Environmental Health

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Air pollution is linked to cognitive decline independent of hypersensitive C-reactive protein: insights from middle-aged and older Chinese

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Abstract

Background Long-term air pollution exposure and inflammation are considered to be associated with cognitive decline. However, whether air pollution exposure related cognitive decline is dependent on inflammation remains uncertain.

Materials and methods The present study collected data from China Health and Retirement Longitudinal Study (CHARLS) at baseline in 2011, with a follow up period in 2015. Concentration of air pollutants (particles with diameters ≤ 1.0 μm [PM_1], ≤ 2.5 μm [$PM_{2.5}$], ≤ 10 μm [PM_{10}], nitrogen dioxide [NO_2] and ozone [O_3]) were obtained from China High Air Pollutants (CHAP) dataset. Hypersensitive C-reactive protein (hs-CRP), a systemic inflammation marker, was measured in blood of subjects and cognitive function was assessed by standardized questionnaire.

Results A total of 6434 participants were included in the study. Lower exposure to $PM_{2.5}$, PM_1, PM_{10} and NO_2 were associated with mitigated cognitive decline. The odds ratios (ORs) for air pollutants changes and cognitive decline and 95% confidence intervals (CIs) were as follows: $PM_{2.5}$-0.934(0.925, 0.943), PM_1- 0.945 (0.935,0.955), PM_{10}-0.977(0.972,0.982) and NO_2-0.962(0.950,0.975), respectively. Hs-CRP showed no significant correlation with cognitive decline or change in levels of air pollution. The interaction regression analyses, both unadjusted and adjusted, did not uncover any significant correlation between hs-CRP and air pollution with respect to cognitive decline. Bootstrap test exhibited no significant mediating effect of hs-CRP on the relationship between any air pollutants and cognitive decline, the indirect effects of hs-CRP in conjunction with exposure to different air pollutants were all found to be non-significant, with the following bootstrap CIs and *p*-values: $PM_{2.5}$-1.000([1.000,1.000], $P=0.480$),PM_1-1.000([1.000,1.000], $P=0.230$),PM_{10}-1.000([1.000,1.000], $P=0.650$), O_3-1.000([1.000,1.000], $P=0.470$), ΔNO_2-1.000([1.000,1.000], $P=0.830$) .

Conclusion Ambient air pollution exposure was linked to cognitive decline independent of hs-CRP level.

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Keywords Air pollution, Cognitive function, Systemic inflammation, Hypersensitive C-reactive protein, CHARLS, Particulate matter

Background

Dementia, a cognitive disorder, is a devastating neurological condition seen in older adults, affecting individuals, families and imposing a significant public health cost. According to a report by World Health Organization (WHO), the global population affected by dementia is estimated to reach 131.5 million by 2050 [1]. Multiple studies have reported the increased risk of incident dementia with exposure to air pollution. Indoor air pollution arising out of household fuel use in China has been linked to cognitive deficits, a trend observed in other low and middle-income countries including India [2, 3]. A systematic review reported exposure to air pollution with elevated risks of cognitive impairment in adults, and dementia in older adults [4], indicating a potential impact of air pollution on cognitive health across the life-course. Though, epidemiological studies have shown a strong association between air pollution and cognitive disorder, the underlying mechanism is largely unknown.

Recent research has sparked interest in understanding the role of neuroinflammation and oxidative stress as potential mechanisms linking air pollution with neuropsychiatric disorders [5]. Neuroinflammation activates abnormal microglia releasing excessive inflammatory cytokines and chemokines, causing neuronal death and cognitive impairment [6]. C-reactive protein (CRP, or hypersensitive CRP), acknowledged as a marker indicating persistent chronic systemic inflammation, has been demonstrated to be associated with the progression of atherosclerosis. Elevated levels of CRP have been linked to an augmented risk of cardiovascular disease (CVD)-related events and mortality [7, 8]. Several observational studies have indicated a positive relationship between CRP levels and dementia [9]. High plasma CRP level was associated with accelerated cognitive decline in Chinese elderly mild cognitive impairment patients [10]. However, contrary findings exist, as several studies have indicated lower plasma C-reactive protein (CRP) levels in patients with Alzheimer's disease (AD) [11, 12]. Furthermore, some studies have reported a lack of significant association between CRP and dementia [13, 14]. The discrepancies in results regarding the relationship between CRP and cognitive decline are likely attributed to variations in the studied populations. To better understand whether CRP levels are associated with cognitive decline in populations exposed to air pollution, additional investigation is warranted.

Several studies have presented that air pollution exposure influences inflammation-related protein level (interferon-gamma and IL-12B, IL-8), and increases proinflammatory cytokines (monocyte chemoattractant protein 1) and inflammatory response that characterized by elevated circulating cluster of differentiation level [15, 16]. In a previous population study, a positive correlation was observed between air pollution and CRP [17]. However, this conclusion did not hold true in certain other observational studies [18, 19]. The connection between air pollution and inflammation seems to fluctuate based on the specific air pollutants, the studied population, and the inflammatory markers investigated. Moreover, the impact of systemic inflammation on the correlation between air pollution and cognitive dysfunction is not firmly established. Consequently, in this study, we investigated the impact of air pollutants exposure on cognitive function under varying inflammatory state (indicated by hs-CRP levels) in middle-aged and elderly Chinese, and explore the effect of hs-CRP on the relationship between air pollution and cognitive decline. We aim to figure out whether cognitive decline attributed to air pollution is influenced or mediated by hs-CRP levels.

Materials and methods

Study population

The data set was derived from China Health and Retirement Longitudinal Study (CHARLS), a multistage-stratified longitudinal study, which recruited middle- and old-aged community-dwelling residents from 450 villages in 150 counties of 28 provinces in China. The detailed design of CHARLS is described elsewhere [20]. In summary, the baseline survey was conducted in 2011, with a small subset of participants completing the survey in 2012. Follow-up interviews were conducted in 2013, 2015 and 2018. Due to the absence of blood sample data in the CHARLS surveys from 2013 to 2018, this study has opted to utilize the CHARLS 2015 dataset for the analysis. Individuals were excluded if they met one or more of the following criteria: (1) lack of community information; (2) age < 45 years; (3) missing data on cognitive function score, CRP levels, demographic and covariates information; and (4) attrition during the follow-up period. The flowchart of patient enrollment is shown in Fig. 1. A total of 17,708 individuals from the wave of 2011–2012 were initially included in the study. Of these, 9,348 individuals were excluded during the baseline screening, and an additional 1,906 individuals were excluded during the follow-up period based on the exclusion criteria. Finally, 6434 individuals were included in the analyses. This study was approved by Ethics Review Committee of Peking University. All subjects provided informed consent.

