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Impact of airborne particulate matter exposure on hospital admission for Alzheimer's disease and the attributable economic burden: evidence from a time-series study in Sichuan, China

Xi Yang[1], Wanyanhan Jiang[1], Xi Gao[1], Yi He[1], Chenwei Lin[1], Jiushun Zhou[2*] and Lian Yang[1*]

Abstract

Background Alzheimer's disease (AD) and other forms of dementia are the seventh leading cause of death. Studies discern the inclusion of air pollution among modifiable risk factors for dementia, while limited studies are for China. This study aims to examine the short-term association between airborne particulate matter (PM) and the hospitalizations of AD, including the economic costs in China.

Methods A total of 4975 cases of AD patients hospitalized from 2017 to 2019, were collected from nine city and 411 medical institutions in Sichuan Province, China. Data on air pollutants such as $PM_{2.5}$, PM_{10}, and NO_2 were obtained from 183 air quality monitoring stations in Sichuan Province. A time series-generalized additive model was used to estimate the association between short-term exposure to PM (lag1–lag7 and moving average lag01–lag07) and AD hospital admissions (HAs), stratified by gender, age, and season.

Results Positive short-term exposure to airborne PM was found for the HAs of AD. The greatest effect on the number of AD inpatients was on single-day lag1 ($PM_{2.5}$:1.034 (95% confidence interval (CI) 1.011, 1.058)). The association was also significant in the two-pollutant model. In the study period, 16.48% of AD HAs were attributed to the effect of PM. The total economic costs of AD attributable to PM exposure were US$ 2.56 million, including US$ 2.25 million of direct medical costs and US$ 0.31 million of indirect economic costs.

Conclusions This study suggests that short-term exposure to airborne PM may increase the risk of AD HAs in Sichuan Province and result in associated economic costs.

Keywords Alzheimer's disease, Air pollution, Hospital admissions, Economic burden

Introduction

Alzheimer's disease (AD) has an insidious onset and is a progressive, irreversible neurodegenerative disease affecting cognition, function, and behavior [1]. As the most common cause of dementia, it accounts for 60–70% of all dementia cases [2]. According to the World Health Organization (WHO) report 2021, the population with AD and other forms of dementia is expected to rise to 78 million by 2030 and to 139 million by 2050 [3]. China

*Correspondence:
Jiushun Zhou
zzzzjs@hotmail.com
Lian Yang
yyanglian@163.com
[1] HEOA Group, School of Public Health, Chengdu University of Traditional Chinese Medicine, No. 1166 Liutai Road, Chengdu 611137, China
[2] Sichuan Center for Disease Control and Prevention, Chengdu 610041, China

has the largest population of AD patients in the world [4], and the number will continue to increase with extended life expectancy and population aging. A recent study has indicated that 9.83 million people aged 60 years and older in China have AD [5], and the number is expected to increase to over 16 million by 2030 [6]. AD and other dementia are currently the seventh leading cause of death in the world, and also are among the top 10 causes of disability-adjusted life years (DALYs) occurring in people aged 75 years and older [7]. At present, AD has become the fifth leading cause of death for urban and rural residents in China [8], and is listed as one of the "four killers" threatening the health of the elderly, posing a huge challenge to social and economic development.

The global cost of AD and other dementia is about $1 trillion per year [9]. It is estimated that these costs will increase to 1.7 trillion USD by 2030 [3]. Researchers have predicted that the economic burden of disease attributable to AD in China will increase from 91 billion yuan in 2010 to 332 billion yuan in 2050 [10]. However, the current rate of AD diagnosis and treatment is low compared to its high prevalence [11], meaning that the actual number of AD patients is probably much higher. Meanwhile, there is still no treatment that can alter the progression of AD [12]. Therefore, it is necessary to employ effective prevention and control strategies to address the potential risk factors, reduce the number of AD patients, improve their life quality, and thus alleviate the associated social and economic burden.

AD has a wide range of etiologies, and notably, there is growing evidence for association between AD and air pollution. Livingston et al. included air pollution as one of the new modifiable risk factors [9]. Scientific evidence from experimental studies suggests that acute particulate matter exposure typically has two pathways to brain. A fraction of particles that deposit in the nose (nasal deposition) can reach the brain via uptake over the nasal epithelium and retrograde axonal transport along the olfactory nerve. The other is that deposited in the lower respiratory tract (alveolar deposition) can translocate from the alveoli into the blood and subsequently over the blood–brain barrier into the brain. Then this process is associated with the development of AD through mechanisms such as oxidative stress, mitochondrial dysfunction, microglia activation and neuroinflammation, accelerating emergency hospital admissions for normal person or AD patients through these pathways [13–16]. At present, many studies worldwide have analyzed the relationship between long-term exposure to airborne PM and the incidence of AD. Studies in several countries [17, 18] and multiple regions of China1 [19–21] have confirmed that long-term exposure to $PM_{2.5}$ and PM_{10} increases the risk of AD. However, evidence for a short-term association between AD hospitalizations and particulate matter remains limited. In Madrid, a time-series study found that short-term exposure to $PM_{2.5}$ was associated with emergency hospitalizations for AD with a relative risk (RR) of 1.38 (95% confidence interval (95% CI) 1.15, 1.65) [22]. An ecological study from an aged European metropolis also reported that short-term exposure to $PM_{2.5}$ was associated with emergency hospital admissions for AD, reporting that for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations is linked with the increasing rate of AD admission by 3.75% (95% CI 1.91,5.63) [23]. The above studies justify the plausibility of testing the short-term effects of air pollution on the occurrence of Alzheimer's disease in humans. Therefore, more research is urgently needed to explore whether short-term exposure to PM increases the risk of AD.

