated with O_3, whereas $PM_{2.5}$ exposure was moderately positively ($r = 0.55$) correlated with O_3 (all $p < 0.05$, Table S1). The Mann–Whitney *U* test was carried out to investigate the regional differences in air pollution. We observed higher monitored values of $PM_{2.5}$ and O_3 in rural and elevated concentrations of NO_2 in

Table 1. Characteristics of study participants from the CABLE database.

Characteristics	Participants
N	1131
Age (years, mean ± SD)	62.47 ± 10.34
Gender (F/M)	465/666
BMI (kg/m^2, mean ± SD)	25.54 ± 3.49
APOE-ε4 carriers (N, %)	172/15.2
Education (years, median, IQR)	9 (9–12)
CM-MMSE score	28 (27–30)
Residence (Rural, %)	352/31.3
Smoking status (Yes, %)	350/31.1
Alcohol habits (Yes, %)	527/47.1
Physical Activities (Yes, %)	283/25.3
Employment (Yes, %)	370/32.7
Comorbidities (*N*, %)	
CHD	166/14.7
Diabetes	174/15.5
Hypertension	441/39.1
Stroke	40/3.6
CSF AD biomarkers (median, IQR)	
Aβ42 (pg/ml)	136.44 (112.78–215.75)
p-tau (pg/ml)	34.36 (30.43–41.12)
t-tau (pg/ml)	149.50 (120.77–198.75)
p-tau/Aβ42	0.24 (0.16–0.30)
t-tau/Aβ42	1.02 (0.71–1.29)
Neuroinflammation index (median, IQR)	
CSF sTREM2 (mg/L)	18310.87 (12047.88–22914.61)
Systemic inflammation index	
hsCRP (*N*, %)	
<3(mg/L)	223/71.9
3–10 (mg/L)	87/28.1
WBC (10^9/L, median, IQR)	5.78 (4.93–7.22)
NEUT (10^9/L, median, IQR)	3.10 (2.48–4.28)
LY (10^9/L, median, IQR)	1.92 (1.49–2.31)
NLR (median, IQR)	1.65 (1.25–2.41)

Variables were expressed as proportions, means ± SD or median and interquartile range (IQR), as appropriate.

Abbreviations: AD, Alzheimer's disease; *APOE*, *Apolipoprotein E*; Aβ42, amyloid beta-peptide 42; BMI, body mass index; CHD, coronary heart disease; CM-MMSE, China-Modified Mini-Mental State Examination; CSF, cerebrospinal fluid; F, Female; hsCRP, hypersensitive C reaction protein; IQR, interquartile range; LY, lymphocyte count; M, male; NEUT, neutrophil count; NLR, neutrophil to lymphocyte ratio; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; p-tau, phosphorylated tau; SD, standard deviations; sTREM2, soluble TREM2; t-tau, total tau; WBC, white blood cell count.

urban (all $p < 0.01$). Specifically, the 2-year average exposure levels of $PM_{2.5}$, NO_2, and O_3 were 41.29 μg/m^3, 12.66 ppb, and 41.34 ppb for urban individuals, and were 42.16 μg/m^3, 8.95 ppb, and 44.80 ppb for rural individuals, respectively (Fig. S1).

Association between air pollution and neuroinflammation

Participants residing in areas with higher $PM_{2.5}$ exhibited attenuated neuroinflammation indicated by decreased CSF sTREM2 in both single-pollutant models ($\beta = -0.116$, $p = 0.0002$) and multi-pollutants models ($\beta = -0.114$, $p = 0.0010$, Fig. S2). However, no significant associations between NO_2 and O_3 with sTREM2 were found. As for sensitivity analyses, the correlations between $PM_{2.5}$ and sTREM2 were attenuated but remained significant in lifestyle and socioeconomic characteristics, comorbidities, and core biomarkers of AD adjusted (Table 2). Consistently, the identified results mentioned above were barely changed in all the three sensitivity analyses (Fig. 1).