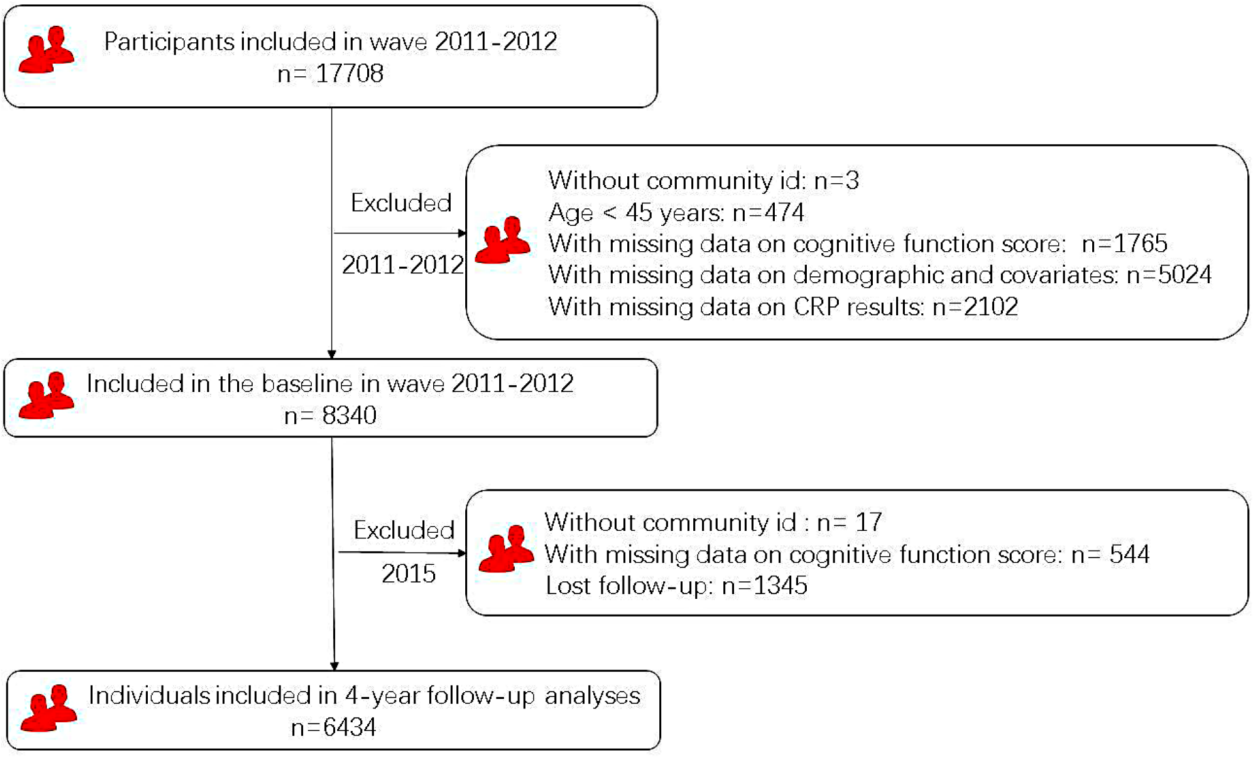

Fig. 1 The flowchart of patient enrollment

Cognitive function

The participants underwent a telephonic interview for assessing their cognitive status (TICS) The TICS determined by scoring three aspects of cognitive health i.e., orienting attention (0–10 points), episodic memory (0–10 points) and visuoconstruction (0–1 points). The total score of cognitive function ranges from 0 to 31 points, with higher scores implying higher cognition. The TICS is a widely used and standardized methodology for assessing cognitive function in various research studies [21, 22].

Inflammation marker

We measured serum hypersensitive CRP (hs-CRP) as the inflammation marker. Fasting venous blood sample was collected from respondents by trained staff from the local Chinese Center for Disease Control (China CDC) and preserved in 0.5 mL cryovials at −20 °C−80 °C. All the samples were delivered to Beijing CDC within 2 weeks and measured with immunoturbidimetric assay in the Clinical Laboratory of Capital Medical University. The sampling and measurements were followed adopting CDC manual about blood collection and handling [23]. The high sensitivity CRP test had a detection limit ranging from 0.1 to 20 mg/L. The coefficient of variation within the assay for high sensitivity CRP was less than 1.3%, indicating low variability in the results. Additionally, the coefficient of variation between different assays was less than 5.7%, indicating consistent and reliable measurements. Systemic inflammation is defined as CRP ≥ 3 mg/L levels.

Air pollution exposure assessments

Ground-level air pollution concentrations for 2011 and 2015, namely particles with diameters ≤ 1 μm (PM_1), particles with diameters ≤ 2.5 μm ($PM_{2.5}$), particles with diameters ≤ 10 μm (PM_{10}), nitrogen dioxide (NO_2) and ozone (O_3), were collected from the China High Air Pollutants (CHAP) dataset (available at https://weijing-rs.github.io/product.html), which has been successfully applied in several studies on the impact of air pollution on public health, such as metabolic syndrome and physical function [24, 25]. The air pollution exposure assessment was executed through a sophisticated, multi-pronged strategy that amalgamated satellite-derived spatiotemporal data with on-ground air quality surveillance, meteorological parameters, and land use patterns. This robust methodological framework facilitated the precise prediction of daily exposures to fine particulate matter with diameters ≤ 1 μm (PM_1) and ≤ 2.5 μm ($PM_{2.5}$), utilizing a high spatial resolution of 0.01° × 0.01°. In estimating PM_1 and PM_{10} concentrations, we adopted a hybrid approach, merging satellite-derived data with measurements from ground-based air quality monitoring

stations. The data from these stations were meticulously collected and analyzed in accordance with the protocols established by the State Environmental Protection Administration of China (1992), thereby bolstering the credibility of our exposure assessments. Daily concentrations for PM_{10}, nitrogen dioxide (NO_2), and the 8-hour average for ozone (O_3) were calculated from continuous hourly readings throughout the day, ensuring that at least 75.0% of 1-hour data points were available to secure reliable estimates. The air monitoring stations are located within the residential areas of each study participant, at a considerable distance from major traffic roads, gas stations, industrial fuel exhaust outlets, and landfills.

The details on air pollution estimation were described in previous study [26–28].

Covariates

Standard self-administered questionnaire in CHARLS was used to collect sociodemographic information, lifestyle behaviors, health status information, and other data. We considered the potential confounding variables in the analysis as following: (1) socio-demographic characteristics including age (continuous), sex (male/female), birthplace (urban/rural), education level (junior high school and below/high school and above) and Regional Per Capita Gross Domestic Product (GDP). (2) lifestyle behaviors, including sleep time (continuous), smoking (yes/no), current alcohol consumption (never/> 1 time per month/< 1 time per month), physical activity (0 indicates missing value, 1 indicates walking for at least 10 min continuously per week, 2 indicates moderate physical activity for at least 10 min continuously per week, 3 indicates vigorous physical activity for at least 10 min continuously per week), cooking fuel use (clean fuel/ solid fuel) and heating fuel use (clean fuel/ solid fuel). (3) health status-related variables, including numbers of types of chronic diseases (medical history, such as hypertension, dyslipidemia, diabetes, cancer, chronic lung disease, liver disease, chronic heart disease, stroke, chronic kidney disease, stomach disease, emotional problem, memory related disease, rheumatism, or asthma. score of 0 indicates no chronic disease, 1 indicates one chronic disease, 2 indicates two chronic diseases, and 3 indicates more than two chronic diseases), brain injury (yes/no) and hearing loss (yes/no).