Sichuan Province, located in southwestern China, consists of the Sichuan Basin (SCB) and the Western Sichuan Plateau. Highly industrialized and/or urbanized cities in the basins and mountains often experience severe air pollution; thus, the SCB is also known as one of the four most polluted areas in China [24]. The complex topography forms a unique weather system in the region [25, 26], which, coupled with accelerated urbanization and industrialization, results in the severe PM pollution in the SCB region. Therefore, a time-series design was applied in this study to explore the association between short-term exposure to airborne PM and the number of AD inpatients based on statistics of AD hospital admission (HAs) from January 1, 2017, to December 31, 2019, collected from 411 medical institutions in Sichuan Province, China, and to estimate the economic loss of disease attributable to airborne PM exposure.

Material and methods

Study population

This study collected the residential addresses, dates of admission and discharge, hospital charges, and disease diagnoses of AD-related inpatient cases from January 1, 2017, to December 31, 2019, in nine cities in Sichuan Province, namely, Chengdu, Guang'an, Luzhou, Mianyang, Meishan, Nanchong, Yibin, Zigong, and Liangshan Yi Autonomous Prefecture. Among them, Liangshan Yi Autonomous Prefecture is located in the Western Sichuan Plateau, while the other eight cities are located in the SCB. The International Classification of Diseases, tenth edition code (ICD-10) G30 was used to identify the AD cases diagnosed in 2017–2019, and a total of 411 hospitals and 4975 AD patients were covered after excluding cases with missing residential addresses.

Environment data

Based on the residential addresses of cases in the database, latitude and longitude were matched using the Gaode Map Application Programming Interface (API) and R software version 4.1.2 (https://lbs.amap.com/). The daily mean data on the concentrations of air pollutants ($PM_{2.5}$, PM_{10}, CO, SO_2, NO_2, and O_3) from January 1, 2017, to December 31, 2019, were obtained from 183 air quality monitoring stations in Sichuan Province. To adjust the effect of meteorological factors on the number of AD inpatients, meteorological data on average daily temperature and relative humidity were also collected. The geographical locations of the air quality monitoring stations and hospitals involved in this study are shown in Fig. 1.

Statistical analysis

Effects of air pollutants on AD HAs

Based on the number of days of HAs and monitoring station data for each AD case, the inverse distance (1/d2) weighted average of concentration at all monitoring stations was used to estimate air pollutant exposure on the day of HAs (lag0) [27]. The day of the AD-related HAs was defined as lag0, with the day before the episode being defined as lag1, and so on. Single-day lagged exposures (lag1–lag7) and moving average daily lagged exposures (lag01–lag07) were identified as time windows to estimate the immediate, delayed, or extended effects of pollutants [28]. Since the daily number of hospitalizations for AD usually obeys an over-dispersed Poisson distribution, a quasi-Poisson generalized additive model (GAM) was adopted in this study [29, 30]. This study analyzed the associations between the two air pollutants ($PM_{2.5}$, PM_{10}) and the daily average number of hospitalized for AD with single-day lags from the current day (lag0) and each 1–7 days and moving average exposure of multiple days (lag01–lag07). In the GAM model, a smoothing spline function was selected to control the confounding effects of the long-term trend and meteorological factors (on average daily temperature and relative humidity). Its lag effect is the same as that of air pollutants, yielding the following equation:

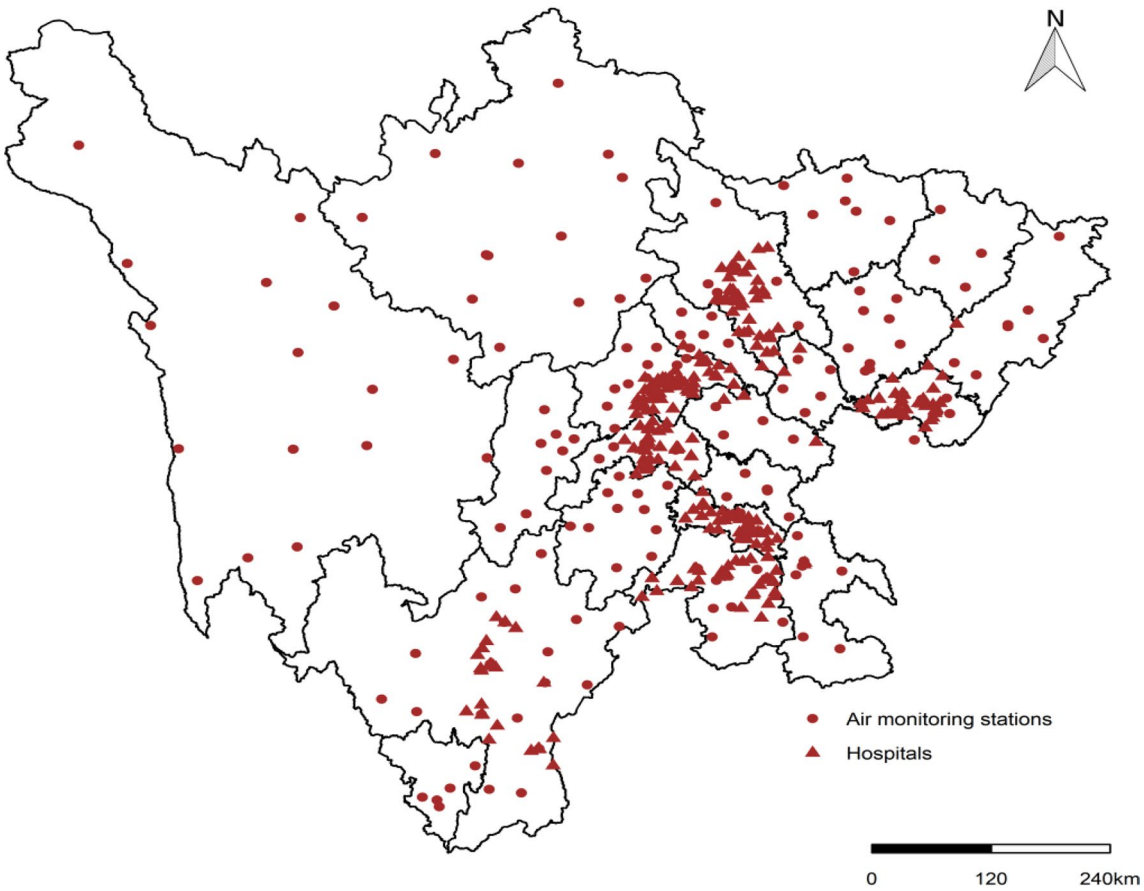

Fig. 1 Locations of air quality monitoring stations and hospitals in Sichuan Province, China

$$\begin{aligned} Log(E(Y_i)) = \alpha + \beta Zi + s(time, k = df + 1) \\ + s(temperature, k = df + 1) \\ + s\left(humidity, k = df + 1\right) \\ + as.factor(dow) \end{aligned} \quad (1)$$

where E (Yi) is the expected number of hospitalized for AD on day i; α stands for the model intercept; Zi represents the air pollutant concentration on day*i* (μg/m^3); β represents the exposure–response coefficient, which is the increase in the number of daily hospitalizations caused by the per unit increase in pollutant concentration; s is a non-smooth parameter item; and df is the degree of freedom. The time stands for a date variable with a degree of freedom of 7/year; as.factor is a join function, which is to convert the factor vector into a string vector using the as factor function; dow is an indicator variable of "day of the week"; temperature and humidity stand for the average daily temperature and relative humidity, whose degrees of freedom are both 4.

RR represents the risk of AD HAs for each 10 μg/m^3 increase in the concentrations of $PM_{2.5}$ and PM_{10}, and the 95% CI represents its significance [31]. The equations are as follows:

$$RR = exp(\beta \times 10) \quad (2)$$

$$RR(95\%CI) = exp(10 \times (\beta \pm 1.96SE)) \quad (3)$$

Subgroup analysis was performed in the second stage. Considering that age is the greatest risk factor for AD and a fundamental driver of AD development [32]; complex interaction between AD and gender [33]; and extremely low and high temperatures may exacerbate PM-related mortality/incidence [34]. This study performed stratified analyses according to age (<75, 75–85, ≥85), gender (male and female), and season (warm season: April–September, cool season: October–March) subgroups, and z tests were used to estimate statistical differences in the stratified analysis [35]. The statistical significance of differences between effect modifiers (e.g., between cool and warm seasons) was tested by calculating the 95% CI with the following equation:

$$\left(\hat{Q_1} - \hat{Q_2}\right) \pm 1.96\sqrt{\left(S\hat{E_1}\right)^2 + \left(S\hat{E_2}\right)^2} \quad (4)$$

where $\hat{Q_1}$ and $\hat{Q_2}$ are the adjusted estimated values for different categories in each stratified subgroup (e.g., cool and warm seasons) and $S\hat{E_1}$ and $S\hat{E_2}$ are the respective standard errors [36, 37].

Calculation of number of AD HAs and economic loss of AD attributable to exposure to air pollution

Based on the exposure–response coefficients obtained from the R "mgcv" package, the number of AD inpatients [38] and economic costs of disease [37, 39] attributable to airborne PM exposure were further calculated using the attributable risk method. The 24-h mean concentrations were determined as the reference pollutant concentrations (15 μg/m^3 for $PM_{2.5}$ and 45 μg/m^3 for PM_{10}) based on the WHO AQGs 2021 [40]. The coefficient β_s is the sum of the coefficients of the days affecting significant lags [39, 41]. The indirect economic burden attributable to AD HAs was estimated using the per capita daily disposable income in Sichuan Province [31]. The economic burden was calculated according to the following equations:

$$AR_{ij} = (exp(\beta_s \times \Delta AP_i) - 1)/exp(\beta_s \times \Delta AP_i) \quad (5)$$

$$AN = \sum_{i=1}^{1095} (AR_i \times N_i) \quad (6)$$

$$DC = AN \times Cost_{total} \quad (7)$$

$$IC = AN \times dPCDI \times meanH_d \quad (8)$$

where i denotes the number of days in the study period (from 1 to 1095), j represents the air pollutants PM_{10} and $PM_{2.5}$, AR_{ij} is attributable risk, ΔAP_i is the difference between the observed pollutant concentration on day i and the reference concentration, N_i is the number of AD inpatients on day i, and AN is the total number of AD inpatients due to air pollution, DC is the direct medical costs of HAs caused by air pollution, $Cost_{total}$ is the average direct medical costs per HA case during the study period, IC is the indirect economic costs attributable to air pollution, Hd denotes the average number of days of HA per case, and dPCDI is the per capita daily disposable income in Sichuan Province.