To determine the potential strata effect on the associations between ambient pollution and neuroinflammation, subgroup analyses were approached stratifying by a series of potential confounders which covered major epidemiological, socioeconomic, and private lifestyle characteristics. The estimate of the association between ambient $PM_{2.5}$ and sTREM2 was significant in males and *APOE-ε4* carriers, whereas not in females and *APOE-ε4* non-carriers (Fig. 2A,B). Notably, explicitly inverse associations of $PM_{2.5}$ and O_3 with sTREM2 only existed among the late-life individuals whose ages were over 65 years, but not among the mid-life (Fig. 2C,D). Similar findings remained in participants residing in urban areas, but not in the rural regions (Fig. 2E,F). Besides, the relationship between ambient $PM_{2.5}$ and sTREM2 was more pronounced in smokers than non-smokers but equivalent in subgroups stratified obesity, physical activity status (Fig. 2G–I) and regular physical activity. Additionally, there was no significant strata effect for individuals exposed to NO_2 (Table S2). Outliers for air pollutants were included in the above analyses, and similar results were obtained after excluding extreme values (not shown).

Association of air pollution with systemic inflammation

As for hsCRP, we did not reveal any marked correlations with each air component in single-pollutant models and the results of sensitivity analyses using average exposures of different years maintained consistent. While in multi-pollutant models, individuals residing in areas with greater O_3 pollution presented higher levels of systemic inflammation (OR = 1.600, $p = 0.0185$), a similar finding was found in sensitivity analyses adjusting socioeconomic and lifestyle characteristics, comorbidities, and AD core biomarkers (Tables S3, S4).

In respect to immune cell count, we observed that inhaled O_3 (but not $PM_{2.5}$ and NO_2) was correlated with high systemic inflammation levels indicated by an elevated count of NEUT ($\beta = 0.076$, $p = 0.0426$) and NLR ($\beta = 0.115$, $p = 0.0019$) in main models. The above results were broadly robust in sensitivity analyses. However, slight but inconsistent estimates were detected in our studies that high $PM_{2.5}$ was associated with low WBC, and elevated NO_2 was associated with reduced NEUT and NLR (Tables S5–S7).

Causal mediation analyses

After adjusting for gender, age, educational level, and *APOE-ε4* status, individuals surrounding with higher

Table 2. Associations between air pollution and CSF sTREM2.

	$PM_{2.5}$				NO_2				O_3			
Models	β	95% CI		p	β	95% CI		p	β	95% CI		p
Model 1	−0.116	−0.176	−0.056	0.0002	0.015	−0.050	0.079	0.6570	−0.053	−0.117	0.012	0.1110
Model 2	−0.112	−0.174	−0.050	0.0004	−0.002	−0.072	0.069	0.9570	−0.040	−0.109	0.029	0.2565
Model 3	−0.111	−0.174	−0.048	0.0005	−0.006	−0.077	0.065	0.8609	−0.036	−0.106	0.034	0.3135
Model 4	−0.097	−0.159	−0.035	0.0021	−0.016	−0.086	0.054	0.6620	−0.016	−0.084	0.051	0.6356

Model 1: adjusted for fundamental information, including age, gender, *APOE-ε4* carrier status, education level.
Model 2: adjusted for fundamental information and socioeconomic and lifestyle characteristics (BMI, physical activity, smoking status, alcohol habits, residence, employment status).
Model 3: clinical comorbidities including stroke, hypertension, diabetes, and coronary heart disease were added for adjustment according to model 2.
Model 4: CSF AD biomarkers (Aβ42 and p-tau) were added for adjustment based on model 3.
Abbreviations: AD, Alzheimer's disease; *APOE, Apolipoprotein E*; Aβ42, amyloid beta-peptide 42; BMI, body mass index; CSF, cerebrospinal fluid; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; p-tau, phosphorylated tau.