Statistical analysis

Descriptive analyses were conducted for population characteristics. Continuous variables were described as the mean ± standard deviation (SD) and categorical variables were presented as frequencies and percentages. For evaluation, absolute changes of air pollutants (etc. ΔPM_1, $\Delta PM_{2.5}$, ΔPM_{10}, ΔO_3, and ΔNO_2) were defined as follows: Δambient air pollutants = ambient air pollutants in 2011 – ambient air pollutants in 2015. The absolute change in cognitive function in individual was calculated as follows: Δcognitive function = cognitive function score 2011 − cognitive function score 2015. Cognitive decline was determined as a positive difference (Δ cognitive function score > 0) between the 2011 and 2015 cognitive function assessments; null or negative changes (Δ cognitive function score ≤ 0) indicated "without cognitive decline". Chi-square test, Student's t-test or Wilcoxon test were used to compare the differences between cognitive decline group and without cognitive decline group.

Logistic regression models were applied to examine the effects of air pollution change and CRP on cognitive decline, and the interaction between air pollution and CRP on cognitive decline. Both unadjusted and adjusted models were employed in the analyses. Model 0 was unadjusted, model 1 was adjusted for age, sex, birthplace and education level, Model 2 was adjusted for age, sex, birthplace, education level, smoking, cooking fuel use and heating fuel use. Spearman's correlation analysis was conducted to investigate the correlation coefficients between hs-CRP and ambient air pollutants. The effect estimates were presented as the odds ratio (OR) and 95% confidence intervals (95% CI) We further performed stratified regression analyses based on hs-CRP levels, categorizing as < 3 mg/L or ≥ 3 mg/L, to explore the potential influence of varying hs-CRP levels on the association between air pollution and cognitive decline.

Furthermore, the unadjusted and adjusted interaction regression analyses were used to examine whether the interaction effects of hs-CRP and air pollution on cognitive function. In addition, we conducted stratified regression analyses by several key covariates, including smoking status, use of cooking fuels, heating fuels, and sex, to assess their individual impacts on this relationship. Moreover, to ascertain whether hs-CRP, considered both as a continuous and categorical variable (< 3 mg/L or ≥ 3 mg/L), serves as a mediator in the relationship between air pollution exposure and cognitive decline, we employed the bootstrap method to rigorously test for this mediation effect. Data analyses were conducted using the SPSS 26.0 (Statistical Package for the Social Science, Chicago, IL, USA) and R 3.4.1 (Lucent Technologies, USA). A two-tailed P value < 0.05 was regarded as statistically significant.

Results

Demographics of the study population

The population characteristics were shown in Table 1. The individuals span across 186 villages or towns throughout the country (Fig. 2). The mean age of the population was 58.89 ± 8.64 years and 3904 participants showed impaired cognitive status. Females, individuals living in rural areas, and those with lower levels of

Table 1 Population characteristics

Characteristics	Total (*n* = 6434)	Without cognitive decline (*n* = 2530)	Cognitive decline (*n* = 3904)	*P*-value
Age, years	58.89 ± 8.64	59.37 ± 8.81	58.14 ± 8.31	< 0.001
Sex				< 0.001
Female	3404(52.91)	1405(55.53)	1999(51.20)	
Male	3030(47.09)	1125(44.47)	1905(48.80)	
Birthplace				< 0.001
Rural	4356(67.70)	1633(64.55)	2723(69.75)	
Urban	2078(32.30)	897(35.45)	1181(30.25)	
Education level				0.002
Junior high school and below	4646(72.21)	1881(74.35)	2765(70.82)	
High school and above	1788(27.79)	649(25.65)	1139(29.18)	
Sleep time per day, hours	6.00(5.00,8.00)	6.00(5.00,8.00)	6.00(5.00,8.00)	0.599
Smoking	2526(39.26)	912(36.05)	1614(41.34)	< 0.001
Cooking fuel use				0.003
Clean fuel	2557(39.74)	1063(42.02)	1494(38.27)	
Solid fuel	3877(60.26)	1467(57.98)	2410(61.73)	
Heating fuel use				< 0.001
Clean fuel	2613(40.61)	1109(43.83)	1504(38.52)	
Solid fuel	3821(59.39)	1421(56.17)	2400(61.48)	
Brain injury	147(2.28)	60(2.37)	87(2.23)	0.709
Hearing loss[a]	495(7.69)	181(7.16)	314(8.05)	0.194
Alcohol consumption				0.814
> 1 time/month	4322(67.17)	1710(67.59)	2612(66.91)	
< 1 time/month	495(7.69)	195(7.71)	300(7.68)	
Never	1617(25.13)	625(24.70)	992(25.41)	
Physical Activity[a]				0.828
0	278(4.32)	119(8.94)	159(8.87)	
1	645(10.02)	265(19.91)	380(21.21)	
2	933(14.50)	398(29.90)	535(29.85)	
3	1267(19.69)	549(41.25)	718(40.07)	
Number of chronic diseases				0.244
0	2000 (31.10)	752(29.72)	1248(31.97)	
1	1955 (30.40)	773(30.55)	1182(30.28)	
2	1297 (20.20)	522(20.63)	775(19.85)	
≥ 3	1182 (18.40)	483(19.09)	699(17.90)	
Regional Per Capita GDP(CNY)	35711.00(29608.00 , 52763.00)	33480.00(29608.00 , 51768.00)	33480.00(29608.00 , 51768.00)	0.160

Note: For continuous variables, numbers represent the mean ± standard deviation and for categorical variables, numbers represent count (percentage). [a] Starsymbol indicates missing data

education exhibited a higher proportion of cognitive decline. Lifestyles factors, such as smoking or the use of solid fuels for cooking or heating, were associated with increased cognitive decline.

Association of air pollution and cognitive decline

Numeric range of cognitive function score and the air pollutants exposure changes from 2011 to 2015 were presented in Supplementary data. Overall, the participants experienced an average decline of 1.64±4.95 points in their total cognitive function score, with particular impact observed in the areas of orienting attention (1.09±2.53 points) and episodic memory (0.5±3.89 points) (Supplementary Table 1, Supplementary Fig. 1). For the 2011 baseline, the air pollutant exposure levels were: $PM_{2.5}$ at 53.01 μg/m^3±15.08, PM_1 at 40.18 μg/m^3±13.24, PM_{10} at 93.64 μg/m^3±26.95, O_3 at 95.13 μg/m^3±6.60, and NO_2 at 29.03 μg/m^3±10.53. (Supplementary Table 2). And the general air pollutants exposure (PM_1, PM_{10} and O_3) decreased from 2011 to 2015, while $PM_{2.5}$ and NO_2 presented a slightly increase (Supplementary Table 3).