Sensitivity analysis

Two types of sensitivity analyses were performed to verify the stability of the model. First, the stability of the time trend was tested, and the model was fitted by changing the degree of freedom of the time-series (df=5, 6, 8, 9 per year). Second, a sensitivity analysis was performed on cases within a 50-km circular area of the air monitoring stations to assess the robustness of these results. Data from AD inpatients residing outside the 50-km radius of the nearest air monitoring station were excluded to

Table 1 General characteristics of Alzheimer's disease inpatients

Variables	Cases (%)
Total	4975
Region	
Sichuan basin	4951 (99.52%)
Western sichuan plateau	24 (0.48%)
Gender	
Male	2299 (43.21%)
Female	2676 (53.79%)
Age (*Mean* ± *SD*)	79.82 ± 9.70
< 75	1302 (26.17%)
75–85	1820 (36.58%)
≥ 85	1853 (37.25%)
Season	
Cold season	2418 (48.60%)
Warm season	2557 (51.40%)

reduce bias due to spatial variability of pollutant measurements [42]. Nearest neighbor analysis was performed using the "Distance to nearest hub" and "Distance matrix" toolkits in QGIS software.

Results

Study population

As shown in Table 1, a total of 4975 AD patients were included in this study during the 3-year period from 2017 to 2019. Among them, there were slightly more female patients than male patients, with 2299 (43.21%) being male and 2676 (53.79%) being female. Regarding their locations, 99.52% of AD patients resided in the SCB. Meanwhile, AD inpatients were predominantly elderly patients ≥ 85 years old (1853, 37.25%). In addition, there were slightly more AD inpatients in the warm season (2557, 51.40%) than in the cold season (2418, 48.60%).

Data description of air pollution and meteorological factors

As shown in Table 2, the daily average concentrations ($\bar{x} \pm s$) of pollutant exposure in AD patients during the study period were as follows: 45.12 ± 32.37 μg/m^3 for $PM_{2.5}$, 69.85 ± 43.68 μg/m^3 for PM_{10}, 0.78 ± 0.27 mg/m^3 for CO, 10.09 ± 4.78 μg/m^3 for SO_2, 33.36 ± 17.45 μg/m^3 for NO_2, and 84.03 ± 44.30 μg/m^3 for O_3. The daily average temperature was 17.44 ℃, and the relative humidity was 77.71%.

Health effects of PM pollution on overall and subgroup populations

Figure 2 presents the single-pollutant models on different lag days, indicating a positive association between $PM_{2.5}$ exposure (every 10-μg/m^3 increase in airborne PM concentration) and AD HAs. The association between $PM_{2.5}$ and AD was statistically significant on single-day lag 0–1 and moving average lag days (lag01–lag03). However, the difference between PM_{10} and AD was not statistically significant for single-day lag and moving mean lag days. $PM_{2.5}$ had the greatest effect on the number of AD inpatients on lag1 with the RR values being 1.034 (95% CI 1.011,1.058).

Figure 3 analyzes the effects of each 10-μg/m^3 increase in $PM_{2.5}$ and PM_{10} concentrations on AD in different gender, age, and season groups on lag0, lag1, and lag01 after adjusting temperature and relative humidity. Regarding the gender subgroups, the effects of $PM_{2.5}$ and PM_{10} exposure were significant on both male and female

Table 2 Descriptive statistics of air pollutant concentrations and meteorological variables (lag 0) in nine cities of Sichuan Province, 2017–2019

Pollutant	Mean ± SD	Min	Max	Percentage		
				P25	Median	P75
Concentration						
$PM_{2.5}$ (μg/m^3)	45.12 ± 32.37	4.87	22.61	35.82	57.69	264.15
PM_{10} (μg/m^3)	69.85 ± 43.68	8.38	37.40	57.75	90.57	441.48
CO (mg/m^3)	0.78 ± 0.27	0.17	0.60	0.73	0.91	2.36
O_3 (μg/m^3)	84.03 ± 44.30	6.05	51.28	76.15	109.75	322.11
SO_2 (μg/m^3)	10.09 ± 4.78	1.15	6.88	9.05	12.02	39.00
NO_2 (μg/m^3)	33.36 ± 17.45	3.07	19.70	30.59	44.08	127.10
Meteorological factors						
Temperature (°C)	17.44 ± 7.30	1.02	10.68	17.89	23.70	33.32
Relative humidity (%)	77.71 ± 11.41	15.52	69.95	78.72	86.74	99.76

SD, Standard Deviation; $PM_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤ 10 μm in aerodynamic diameter; CO, carbon monoxide; O_3, ozone; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; P25, 25th percentile; Median, 50th percentile; P75, 75th percentile