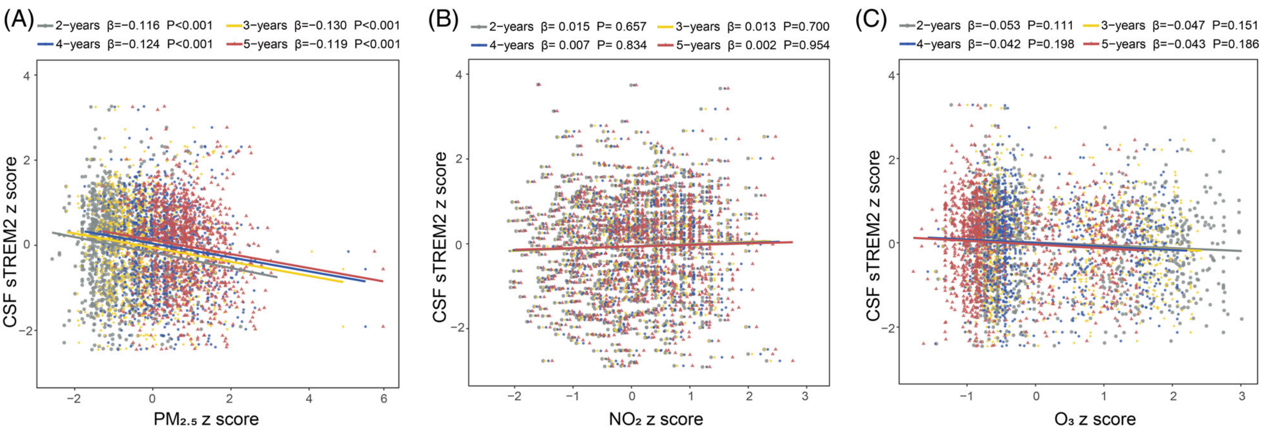

Figure 1. Associations between air exposure averaged in different years and CSF sTREM2. Linear models with adjustment of age, gender, educational level, and *APOE-ε4* carrier status presented that individuals with higher residential $PM_{2.5}$ exposure had a decreased neuroinflammation, as reflected by lower levels of sTREM2 in cerebrospinal fluid (A). But no significant evidence showed the associations of different years averaged (2-year, 3-year, 4-year, and 5-year) NO_2 (B) and O_3 (C) with sTREM2. *APOE*, *apolipoprotein E*; CSF, cerebrospinal fluid; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; sTREM2, soluble TREM2.

ambient $PM_{2.5}$ presented lower CSF Aβ42 ($\beta = -0.306$, $p < 0.001$), higher CSF p-tau/Aβ42 ratio ($\beta = 0.324$, $p < 0.001$), and CSF t-tau/Aβ42 ratio ($\beta = 0.229$, $p < 0.001$). In addition, individuals exposed to higher NO_2 showed higher CSF p-tau ($\beta = 0.074$, $p = 0.0285$). However, no significant evidence supported O_3 related to AD pathologies (Table S8).

Besides, CSF sTREM2 was elucidated to be correlated with amyloid-related biomarkers, consisting of CSF Aβ42 ($\beta = 0.352$, $p < 0.001$) and CSF p-tau/Aβ42 ($\beta = -0.168$, $p < 0.001$), and with CSF tau-related proteins, that is, p-tau ($\beta = 0.315$, $p < 0.001$) and t-tau ($\beta = 0.354$, $p < 0.001$, Table S9). Moreover, only LY in plasma related to CSF Aβ42 ($\beta = \beta = 0.077$, $p = 0.0421$) and NLR linked to tau pathology including t-tau ($\beta = -0.0815$, $p = 0.0295$) and t-tau/Aβ42 ($\beta = -0.097$, $p = 0.0120$, not shown).