The associations between each air pollutant changes and cognitive decline are described in Fig. 3. Lower exposure to $PM_{2.5}$, PM_1, PM_{10} and NO_2 were significantly related to mitigated cognitive decline, with the OR (95% CI) for 0.934(0.925, 0.943), 0.945(0.935, 0.955), 0.977(0.972, 0.982) and 0.962(0.950, 0.975), respectively.

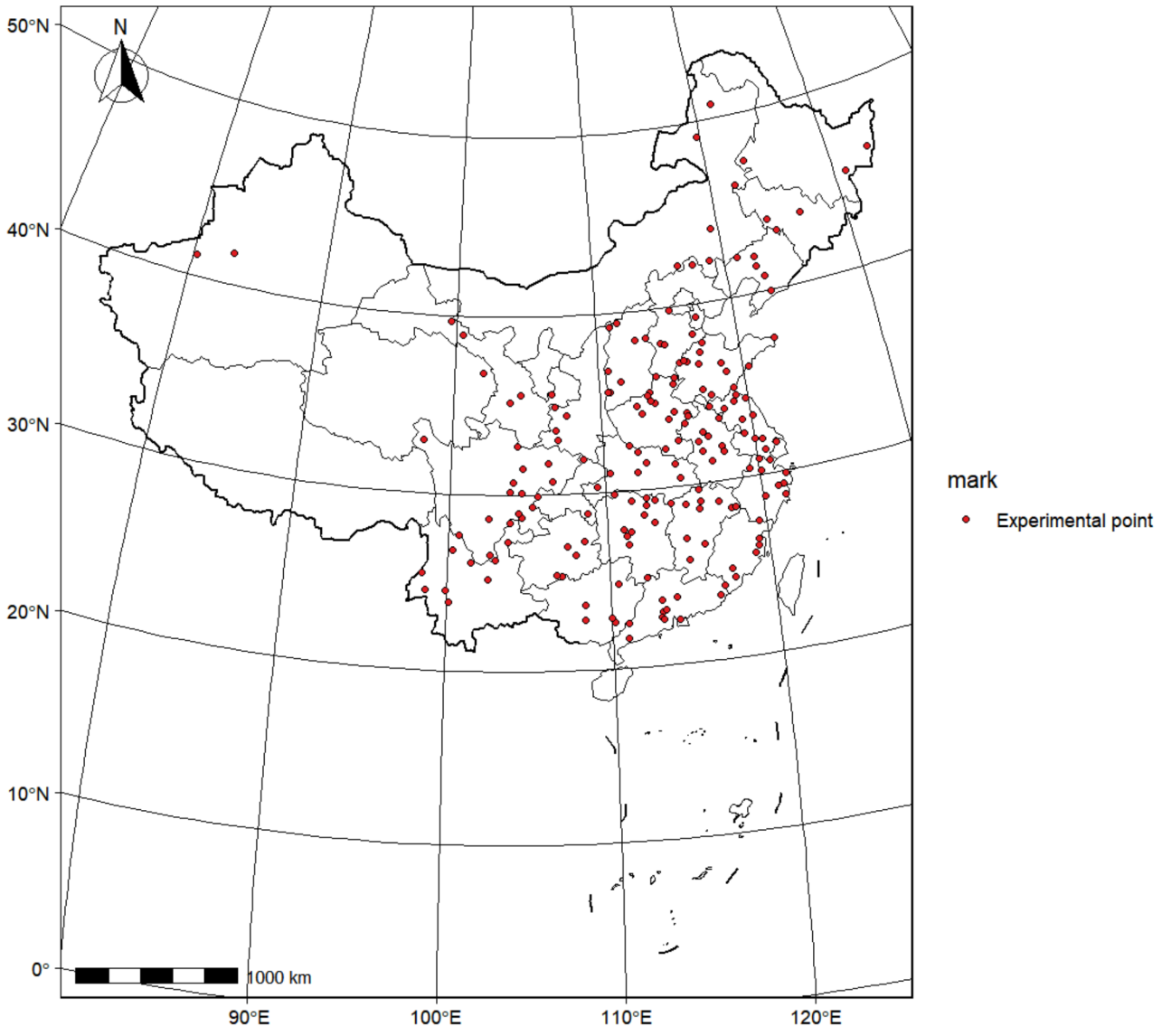

Fig. 2 The distribution map of the survey points for individuals included

Similar results were observed when adjusted for age, sex, birthplace, education level, smoking, cooking and heating fuel use. This main finding was also validated in the univariate linear regression analysis (Supplementary Table 4). However, the exposure level change of O_3 showed no relationship with cognitive decline.

Association between hs-CRP and cognitive decline, and the interaction of hs-CRP with air pollution on cognitive decline

We did not observe any statistical significance between hs-CRP and cognitive decline (Supplementary Table 5), nor find a statistical correlation between air pollution exposure changes and hs-CRP (Supplementary Table 6). No significant interactions of hs-CRP and air pollutants changes on cognitive decline were observed, the OR (95%CI) for hs-CRP with $\Delta PM_{2.5}$, ΔPM_1, ΔPM_{10} and ΔO_3 were 1.001([0.999,1.002] P=0.331), 1.001([0.999,1.002] P=0.568), 1.000([1.000,1.001] P=0.304) and 0.999([0.998,1.001] P=0.304), respectively, as well as in the adjusted model for age, sex, birthplace, education level, smoking, cooking and heating fuel use. Levels of hs-CRP appeared to have slightly interactive association with ΔNO_2 on cognitive decline (OR: 1.002, (95% CI: 1.000, 1.004). However, this association was nullified in when adjusted for age, sex, birthplace, education level, smoking, cooking and heating fuel use (P=0.055). (Supplementary Table 5)