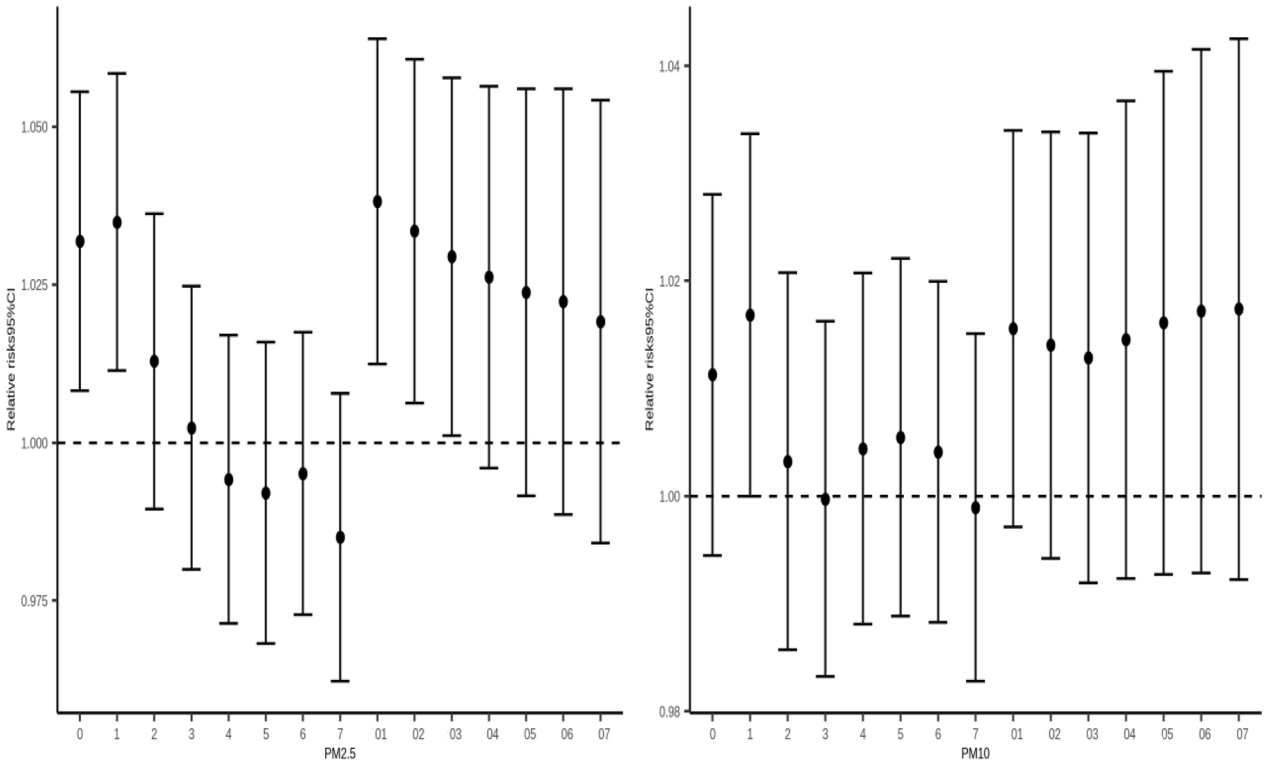

Fig. 2 Relative risks and 95% confidence intervals of Alzheimer's disease hospital admissions associated with every 10-μg/m^3 increase in $PM_{2.5}$ and PM_{10} on different lag days.$PM_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤ 10 μm in aerodynamic diameter

populations, but the difference between the genders was not statistically significant ($p > 0.05$). As for the different age groups, on lag0 and lag01, the effects of $PM_{2.5}$ and PM_{10} were not significant for those aged 75–85 years, but people aged 85 years and above were more sensitive to $PM_{2.5}$ and PM_{10} exposure; however, none of the differences between different age groups was statistically significant ($p > 0.05$). On lag1, the effects of $PM_{2.5}$ exposure were found to be positive and significant for all age groups, but none of the differences between different age groups was statistically significant ($p > 0.05$). As for their effects in different seasons, on lag0, lag1, and lag01, $PM_{2.5}$ had positive and significant effects on AD HAs in the cold season, but the difference between the cold and warm seasons was not statistically significant ($p > 0.05$). (Additional file 1: Tables S1, S2).

According to Table 3, there may be an independent relationship between $PM_{2.5}$ in the air and AD HAs risk. Upon introducing SO_2, NO_2, and O_3 in the two-pollutant model for adjustment, the association between $PM_{2.5}$ and AD remained significant and the effect size increased slightly. For example, the AD risk went up from 3.5% (95% CI 1.011, 1.058) to 4.1% (95% CI 1.015,1.069) for each 10-μg/m^3 increase in $PM_{2.5}$ after the introduction of NO_2 to the $PM_{2.5}$ model. Similarly, as a result of the introduction of SO_2 to the $PM_{2.5}$ model, the AD risk went up from 3.5% (95% CI 1.011, 1.058) to 4.2% (95% CI 1.017,1.068).

Table 4 shows the attributable number (AN), attributable risk (AR), and economic burden of disease of AD HAs caused by exposure to $PM_{2.5}$ in Sichuan Province from 2017 to 2019, with the WHO air quality standards as reference concentrations. After adjusting for other pollutants, the effect of $PM_{2.5}$ pollution on AD remained significant. During the study period, the number of AD inpatients attributable to $PM_{2.5}$ pollution was 820. In this study, the per capita disposable income of Sichuan Province from 2017 to 2019 (US$2995.63, US$3269.37, US$3595.80) was obtained from the Statistical Yearbook of Sichuan Province. Further calculate the per capita daily disposable income of Sichuan residents during the study period (US$ 9.01). The associated economic costs totaled US$ 2.56 million. The direct disease economic burden from $PM_{2.5}$ is US$ 2.25 million (87.83%).