All the above findings indicated that $PM_{2.5}$ exposure was not only an independent risk factor for neuroinflammation but was also related to amyloid pathology. In the further mediation analyses, the influences of the $PM_{2.5}$ exposure on AD pathological biomarkers remained but were attenuated when CSF sTREM2 entered into the model. It demonstrated that the relationship between $PM_{2.5}$ exposure and aggravated deposition of amyloid was partly mediated by CSF sTREM2, with the mediation proportion of 14.22% for CSF p-tau/Aβ42 and 41.75% for CSF Aβ42 ($p < 0.05$, Fig. 3).

Given the lack of associations of ambient O_3 and NO_2 with AD biomarkers protein and the nonsignificant links of WBC and NEUT with AD core pathologies, we could not establish the mediation effect of systemic inflammation on the associations between ambient air pollutants and AD pathologies.

Discussion

This large-scale study comprehensively assessed the associations of air pollution with neuroinflammation and systemic inflammation in cognitively normal older adults, which replenishes the gap in current research. Several prominent evidences were as follows: (1) this study demonstrated that exposure to $PM_{2.5}$ manifested as impaired neuroinflammatory mechanisms as evidenced by a decrease in sTREM2; (2) some potential strata effects were identified that the association between $PM_{2.5}$ and sTREM2 was strengthened among the elderly and smokers, meanwhile, the association presented only in males, urban dwellers and *APOE-ε4* carriers; ambient O_3 might only modulate the burden of neuroinflammation among the late-life and the urban individuals; (3) $PM_{2.5}$ and NO_2 played discordant roles with O_3 in systemic inflammation; and (4) neuroinflammation partly mediated the influence of ambient $PM_{2.5}$ exposure on brain amyloid pathology. Our findings proved that air pollution exposure was associated with inflammatory dysregulation and supported the hypothesis that neuroinflammation was a biological pathway by which the impact of air pollution on accelerated AD pathologies was generated or enhanced.

Our findings indicate that high levels of air pollution exposure lead to neuroinflammatory dysregulation represented by the reduction of CSF sTREM2. As reported in a murine study, mice exposed to diesel exhaust for more than 1 month exhibited reduced TREM2 expression and dysregulated mRNA expressions of markers of the disease-associated microglia (DAM) phenotype in the hippocampus and frontal cortex. The loss of TREM2