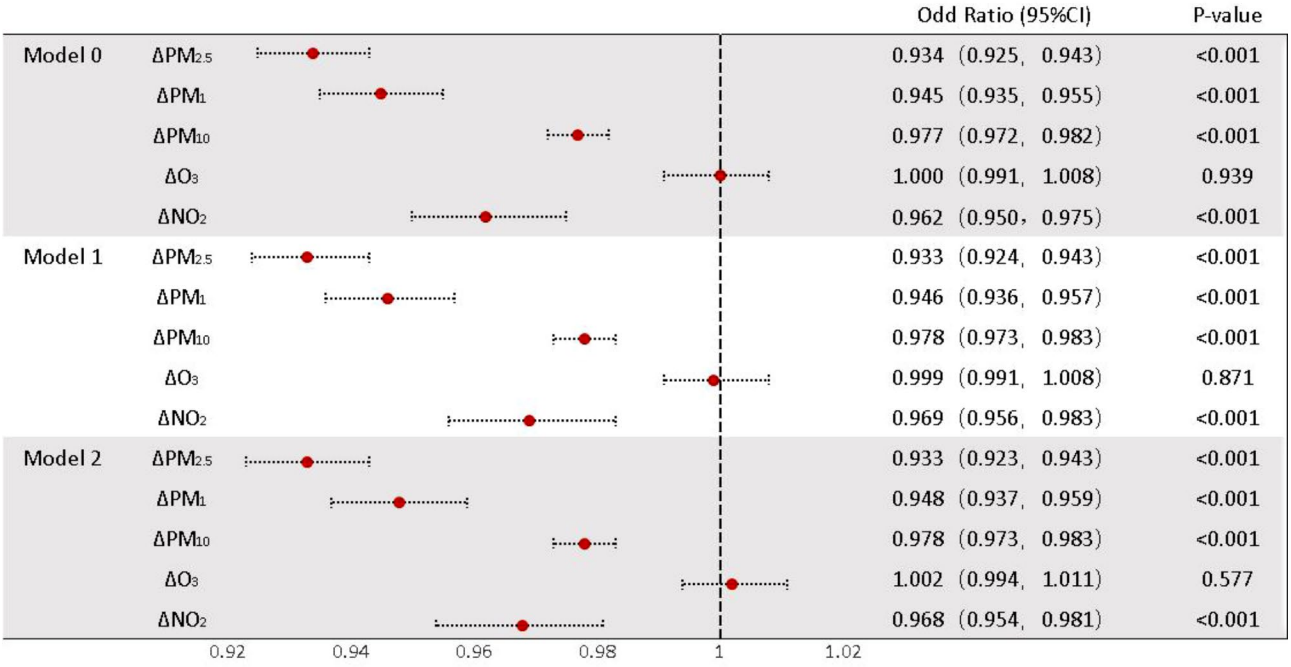

Fig. 3 Association of air pollutants changes from 2011 to 2015 with cognitive decline. Model 0 are unadjusted (no covariates). Model 1 adjusted for age, sex, birthplace and education level. Model 2 adjusted for age, sex, birthplace, education level, smoking, cooking fuel use and heating fuel use

Table 2 The mediating role of hs-CRP on the relationship between air pollution and cognitive decline

	hs-CRP(continuous)		hs-CRP(categorical ≥ 3 mg/L)	
	OR-(95%CI)	***P*-value**	**OR-(95%CI)**	***P*-value**
$\Delta PM_{2.5}$*hs-CRP				
Indirect	1.000 (1.000, 1.000)	0.480	1.000 (1.000, 1.000)	0.990
Direct	0.984 (0.981, 0.990)	< 0.001	0.984 (0.981, 0.990)	< 0.001
ΔPM_1*hs-CRP				
Indirect	1.000 (1.000, 1.000)	0.230	1.000 (1.000, 1.000)	0.920
Direct	0.987 (0.984, 0.990)	< 0.001	0.987 (0.984, 0.990)	< 0.001
ΔPM_{10}*hs-CRP				
Indirect	1.000 (1.000, 1.000)	0.650	1.000 (1.000, 1.000)	0.930
Direct	0.995 (0.994, 1.000)	< 0.001	0.995 (0.994, 1.000)	< 0.001
ΔO_3*hs-CRP				
Indirect	1.000 (1.000, 1.000)	0.470	1.000 (1.000, 1.000)	0.950
Direct	1.000 (0.998, 1.000)	0.940	1.000 (0.998, 1.000)	0.960
ΔNO_2*hs-CRP				
Indirect	1.000 (1.000, 1.000)	0.830	1.000 (1.000, 1.000)	0.960
Direct	0.991 (0.987, 0.990)	< 0.001	0.991 (0.987, 0.990)	< 0.001

The interaction of hs-CRP with air pollution on cognitive decline among different population

We observed that decreased exposure of $PM_{2.5}$, PM_1, PM_{10} and NO_2 were more likely to alleviate cognitive decline, independent of stratified hs-CRP level. Exposure to O_3 showed no association with cognitive decline stratified by different hs-CRP level. (Supplementary Fig. 2)

When further stratified by the sex, smoking, cooking and heating fuel use analyses, no significant interactions was observed between hs-CRP and $\Delta PM_{2.5}$, ΔPM_1, ΔPM_{10} and ΔO_3 on cognitive decline. However, a significant interaction of CRP with ΔNO_2 on cognitive decline was found in male and population cooking or heating using solid fuels. (Supplementary Table 7)

The mediating role of hs-CRP on the relationship between air pollution and cognitive decline

The bootstrap test results for mediation analysis are shown in Table 2. No significant mediating effect of hs-CRP on the relationship between air pollution and cognitive decline was observed, and the indirect effect of hs-CRP with any of the air pollutants was non-significant:

$\Delta PM_{2.5}$-P=0.480, ΔPM_1-P=0.230, ΔPM_{10}-P=0.650, ΔO_3-P=0.470, ΔNO_2-P=0.830. Meanwhile, the negative effect persisted when the hs-CRP was further analyzed as a categorical variable (≥3 mg/L) (Table 2).

Discussion

This study presents the first nation-wide comprehensive assessment of the association between ambient air pollution, inflammation and cognitive changes among Chinese middle-aged and older adults. We found that exposure to $PM_{2.5}$, PM_1, PM_{10} and NO_2 were significantly associated with the cognitive function, improving air pollution exposure could alleviate cognitive decline. Hs-CRP showed no direct significant correlation with cognitive decline or air pollution exposure level in our present study. The association between air pollution and cognitive decline was independent of hs-CRP level.

Studies have linked air pollution with cognitive decline but with contrasting findings as regarded to different pollutants and population. One Swedish National study on Aging and Care in Kungsholmen found an inverted U-shape relationship between $PM_{2.5}$ and cognitive decline, low to mean $PM_{2.5}$ levels were associated with higher risk of accelerated cognitive decline [29]. Tzivian et al. reported a significant dose-dependent relationship between chronic exposure to $PM_{2.5}$ and the likelihood of mild cognitive impairment, noting a 16% heightened risk [30]. A community health study of California, US for individuals≥45 years of age showed verbal fluency worsened by 21% as increase in $PM_{2.5}$ per 10 μg/m^3, while verbal fluency and executive function worsened by 19% with increase in O_3 every 10 ppb [31]. A cohort study in England (aged 50–79 years) found a positive exposure-response relationship between dementia and $PM_{2.5}$, NO_2, but not O_3 [32]. Zhejiang Major Public Health Surveillance (ZJMPHS) in China (7,311 participants, aged≥60 years) demonstrated that encounters with $PM_{2.5}$, PM_{10}, and sulfur dioxide (SO_2) are associated with a modest yet significant elevation in cognitive impairment risk, ranging from 3 to 4%. However, no such association was observed with nitrogen dioxide (NO_2), ozone (O_3), or the overall air quality index [33]. Our study also found a significant association between air pollution changes and cognitive decline which is consistent with previous findings. Particulate matter exposure seemed to be more certainly associated with cognitive decline regardless of their country of origin or age group, following by NO_2, but not with O_3. While the effect of O_3 exposure on cognitive function remained inconclusive, more population-based study will be needed.