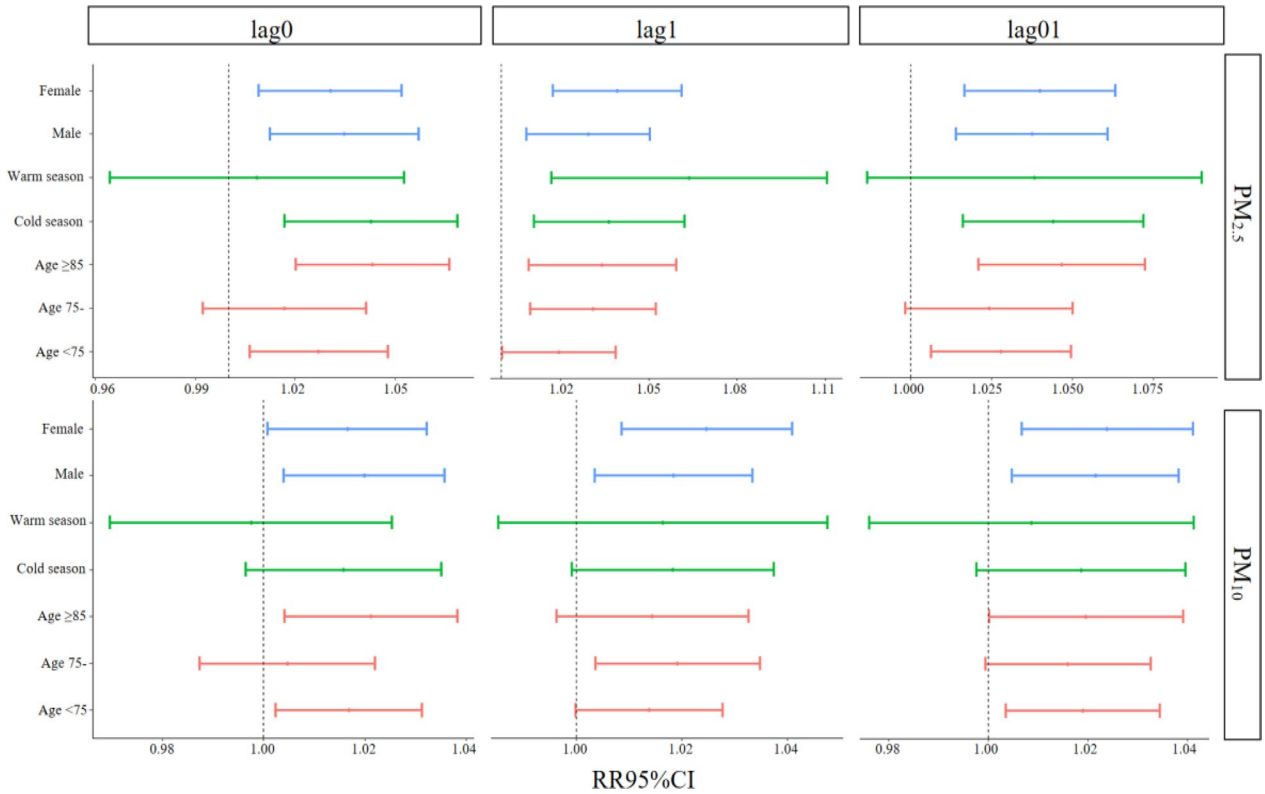

Fig. 3 Relative risks and 95% confidence intervals of hospital admissions for Alzheimer's disease by gender, age, and season (lag0, 1, 01).$PM_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤ 10 μm in aerodynamic diameter

Table 3 RR(95% CI) of AD hospital admissions per 10μg/m^3 increase in concentrations of pollutants in the single and two-pollutant models

Two-pollutant models		RR	95% CI
$PM_{2.5}$	–	1.035	(1.011,1.058)
	Adjusted for O_3	1.036	(1.012,1.060)
	Adjusted for SO_2	1.042	(1.017,1.068)
	Adjusted for NO_2	1.041	(1.015,1.069)
	Adjusted for CO	1.023	(0.994,1.052)
PM_{10}	–	1.017	(1.000,1.034)
	Adjusted for O_3	1.017	(1.000,1.034)
	Adjusted for SO_2	1.02	(1.002,1.039)
	Adjusted for NO_2	1.019	(0.999,1.039)
	Adjusted for CO	1.005	(0.985,1.025)

Maximum effect size analysis based on single-pollutant models; maximum effects of $PM_{2.5}$ and PM_{10} on AD are on lag 1

Table 4 AN, AR, and economic costs of Alzheimer's disease hospital admissions associated with PM pollution according to WHO air quality guidelines for Sichuan Province, 2017–2019 (million CNY)

Variables	$PM_{2.5}$	Total
AN	820	820
AR	0.174	–
DC	15.45	15.45
IC	2.14	2.14
Costs	17.59	17.59

$PM_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤ 10 μm in aerodynamic diameter. AN: the total number of AD HAs attributable to air pollution; AR: the attributable risk; DC: the direct medical costs of HAs due to air pollution; IC i:the indirect economic costs due to air pollution

Sensitivity analysis

In the sensitivity analysis, the acute impact of PM on the hospitalizations with AD not change substantially after replacing the annual degree of freedom of the time-series (df) with 5, 6, 8 and 9 (Additional file 1: Table S3). Second, data from 239 AD inpatients residing outside the 50-km radius of the nearest air monitoring station were excluded, and the relationship between PM exposure and AD was then reanalyzed. Compared with the results of the original models before sensitivity analysis, the results obtained showed no significant

difference. The estimated effects of $PM_{2.5}$ still remained at the maximum levels on lag1. The RR values for $PM_{2.5}$ was 1.034 (95% CI 1.011, 1.058) before lag1 adjustment and 1.032 (95% CI 1.009, 1.056) after adjustment, indicating that the main model is robust overall (Additional file 1: Table S4).