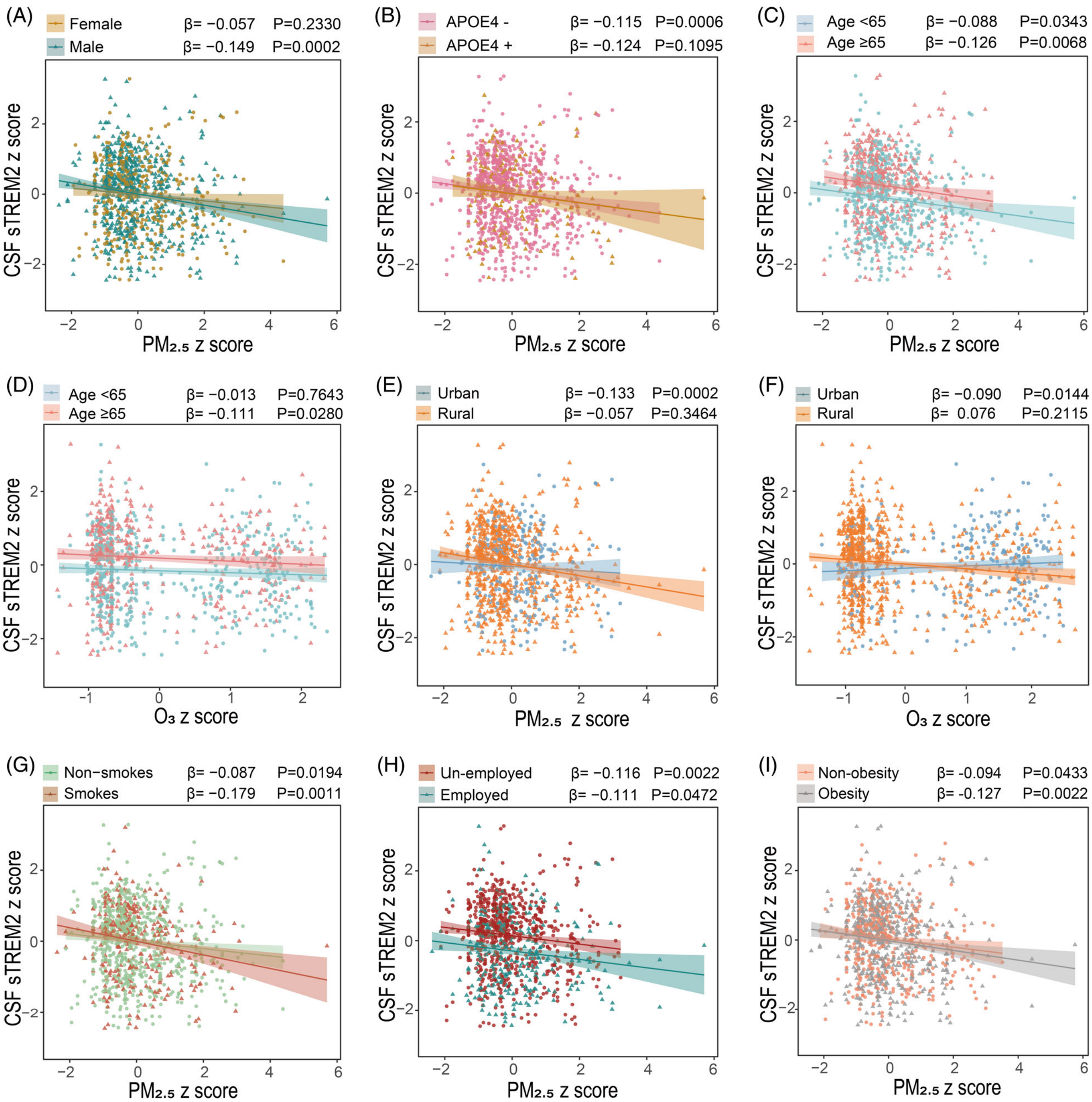

Figure 2. Subgroup analyses of the relationship between air pollutants and CSF sTREM2. Scatter plots represent the associations of air pollutants and CSF sTREM2. CSF sTREM2 level was normalized and z scaled, and all air pollutants were z scaled. Linear models with adjustment of age, gender, educational level, and *APOE-ε4* carrier status were performed to detect potential modifying factors on the associations between air pollutants and CSF sTREM2. *APOE*, *apolipoprotein E*; CSF, cerebrospinal fluid; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; sTREM2, soluble TREM2.

modifies CNS pro-inflammatory responses to diesel exhaust in a gene- and brain region-specific manner.[30] Some previous experiments and a human autopsy study showed that exposure to PM and O_3 induced alterations in microglial morphology and phenotypes, increased pro-inflammatory factors, and decreased anti-inflammation cytokines.[10,15] Compared with these studies, our findings suggest that air pollution exposure plays detrimental effects on neuroinflammation by lowering CSF sTREM2, providing novel insights into the mechanism underlying the influence of air pollution on neuroinflammation. Further prospective cohort studies and experimental models