Inflammation has been considered as a risk factor for neurodegenerative and cognitive changes in the aging population. Certain population studies have revealed a noteworthy association between CRP or hs-CRP and cognitive function, including recognition memory and visuospatial impairment [34, 35]. Systematic reviews have consistently indicated that elevated concentrations of CRP are linked to an elevated risk of cognitive impairment [36]. Inflammatory markers like CRP can prospectively predict poorer cognitive function and faster cognitive decline over time [37]. However, other studies demonstrated a minor or virtually nonexistent association between CRP and cognitive function [38, 39]. Meanwhile, study also have noted that CRP only affects the memory function performance [40]. Higher baseline hs-CRP or CRP levels are associated with poorer memory function or elevated risk of cognitive memory decline [41–43]. In this study, a high hs-CRP level did not show a significant increase in the risk of cognitive decline among the middle-aged and older population exposed to air pollution. The inconsistency in these results may be attributed to variations in the characteristics of the studied populations and the diverse methods employed to assess cognitive function across studies. However, this raises speculation that hs-CRP levels may not influence the association between cognitive decline and air pollution.

A previous study found that short-term exposure to $PM_{2.5}$ was associated with higher circulating CRP, a 5 μg/m3 increase in the 5-day moving average of fine $PM_{2.5}$ was linked to a 4.2% increase in circulating CRP [17]. While other studies also indicated negative relation for $PM_{2.5}$ and NO_2 exposure with CRP or hs-CRP [18, 19]. Our study revealed no significant association between the baseline level of hs-CRP and changes in exposure concentrations of any air pollutants. Given the complexity and continual fluctuations in both inflammation states and air pollution exposure, it becomes challenging to establish a clear relationship between them over the long-term. Different pollutants may induce distinct alterations in specific inflammation markers.

Meanwhile, hs-CRP played no modification or mediating role in the relationship between ambient air pollution exposure and cognitive decline in this study. This finding partially aligns with another study utilizing the CHARLS dataset, indicating a significant relationship between solid fuel use and white blood cell (WBC) levels, but not with hs-CRP. Moreover, hs-CRP did not serve as a mediator in the association between solid fuel use and outcomes related to depression or cognition [44]. Another longitudinal study from China reported that low cognitive function was linked to an elevated risk of all-cause mortality independently of hs-CRP concentration. However, it was noted that in males, there was an increased risk of all-cause mortality [45], suggesting that hs-CRP may not exacerbate cognitive decline, but gender could play a significant role. Stratified analyses revealed significant interactions for ΔNO_2 with hs-CRP only in males and the population using solid fuels. This suggests that

being male and using solid fuels might be the primary factors influencing the relationship between NO_2 exposure and cognitive decline, irrespective of hs-CRP levels. Therefore, it is reasonable to conclude that the association between air pollution and cognitive decline appears to be independent of hs-CRP levels. In the presence of underlying ambient air pollution, systemic inflammation may not directly mediate or facilitate cognitive decline.

Given the intricate pathological mechanisms involved in cognitive decline, pinpointing the key factors responsible for cognitive changes related to underlying air pollution exposure poses a considerable challenge. Studies have documented that exposure to $PM_{2.5}$ induces mitochondrial dysfunction, neuronal and neurovascular dysfunction, along with elevated levels of amyloid beta and tau phosphorylation. These factors may contribute to the development of Alzheimer's disease. Further, oxidative stress and the oxidative stress-sensitive transient receptor potential melastatin 2(TRPM2) channel play important roles in the process [46]. $PM_{2.5}$ particles generate reactive oxygen species, leading to oxidative damage in the central nervous system, ultimately accelerating cognitive dysfunction [47]. Studies also have brought up that genetic status can modify the effect of air pollution on cognitive function, such as polymorphisms in apolipoprotein E allele (ApoE4 variants) and hemochromatosis gene (HFE C282Y variant) [4]. Perhaps these findings may provide us with some valuable insights for future research endeavors.

There are also some limitations in our study. Firstly, due to limited data availability, only baseline hs-CRP data were utilized in the analysis. Given the variability of inflammation across different states, it is crucial to acknowledge that a single phase of inflammation may not capture the entire long-term process. Future studies may benefit from considering changes in inflammation and incorporating longer follow-up periods. Additionally, while hs-CRP is considered one of the better markers of inflammation, including other inflammatory indicators such as WBC and interleukin would enhance the robustness of the conclusions.

In conclusion, our study revealed an association between long-term ambient air pollution exposure and cognitive decline in Chinese middle-aged and older adults. As air quality improved, cognitive decline showed varying degrees of mitigation across different air pollutants. Importantly, we did not observe a significant association between the inflammation marker hs-CRP and cognitive decline, nor with changes in air pollution exposure levels. The link between air pollution and cognitive decline appeared independent of hs-CRP levels. This may give us some hints that systemic inflammation alone might not be solely responsible for, or might not significantly exacerbate, the progression of cognitive decline in individuals who have been exposed to prolonged air pollution. There may be other factors at play in this intricate process.

Abbreviations

CHARLS	China Health and Retirement Longitudinal Study
PM_1	Particles with diameters ≤ 1.0 μm
$PM_{2.5}$	Particles with diameters ≤ 2.5 μm
PM_{10}	Particles with diameters ≤ 10 μm
NO_2	Nitrogen dioxide
O_3	Ozone
CHAP	China High Air Pollutants
CRP	C-reactive protein
hs-CRP	Hypersensitive C-reactive protein
OR	Odds ratio
CI	Confidence intervals
WHO	World Health Organization
CNS	Central nervous system
AD	Alzheimer's disease
TSPO	Translocator protein
IL	Interleukin
TICS	Telephonic interview for assessing their cognitive status
CDC	Center for Disease Control
ZJMPHS	Zhejiang Major Public Health Surveillance
WBC	White blood cell
TRPM2	Transient receptor potential melastatin 2
GDP	Gross Domestic Product

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-024-01148-1.

Supplementary Material 1

Acknowledgements

The authors acknowledge all the participants and administrators of this study.

Author contributions

Li Huang and Xiangming Hu contribute equally to this article and guide the study design and the final data analysis. Jia Liu contributes to the data collection and arrangement. Li Huang and Jiajia Wang draft the article. Yingling Zhou and Guang Li help with the study design and article revision. Haojian Dong and Guanghui Dong take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors reviewed the manuscript.