Discussion

Our study found that short-term exposure to airborne PM was significantly associated with the number of AD inpatients. In single-pollutant models, $PM_{2.5}$ was positively associated with AD HAs. Although the possible mechanisms underlying the relationship between short-term exposure to particulate matter and the risk of AD hospitalization have not been fully elucidated, current toxicological studies have provided some clues to the underlying biological mechanisms. Short-term exposure to environmental particulate matter can induce or enhance biological processes in the brain, such as oxidative stress and neuroinflammation. Oxidative stress induced by PM could initiate neurotoxicity or enhance pre-existing (e.g., Aβ-induced) pathology and thus form a vicious cycle that promotes the initiation and progression of AD [43]. And there is evidence that neuroinflammation can precipitate AD. In a study of the World Trade Center exposed responders found that acute high exposure to particulate matter, particulate matter may infiltrate directly into the brain, and induce neuroinflammation via the neural infiltrate model leading to cognitive impairment, which may be similar to the hallmarks of Alzheimer's disease and related dementias [16]. Similar to our findings, a recent US study also discovered that Medicare beneficiaries with AD were at higher risk of AD after acute exposure to PM; they may be more sensitive to air pollution-related inpatient treatment and more susceptible to neuroinflammation caused by the deleterious effects of $PM_{2.5}$ [44]. In addition, there is substantial evidence that short-term exposure to particulate matter activates microglia (a classic pathological feature of AD) [45, 46]. When activated microglia are further activated by subsequent systemic infections, this leads to significantly elevated levels of the acute phase cytokine interleukin 1β in the CNS and ultimately leads to the occurrence of AD [47]. Similarly, short-term exposure to particulate matter induced systemic inflammation triggers regulatory pathways activated by microglia and astrocytes in the brain, and this microglial over-response to systemic inflammation is observed in animal models of normal aging and neurodegeneration, as well as in patients with AD [48, 49]. In patients with pre-existing AD systemic infections will act as effective secondary infections producing stimulation of microglial cells in the brain leading to an accumulation of pathological changes in the brain and cognitive decline, resulting in acute episodes of chronic cognitive deficits (usually of short duration (less than two weeks)), such as delirium and further impairment of premorbid cognitive state, ultimately leading to emergency hospitalization of the patient [45, 47].

In our study, we temporarily did not find a short-term association between PM_{10} and AD admission. Previous epidemiological evidence on PM_{10} and AD is limited and inconsistent. A study in Rome found a negative correlation between PM_{10} and AD (OR = 0.95) [50]. Studies in Taiwan and Barcelona found that long-term exposure to PM_{10} was significantly associated with increased AD risk [51, 52]. This may mainly depend on the different results selected; most previous studies have analyzed the incidence rate of the disease as a result, while we studied emergency hospitalization caused by short-term exposure. Therefore, these results cannot be directly compared with our results. It may also be due to the different sources of environmental PM_{10}, which may lead to differences in the admission rate with neurodegenerative diseases such as AD [53]. In conclusion, due to the differences in the regression model, observation period, population exposure model, auxiliary factor set and exposure type (long-term and short-term) used in the analysis, whether short-term exposure to PM_{10} will increase the risk of AD hospitalization remains to be further verified. Previous studies have found that short-term exposure to high-intensity ultra-fine PM is related to the development of AD [22], and the harmful effects of $PM_{2.5}$ have been confirmed in our study. We agree that $PM_{2.5}$ exposure is the main contributor to AD acute hospitalization. Compared with PM_{10}, $PM_{2.5}$ is actually more toxic than PM_{10}, because it is easy to inhale [54, 55]. This research result has important public health significance for the control of environmental micro-particle pollution.

In addition, it was also confirmed that the association between $PM_{2.5}$ and AD remained significant after the introduction of a second pollutant to the single-pollutant model, with a slight increase in effect, suggesting the possible independent relationship between airborne $PM_{2.5}$ and AD HAs risk. It is noteworthy that the association was even more significant after NO_2 adjustment in the two-pollutant model, especially in the $PM_{2.5}$ model. The sensitivity to NO_2 adjustment may be due to the fact that PM and NO_2 have common anthropogenic sources, such as traffic. Air pollution caused by traffic is of increasing interest to many researchers today, and several studies have found that traffic-related pollutants may contribute to neurodegenerative pathologies and become an important risk factor for AD [56–58].A study conducted in a highway tunnel detected higher levels of proinflammatory cytokines in the brains of mice exposed to

short-term traffic-related pollution [59]. It has also been demonstrated that mice acutely exposed to diesel exhaust (DE) (250–300 μg/m^3 for six hours) showed microglia activation, increased lipid peroxidation, and neuroinflammation in various brain regions (especially the hippocampus and olfactory bulb) [45]. Thus, considering the multicollinearity among air pollutants, there are still too many uncertainties [60, 61]. After adjusting CO, the relationship between $PM_{2.5}$ exposure and AD inpatients became insignificant. Although AD risk rate data related to CO exposure are still limited, the epidemiologic and toxicological evidence indicated that higher concentration of CO exposure increased risks of dementia, implying that CO might have a potential impact on AD [62, 63]. Further studies are needed in the future to unravel the independent effects of air pollutants on AD.