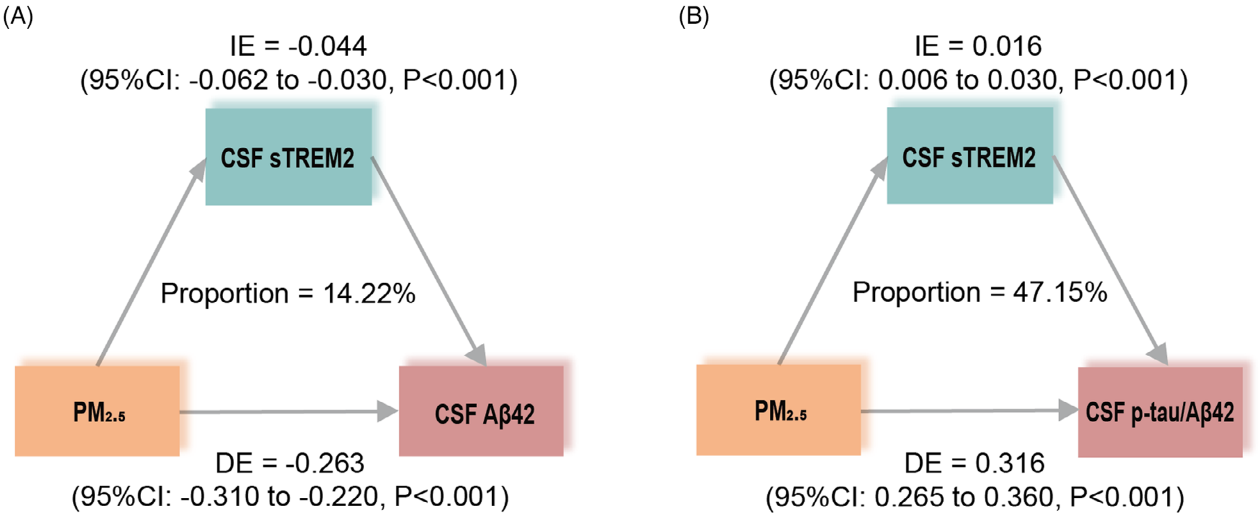

Figure 3. CSF sTREM2 mediated associations between ambient $PM_{2.5}$ and amyloid pathology. Mediation effects of CSF sTREM2 on AD pathology were estimated via 10,000 bootstrapped resamples with the adjustment of age, gender, educational level, and *APOE-ε4* status. The relationship between ambient $PM_{2.5}$ and amyloid pathology (indicated by CSF Aβ42 [A] and CSF p-tau/Aβ42 [B]) was mediated by CSF sTREM2. *APOE*, *apolipoprotein E*; Aβ42, amyloid beta-peptide 42; CSF, cerebrospinal fluid; $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; p-tau/Aβ42, the ratio of phosphorylated tau/amyloid beta-peptide 42; sTREM2, soluble TREM2.

are warranted to validate our conclusion. The association between ozone exposure and brain damage has been demonstrated, although the exact role is not fully understood and is controversial. Medical O_3 has been reported to prevent the retardation of age-related changes in the rat cerebellum.[31] Increasing *in vivo* or *in vitro* evidence showed that inhaling ozone contributed to neuroinflammatory response, neuronal morphological damage, and memory deficits.[32,33] The definite effects and mechanisms of O_3 inhalation on microglial activation require further exploration. To the best of our knowledge, the association between NO_2 and neuroinflammation has never been reported before, but no significant evidence was found in our study.