Funding

This research was supported by the National Natural Science Foundation of China (82373529, 82170259), the Natural Science Foundation of Guangdong Province (2024A1515012943, 2023A1515010801), Science and Technology Project of Tibet Autonomous Region (No.XZ202201ZY0051G).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by Ethics Review Committee of Peking University. All subjects provided informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 19 March 2024 / Accepted: 22 November 2024
Published online: 20 December 2024

Refrences

1. Prince M. World Alzheimer report 2015: the global impact of dementia. 2015.
2. Cao L, Zhao Z, Ji C, Xia Y. Association between solid fuel use and cognitive impairment: a cross-sectional and follow-up study in a middle-aged and older Chinese population. Environ Int. 2021;146:106251. https://doi.org/10.1016/j.envint.2020.106251.
3. Krishnamoorthy Y, Rajaa S, Ramasubramani P, Saya GK. Association between indoor air pollution and cognitive function among nationally representative sample of middle-aged and older adults in India-A multilevel modelling approach. Indoor Air. 2022;32(1):e12929. https://doi.org/10.1111/ina.12929.
4. Chandra M, Rai CB, Kumari N, Sandhu VK, Chandra K, Krishna M, et al. Air Pollution and Cognitive Impairment across the life course in humans: a systematic review with specific focus on Income Level of Study Area. Int J Environ Res Public Health. 2022;19(3):1405. https://doi.org/10.3390/ijerph19031405.
5. Hahad O, Lelieveld J, Birklein F, Lieb K, Daiber A, Münzel T. Ambient air Pollution increases the risk of Cerebrovascular and Neuropsychiatric disorders through induction of inflammation and oxidative stress. Int J Mol Sci. 2020;21(12):4306. https://doi.org/10.3390/ijms21124306.
6. Jin R, Chan AKY, Wu J, Lee TMC. Relationships between inflammation and age-related neurocognitive changes. Int J Mol Sci. 2022;23(20):12573. https://doi.org/10.3390/ijms232012573.
7. Li Y, Zhong X, Cheng G, Zhao C, Zhang L, Hong Y, et al. Hs-CRP and all-cause, cardiovascular, and cancer mortality risk:a meta-analysis. Atherosclerosis. 2017;259:75–82. https://doi.org/10.1016/j.atherosclerosis.2017.02.003.
8. Strandberg TE, Tilvis RS, C-Reactive Protein, Arteriosclerosis. Thromb Vascular Biology. 2000;20(4):1057–60. https://doi.org/10.1161/01.atv.20.4.1057.
9. Darweesh SKL, Wolters FJ, Ikram MA, de Wolf F, Bos D, Hofman A. Inflammatory markers and the risk of dementia and Alzheimer's disease: a meta-analysis. Alzheimer's Dementia: J Alzheimer's Association. 2018;14(11):1450–9. https://doi.org/10.1016/j.jalz.2018.02.014.
10. Xu G, Zhou Z, Zhu W, Fan X, Liu X. Plasma C-reactive protein is related to cognitive deterioration and dementia in patients with mild cognitive impairment. J Neurol Sci. 2009;284(1–2):77–80. https://doi.org/10.1016/j.jns.2009.04.018.
11. O'Bryant SE, Waring SC, Hobson V, Hall JR, Moore CB, Bottiglieri T, et al. Decreased C-reactive protein levels in Alzheimer disease. J Geriatr Psychiatr Neurol. 2010;23(1):49–53. https://doi.org/10.1177/0891988709351832.
12. Nilsson K, Gustafson L, Hultberg B. C-reactive protein level is decreased in patients with Alzheimer's disease and related to cognitive function and survival time. Clin Biochem. 2011;44(14–15):1205–8. https://doi.org/10.1016/j.clinbiochem.2011.07.011.
13. Park JK, Lee KJ, Kim JY, Kim H. The Association of blood-based inflammatory factors IL-1β, TGF-β and CRP with cognitive function in Alzheimer's disease and mild cognitive impairment. Psychiatry Invest. 2021;18(1):11–8. https://doi.org/10.30773/pi.2020.0205.
14. Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, Van Swieten JC, et al. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. Arch Neurol. 2004;61(5):668–72. https://doi.org/10.1001/archneur.61.5.668.
15. He S, Klevebro S, Baldanzi G, Pershagen G, Lundberg B, Eneroth K, et al. Ambient air pollution and inflammation-related proteins during early childhood. Environ Res. 2022;215(Pt 2):114364. https://doi.org/10.1016/j.envres.2022.114364.
16. Pope CA 3rd, Bhatnagar A, McCracken JP, Abplanalp W, Conklin DJ, O'Toole T. Exposure to fine Particulate Air Pollution is Associated with Endothelial Injury and systemic inflammation. Circ Res. 2016;119(11):1204–14. https://doi.org/10.1161/CIRCRESAHA.116.309279.
17. Li W, Dorans KS, Wilker EH, Rice MB, Ljungman PL, Schwartz JD, et al. Short-term exposure to Ambient Air Pollution and biomarkers of systemic inflammation: the Framingham Heart Study. Arterioscler Thromb Vasc Biol. 2017;37(9):1793–800. https://doi.org/10.1161/ATVBAHA.117.309799.
18. Fandiño-Del-Rio M, Kephart JL, Williams KN, Malpartida G, Boyd Barr D, Steenland K, et al. Household air pollution and blood markers of inflammation: a cross-sectional analysis. Indoor Air. 2021;31(5):1509–21. https://doi.org/10.1111/ina.12814.
19. Midouhas E, Kokosi T, Flouri E. Neighbourhood-level air pollution and greenspace and inflammation in adults. Health Place. 2019;58:102167. https://doi.org/10.1016/j.healthplace.2019.102167.
20. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). Int J Epidemiol. 2014;43(1):61–8. https://doi.org/10.1093/ije/dys203.
21. Mo S, Wang Y, Peng M, Wang Q, Zheng H, Zhan Y, et al. Sex disparity in cognitive aging related to later-life exposure to ambient air pollution. Sci Total Environ. 2023;886:163980. https://doi.org/10.1016/j.scitotenv.2023.163980.
22. Tahami Monfared AA, Hummel N, Chandak A, Khachatryan A, Zhang R, Zhang Q. Prevalence Estimation of Dementia/Alzheimer's Disease using Health and Retirement Study Database in the United States. J Prev Alzheimers Dis. 2024;11(5):1183–8. https://doi.org/10.14283/jpad.2024.114.
23. Zhao Y, Strauss J, Yang G, Giles J, Hu P, Hu Y et al. China Health and Retirement Longitudinal Study 2011–2012 National Baseline Blood Data Users' Guide, 2013; 1–56.
24. Han S, Zhang F, Yu H, Wei J, Xue L, Duan Z, et al. Systemic inflammation accelerates the adverse effects of air pollution on metabolic syndrome: findings from the China health and Retirement Longitudinal Study (CHARLS). Environ Res. 2022;215(Pt 1):114340. https://doi.org/10.1016/j.envres.2022.114340.
25. Jiang H, Zhang S, Yao X, Meng L, Lin Y, Guo F, et al. Does physical activity attenuate the association between ambient PM2.5 and physical function? Sci Total Environ. 2023;874:162501. https://doi.org/10.1016/j.scitotenv.2023.162501.
26. Chen G, Li S, Knibbs LD, Hamm N, Cao W, Li T, et al. A machine learning method to estimate PM2.5 concentrations across China with remote sensing, meteorological and land use information. Sci Total Environ. 2018;636:52–60. https://doi.org/10.1016/j.scitotenv.2018.04.251.
27. Chen G, Wang Y, Li S, Cao W, Ren H, Knibbs LD et al. 2018. Spatiotemporal patterns of PM10 concentrations over China during 2005–2016: a satellite-based estimation using the random forests approach. Environ. Pollut.2018; 242 (Pt A): 605–613.https://doi.org/10.1016/j.envpol.2018.07.012
28. Chen G, Chen J, Dong G, Yang B, Liu Y, Lu T, et al. Improving satellitebased estimation of surface ozone across China during 2008–2019 using iterative random forest model and high-resolution grid meteorological data. Sustain Cities Soc. 2021;69:102807. https://doi.org/10.1016/j.scs.2021.102807.
29. Grande G, Wu J, Ljungman PL, Stafoggia M, Bellander T, Rizzuto D. Long-term exposure to PM2.5 and Cognitive decline: a Longitudinal Population-based study. J Alzheimers Dis. 2021;80(2):591–9. https://doi.org/10.3233/JAD-200852.
30. Tzivian L, Dlugaj M, Winkler A, Hennig F, Fuks K, Sugiri D, et al. Long-term air pollution and traffic noise exposures and cognitive function:a cross-sectional analysis of the Heinz Nixdorf Recall study. J Toxicol Environ Health A. 2016;79(22–23):1057–69. https://doi.org/10.1080/15287394.2016.1219570.
31. Ilango SD, Gonzalez K, Gallo L, Allison MA, Cai J, Isasi CR, et al. Long-term exposure to Ambient Air Pollution and cognitive function among Hispanic/Latino adults in San Diego, California. J Alzheimers Dis. 2021;79(4):1489–96. https://doi.org/10.3233/JAD-200766.
32. Carey IM, Anderson HR, Atkinson RW, Beevers SD, Cook DG, Strachan DP, et al. Are noise and air pollution related to the incidence of dementia? A cohort study in London, England. BMJ Open. 2018;8(9):e022404. https://doi.org/10.1136/bmjopen-2018-022404.
33. He F, Tang JJ, Zhang T, Lin J, Li F, Gu X, et al. Impact of Air Pollution on Cognitive Impairment in Older people: a Cohort Study in Rural and Suburban China. J Alzheimers Dis. 2020;77(4):1671–9. https://doi.org/10.3233/JAD-200587.
34. Noble JM, Manly JJ, Schupf N, Tang MX, Mayeux R, Luchsinger JA. Association of C-reactive protein with cognitive impairment. Arch Neurol. 2010;67(1):87–92. https://doi.org/10.1001/archneurol.2009.308.