Identifying potentially sensitive subpopulations could provide new insights into mechanisms, which has great public health significance for targeting strategies to reduce PM exposure in sensitive subpopulations. In our study, no significant difference in the effects of airborne PM pollution on the number of AD inpatients between gender groups was observed. Previous studies have been mostly limited to those of PM in relation to cognitive impairment in women [64, 65], and therefore, whether gender has an effect on this association requires further investigation. As for the analysis regarding age, elderly adults in the ≥ 85 years age group were more sensitive to airborne PM, which is consistent with results from other studies [66, 67]. A study involving 200 cities in China also found that short-term exposure to ambient PM caused an increase in daily inpatients and that elderly adults were more sensitive to $PM_{2.5}$ exposure [68]. There may be multiple reasons, including APOE4 allele and autoimmune decline, for the positive association between airborne PM pollution and HAs in the senior age group population [69, 70]. In terms of the differences in season groups, we observed positive and significant associations in cold season while insignificant association was found in warm seasons, which is consistent with previous research results [71]. One possible reason for the differences is the higher PM concentrations in cold season than in warm season, people have a higher chance of exposure to PM in the cold season [72, 73]. On the other hand, PM have different toxicity profiles in different seasons due to their different varying composition, concentrations and dimensions of the PM [74]. In general, the level of particulate matter pollution in different regions, geographical locations and climatic conditions may lead to different results. More research is needed to further understand whether seasons have an impact on this relationship. From the perspective of public health, these findings are particularly useful, which have far-reaching implications for the coordinated response to the dual challenges of population aging and climate change [75].

Unfortunately, there is currently little evidence on the resource use and associated costs of AD patients in China. However, the economic burden of AD is enormous [76]. Therefore, this study determined the total number of HAs and associated economic burden of AD patients from 2017 to 2019 and identified that 16.48% of AD patients were attributable to environmental PM effects throughout the study period using the attributable risk method. The direct medical costs and indirect economic costs of HAs caused by PM exposure were US$ 2.25 million and US$ 0.31 million, respectively. The study found that particulate matter exposure can cause adverse effects such as increased economic burden of AD, which is consistent with previous studies [77]. Measuring the effects in monetary terms helps to attach great importance to air pollution from a society-wide perspective. Therefore, if effective AD prevention and control strategies can be employed starting from strengthening air pollution control, the AD HAs and associated economic burden can be largely alleviated.

We acknowledge that our current study has some limitations. First, the air pollutant concentrations in this study were derived based on residential addresses. Although the evidence on the associations of air pollutant concentrations (source: residential addresses) and a range of health outcomes has been very strong in recent years [78], our lack of consideration of workplace exposure, exposure during commuting, and exposure to indoor sources may have resulted in some exposure misclassification. This may have led to underestimated effects of short-term exposure to airborne PM on AD and thus an underestimation of the total disease burden of AD. Second, several studies have noted that the APOE4 allele significantly increases the risk of developing AD; however, APOE4 genotyping is not currently recommended in routine clinical practice. Therefore, we were unable to obtain complete data on patient-related confounders to further verify whether carriers of the APOE4 allele living in a contaminated environment are at a higher risk of developing AD [79]. Third, due to data limitations, only the direct economic burden of AD HAs attributable to PM exposure and the indirect economic burden caused by reduced productivity as a result of HAs were estimated. No other types of economic burden were considered. The indirect costs [10, 80] and intangible economic burden [81] associated with social support for AD patients have been demonstrated to be substantial, so the actual economic burden of AD may be even greater. Finally, this is an ecological study of short-term associations

comparing the AD and PM. Its ecological design means that no causal relationship can be established between increases in PM concentrations and emergency AD admissions. Even so, the time series analysis methodology used in our study has been previously tried and tested in a large number of studies linking short-term exposure to atmospheric pollution to emergency hospital admissions for chronic debilitating brain disease (such as Alzheimer's disease, Parkinson's disease and other dementias) [22, 23, 44, 82–86]. In the future, further research is needed to reveal the health effects and underlying mechanisms of short-term exposure to PM on AD.

Conclusions

This multi-city time-series study found that short-term exposure to airborne $PM_{2.5}$ may increase the risk of AD HAs after adjusting temperature and relative humidity. There is a positive association between $PM_{2.5}$ exposure and the number of AD inpatients, and it was found that HAs attributable to airborne PM pollution can impose a heavy disease and financial burden on AD patients and their families. This finding has great public health significance for promoting improved ambient air quality and healthcare services in Sichuan Province, and it provides evidence for the need to reduce health inequities associated with air pollution and to make health policies related to China's rapidly aging population.

Abbreviations

RR	Relative risk
95%CI	95% Confidence interval
$PM_{2.5}$	Particulate matter ≤ 2.5 μm in aerodynamic diameter
PM_{10}	Particulate matter ≤ 10 μm in aerodynamic diameter
CO	Carbon monoxide
SO_2	Sulfur dioxide
NO_2	Nitrogen dioxide
O_3	Ozone
HAs	Hospital admission
API	Application programming interface

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12302-023-00833-1.

Additional file 1: Table S1. RR (95% CI) of stratified analyses for each air pollutant in the single-pollutant model PM2.5 fine particulate matter, PM10 inhalable particulate matter. **Table S2.** Test of interaction between subgroups. **Table S3.** Association between air pollutants (10 μg/m^3 increase) and the daily hospitalization with AD by degrees of freedom per year. **Table S4.** Associations between air pollutants (every 10 μg/m^3 increase in the later period of retention) and hospitalization in Alzheimer's disease (Eliminate the data from the home address to the monitoring station greater than 50 km).

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Author contributions

YH, XY, and XG were major contributors in collecting the data. XY initiated the idea for the study and was involved in writing of the original draft. WJ, XY, CL and JZ developed the formal analysis and software. LY was involved in reviewing and editing. LY was the PI for the fund and designed ideas of research. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki. This study was approved by the Ethics Committee of Hospital of Chengdu University of Traditional Chinese Medicine (approval no. 2020KL-001).

Competing interests

No financial or non-financial interests have been received or will be received from any party related directly or indirectly to the subject of this article. The authors have no competing interests to declare.

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