The gender-dependent effects of $PM_{2.5}$ exposure have been verified in past animal experiments.[34] The differential expression of the antioxidant and anti-inflammatory genes between males and females and potential interactions with the neuroendocrine system has been suggested.[35,36] As the aging, the brain showed vulnerability and increased BBB permeability to neuroinflammatory outcomes of inhaled pollutants,[37] and influential studies have shown the functional role of microglia changed dynamically with aging,[13] which can explain the differential effects between the mid-life and the late-life. Historically, *APOE-ε4* has been considered a risk gene for amyloid deposition, cognition decline, and AD onset.[38] A review suggested that *APOE-ε4* could trigger an inflammatory cascade independent of Aβ, leading to neurovascular dysfunction, including blood–brain barrier breakdown and entry of blood-borne toxic substances into the brain.[39] In the presence of *APOE-ε4,* the high affinity of the sTREM2 and *APOE-ε4* might interfere with the air pollution-TREM2 pathway.[40] The urban–rural difference in the associations of $PM_{2.5}$ and O_3 with CSF sTREM2 was observed in the present study. Interestingly, we observed the rural residents presented higher levels of $PM_{2.5}$ and O_3, which is consistent with the findings of Zhao, S. that the worsening air pollution in rural areas than in urban in developing countries.[41] In addition to ambient air pollutants, agents and conditions in the personal environment collectively constituted the stressors environment, such as population density, noise pollution, indoor air pollution, and availability of green space that varied in rural and urban environments,[42] which alone or in combination affect the neuroinflammatory/ neuroimmune axis and lead to neurodegenerative diseases. In the current study, the urban–rural differences in sTREM2 levels (rural: 17285.77 mg/L, urban: 17913.12 mg/L) might indicate the presence of some environmental stressors confounding the relationship. Besides, our results implied that smoking is also a modifying factor in enhancing the association between $PM_{2.5}$ exposure and neuroinflammation. There is already sufficient epidemiological and animal evidence supporting that smoking-related damaging toxins have the potential to exacerbate neuroinflammation, and oxidative stress injury.[43,44] Even exposure to low concentrations of tobacco smoke, also can evoke a strong inflammatory response in cells, which affects cerebrovascular endothelial cells and circulating immune cells.[45] The detrimental effects of smoke on cognitive impairment and AD pathology have also been reported.[46] The nicotine induces higher BBB permeability by modulating tight junction proteins so that more solute toxicants could enter the CNS.[47] In addition, consistent with the effects of active smoking, passive smoking also showed independent effects on provoking inflammatory response, endothelial damage, and declines in memory.[48,49] Therefore, the exact effect of second hand smoking and other related factors need to be further explored in the later large-scale cohort studies adjusting for more related smoking information. Given the high incidence of AD and the generally high prevalence of human exposure to air pollution, the establishment of susceptible populations is crucial for clinical prevention. Rigorously treating chronic decreased levels of CSF sTREM2 based on susceptible populations may be effective for the prevention and intervention of AD.

Previous findings about the associations between air pollution exposure and systemic inflammation were contradictory and were under debate. Our finding indicates that O_3 exposure is a risk factor for systemic inflammation, which is in line with most previous observational studies[50] and a rodent model.[51] A UK cohort study demonstrated a nonsignificant effect of inhaled O_3 on hsCRP,[52] which was in sympathy with our results without correction for air metrics. In current analyses, the inverse impact was detected of $PM_{2.5}$ (on WBC) and NO_2 (on NEUT and NLR). Past studies showed that PM exposure was accompanied by elevated immune cell counts in bronchoalveolar lavage fluid, which implied an increased inflammatory burden in the lungs, but the evidence for the inflammatory response in the circulatory system was inconsistent. Two studies showed partly consistent results for $PM_{2.5}$[53] and NO_2,[54] the reduction of inflammation levels in these studies might be explained by the movement of immune cells from the bloodstream to stressed tissues such as the lungs.

To the best of our knowledge, it is the first clinical observational study to examine air pollution in the associations with CNS or peripheral inflammation of AD pathology markers. Our findings enhance the evidence for mechanisms of air pollution exposure on AD progress. Decreased CSF sTREM2 mediates the effects of $PM_{2.5}$ exposure on exacerbating brain amyloid deposition. Consequently, it is reasonable to infer that prolonged exposure to air pollution leads to microglial impairment and further accelerates brain amyloidosis. Importantly, the amyloid pathology-mediated effect of ambient $PM_{2.5}$ on cognitive impairment has been reported.[23] Therefore, damaged microglia may contribute to cognitive decline by reducing CSF sTREM2 levels and promoting brain amyloid deposition among preclinical AD individuals with higher $PM_{2.5}$ exposure. It may offer some new prospects on the etiology and therapy of cognitive impairment and AD onset. Published documents claimed that AD pathology and microglial activation might be a complex two-way interaction.[55–57] Therefore, the influence of air pollution on AD pathology and neuroinflammation and the causal relationship warrants further investigation. Besides, in the present study, we cannot conclude the mechanism by which systemic inflammation mediates the culmination of AD lesions caused by air pollution exposure.