35. Bettcher BM, Wilheim R, Rigby T, Green R, Miller JW, Racine CA, et al. C-reactive protein is related to memory and medial temporal brain volume in older adults. Brain Behav Immun. 2012;26(1):103–8. https://doi.org/10.1016/j.bbi.2011.07.240.
36. Kuo HK, Yen CJ, Chang CH, Kuo CK, Chen JH, Sorond F. Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis. Lancet Neurol. 2005;4(6):371–80. https://doi.org/10.1016/S1474-4422(05)70099-5.
37. Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology. 2003;61(1):76–80. https://doi.org/10.1212/01.wnl.0000073620.42047.d7.
38. Alley DE, Crimmins EM, Karlamangla A, Hu P, Seeman TE. Inflammation and rate of cognitive change in high-functioning older adults. J Gerontol Biol Sci Med Sci. 2008;63(1):50–5. https://doi.org/10.1093/gerona/63.1.50.
39. Dik MG, Jonker C, Hack CE, Smit JH, Comijs HC, Eikelenboom P. Serum inflammatory proteins and cognitive decline in older persons. Neurology. 2005;64(8):1371–7. 10.1212/01.WNL.0000158281.08946.68.
40. Bai A, Shi H, Huang X, Xu W, Deng Y. Association of C-Reactive Protein and motoric cognitive risk syndrome in Community-Dwelling older adults: the China Health and Retirement Longitudinal Study. J Nutr Health Aging. 2021;25(9):1090–5. https://doi.org/10.1007/s12603-021-1678-3.
41. Laurin D, David Curb J, Masaki KH, White LR, Launer LJ. Midlife C-reactive protein and risk of cognitive decline: a 31-year follow-up. Neurobiol Aging. 2009;30(11):1724–7. https://doi.org/10.1016/j.neurobiolaging.2008.01.008.
42. Komulainen P, Lakka TA, Kivipelto M, Hassinen M, Penttilä IM, Helkala EL, et al. Serum high sensitivity C-reactive protein and cognitive function in elderly women. Age Ageing. 2007;36(4):443–8. https://doi.org/10.1093/ageing/afm051.
43. Watanabe Y, Kitamura K, Nakamura K, Sanpei K, Wakasugi M, Yokoseki A, et al. Elevated C-Reactive protein is Associated with Cognitive decline in outpatients of a General Hospital: the Project in Sado for Total Health (PROST). Dement Geriatric Cogn Disorders Extra. 2016;6(1):10–9. https://doi.org/10.1159/000442585.
44. Du X, Li X, Qian P, Wu H. Indoor air pollution from solid fuels use, inflammation, depression and cognitive function in middle-aged and older Chinese adults. J Affect Disord. 2022;319:370–6. https://doi.org/10.1016/j.jad.2022.09.103.
45. Zipperer MB, Churilla JR, Stapleton JN, Richardson MR. Joint effect of cognitive function and C-reactive protein on all-cause mortality risk: 1999–2002 NHANES. Ann Epidemiol. 2022;74:111–7. https://doi.org/10.1016/j.annepidem.2022.07.003.
46. Wang L, Wei LY, Ding R, Malko P, Syed Mortadza SA, Wu W, et al. Predisposition to Alzheimer's and Age-related brain pathologies by PM2.5 exposure: perspective on the roles of oxidative stress and TRPM2 Channel. Front Physiol. 2020;11:155. https://doi.org/10.3389/fphys.2020.00155.
47. Moulton PV, Yang W. Air pollution, oxidative stress, and Alzheimer's disease. J Environ Public Health. 2012;2012:472751. https://doi.org/10.1155/2012/472751.

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