The strengths of the current study are as follows: First, the use of cognitively unimpaired participants lets us examine the interrelationships between air pollution, CNS or peripheral inflammation, and CSF pathological proteins during the preclinical stage of AD. Second, the large sample size, representative and available information on neuroinflammatory and systematically inflammatory indicators, fine-scale spatial and temporal exposure modeling data for air pollutants together with comprehensive data of epidemiological information and cerebrospinal fluid profile from CABLE enhanced the credibility and statistical power of our findings. Third, detailed confounding information ensured the accuracy and reliability of our results. Given the lack of clinical studies on the underlying mechanisms between these three common ambient components and AD pathologies, we believe this study is a paramount contribution to the field.

Some limitations should also be acknowledged. Firstly, the application of semi-quantitative questionnaires might be subject to reporting errors. Secondly, we did not consider the impact of the time-location activity, which would result in some misclassification of exposure, but we do not view it as a serious problem due to all enlisted populations are elders and general with less chance of migration or away from residence. Thirdly, since the limitation of individual-level information, our study did not fully adjust for smoke related factors (e.g., second-hand smoking), which may confound our identified correlations between ambient air pollution and neuroinflammation. Fourthly, we failed to screen subjects for possible *TREM2* mutations. Whereas it is highly unlikely that the variation in the present sample would affect our results. Because the most dominant and well-studied variation in AD (the R47H mutation) imposes a minimal effect on cell surface TREM2 protein expression and the soluble form released in the extracellular space.[58] Besides, the prevalence of *TREM2* mutations is low in the general or even AD population.[59] Finally, our findings were based on cross-sectional studies which contributed to the deficiency of necessary causality. In the future, large-scale longitudinal studies with more data on central and peripheral inflammatory cytokines are warranted to obtain definitive causal relationships. Meanwhile, whether peripheral inflammation mediates the link between air pollution and neuroinflammation should also be further detected.

Conclusion

Our study corroborated that air pollution exposure was the modifiable risk factor for the dysregulation of neuroinflammation and systemic inflammation. In addition, CSF sTREM2 was a key mediator of the associations between ambient $PM_{2.5}$ exposure and aggravated amyloid pathology. Activation of microglia might mitigate the burden of air pollution-induced brain amyloid deposition, which indicated clinical implications for individuals living with serious air pollution and an asymptomatic phase of AD, as targeting sTREM2 may help reduce the burden of amyloid deposition and slow down the progression of AD or delay the onset. Moreover, our findings updated the emerging evidence in this field and highlight the urgency of implementing public policies that reassess and control air pollution emissions to achieve the primary prevention of AD.

Author's Contributions

Meng Li contributed to the manuscript drafting. Meng Li, Ya-Hui Ma, He-Ying Hu, Yong-Li Zhao, Liang-Yu Huang, and Lan Tan participated in clinical assessments and data acquisition. Meng Li, Ya-Hui Ma, Yan Fu, and Jia-Yao Liu participated in the acquisition and analysis of data. Lan Tan participated in the study conception and design. All authors assisted in revision of the manuscript and approved the final version for submission.

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Conflict of Interest

The authors declare that they have no competing interests.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Air pollutants concentrations in different residence.
Figure S2. Associations between air pollution and CSF sTREM2 level in multi-pollutants models.
Table S1. Descriptive statistics of pollutants and correlation matrix.
Table S2. Subgroups analyses of associations between air pollutants and CSF sTREM2.
Table S3. Associations between air pollution and hsCRP.
Table S4. Sensitivity analyses of the associations between average air exposure in different years and hsCRP.
Table S5. Associations between air pollution and immune cells in single-pollutant models and multi-pollutants models.
Table S6. Sensitivity analyses of the associations between air pollution and immune cells after adjusting additional covariates.
Table S7. Sensitivity analyses of associations between average air exposure in different years and immune cells.
Table S8. Associations between air pollution and CSF AD biomarkers.
Table S9. Associations between CSF sTREM2 and CSF AD biomarkers.

