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Association between short-term exposure to ambient air pollution and dementia mortality in Chinese adults

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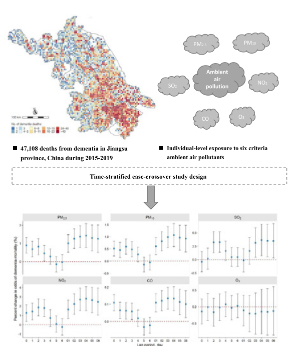
HIGHLIGHTS

- Short-term exposure to ambient air pollution is associated with an increased risk of dementia mortality.
- Considerable excess mortality can be attributable to short-term exposure to ambient air pollution.
- Reducing exposures to ambient air pollutants may help prevent premature dementia deaths.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Short-term exposure to ambient air pollution has been linked to an increased risk of mortality from a variety of causes, but its effects on mortality from dementia remain largely unknown.
Objectives: To investigate the association between short-term exposure to ambient air pollution and dementia mortality, and quantitatively assess the excess mortality.
Methods: In this time-stratified case-crossover study, 47,108 dementia deaths were identified in Jiangsu province, China during 2015–2019. Exposure to particulate matter with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), PM_{10}, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3) was assessed by extracting daily concentrations from a validated grid dataset based on each subject's residential address. Conditional logistic regression models were applied for exposure-response analyses.
Results: There were 47,108 case days and 159,852 control days during the study period. Each 10 $\mu g/m^3$ increase of lag

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04-day exposure to $PM_{2.5}$, PM_{10}, and NO_2 was significantly associated with a 1.43 % (95 % CI: 0.77, 2.09 %), 1.06 % (0.59, 1.54 %), and 2.80 % (1.51, 4.10 %) increase in odds of dementia mortality, corresponding to an excess mortality of 4.87 %, 5.50 %, and 6.43 %, respectively. We estimated that reducing ambient air pollutant exposures to the WHO air quality guidelines would avoid up to 4.17 % of the dementia deaths, while the ambient air quality standards in China would only help avoid up to 0.39 %.

Conclusions: This study provides consistent evidence that short-term exposure to $PM_{2.5}$, PM_{10}, and NO_2 is associated with increased odds of dementia mortality, which can be translated to a considerable excess mortality. Our findings highlight a potential approach to prevent deaths from dementia by reducing individual exposures to ambient air pollution, especially in areas with high levels of ambient air pollution.

1. Introduction

As one of the most prevalent neurodegenerative diseases, dementia including Alzheimer's disease (AD) has caused a heavy disease burden and posed a great public health challenge worldwide (Chen et al., 2017a; GBD 2016 Dementia Collaborators, 2019). According to the Global Burden of Disease (GBD) study, there were 51.6 million people living with dementia in 2019 and approximately two thirds of them lived in low- and middle-income countries (GBD 2019 Diseases and Injuries Collaborators, 2020). Globally, the number of dementia has risen monotonically since 1990, and is expected to increase to 152 million by 2050 due to population aging (Patterson, 2018). China has the largest population of people with dementia (13.1 million in 2019), which accounted for over 25 % of the entire population with dementia worldwide and imposed a critical burden on China's health care systems. Because dementia is a leading cause of death and there is no curative treatment to date (GBD 2016 Dementia Collaborators, 2019), it is important and practical to identify and control modifiable risk factors to prevent deaths from dementia and help alleviate its disease burden.

Short-term exposure to ambient air pollution has been linked to an increased risk of mortality from a variety of causes, especially cardiovascular and respiratory diseases (Liu et al., 2019a, 2019b; Liu et al., 2021). As there is accumulating evidence that air pollution may induce cognitive decline (Ailshire and Crimmins, 2014; Kulick et al., 2020) and the occurrence of dementia (Chen et al., 2017a, 2017b; Wu et al., 2015), the impacts of exposure to air pollution on mortality from dementia have drawn increasing concern globally. Previous studies have proposed that air pollutants may penetrate and deposit in the brain, leading to neurotoxic substance accumulation by changing the permeability of the brain-blood barrier (Calderon-Garciduenas et al., 2008). Air pollutants were also implicated in causing direct inflammatory effects and oxidative stress on the brain and associated with the development of dementia (Block and Calderon-Garciduenas, 2009; Levesque et al., 2011). As short-term exposure to ambient air pollution has been linked with an increased risk of hospital admissions due to the aggravation of dementia (Culqui et al., 2017; Linares et al., 2017), it is plausible that the exposure exacerbates the pathogenic process, worsens the underlying dementia status and further increases the risk of patients dying from dementia due to the poorly controlled disease condition, especially for later stages dementia patients. However, to date only two studies have tried to explore the association between short-term exposure to ambient air pollution and dementia mortality, and the results remain controversial and inconclusive (Ho et al., 2020; Zanobetti et al., 2014). One study of the US Medicare enrollees during 1999–2010 in 121 US communities found that short-term exposure to ambient particulate matter with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$) was associated with increased odds of all-cause mortality among subjects with previous hospital admissions for dementia (Zanobetti et al., 2014). In contrast, the other study in Hong Kong, China reported that short-term exposure to ambient ozone (O_3) was associated with increased odds of mortality from dementia (not including AD), while the exposure to particulate matter with an aerodynamic diameter ≤ 10 μm (PM_{10}) and nitrogen oxides (NO_x) was associated with lower odds of dementia mortality (Ho et al., 2020).

Therefore, we conducted this case-crossover study on adults who died from dementia in Jiangsu province, China during 2015–2019 to explore the acute effects of exposure to ambient air pollution on mortality from dementia. We hypothesized that short-term exposure to certain ambient air pollutants was associated with increased odds of dementia mortality. As a useful measure of health impact, the excess mortality associated with short-term exposure to these air pollutants was further estimated (Vicedo-Cabrera et al., 2020).

2. Methods

2.1. Study population

Using the Jiangsu provincial mortality surveillance system, we identified 47,108 individuals who died from dementia at 18 years or older in Jiangsu province, China during 2015–2019. This mortality surveillance system covered the entire population in Jiangsu province during the study period (Liu et al., 2016). As an eastern-central coastal province of China, Jiangsu province had an area of 107,200 km^2 and a population of 80.7 million (5.8 % of the population in China) in 2019. During 2015–2019, over 2.8 million deaths from any cause were identified with an estimated annual proportion of cause misclassification ranging from 2.63 % to 2.82 %. For each death, we collected information on age, sex, race, marital status, residential address, and date of death. Most dementia patients in China (96 %) were cared for at home by their family members or caregivers due to the filial piety of the Chinese, the economic burden, and the limited number of nursing homes, while only a small proportion of dementia patients (2 %) with high income were cared for by professional clinicians in institutional settings (Jia et al., 2016; Zhang et al., 2004). This study was approved by the Ethical Committee of School of Public Health, Sun Yat-sen University with a waiver of informed consent.

2.2. Study design

We conducted a time-stratified case-crossover study, which is characterized that each subject serves as his or her own control by assessing referent exposures at different periods within the same time stratum, and has been widely used in environmental epidemiology to evaluate acute effects of exposure to ambient air pollution on a variety of health outcomes (Carracedo-Martinez et al., 2010). For a given death, we defined the case day as the date of death, while days sharing the same day of week, month and year as the case day were chosen as the corresponding control days.

2.3. Exposure assessment

Daily grid (resolution: 10 km × 10 km) data on 24-hour average $PM_{2.5}$, PM_{10}, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and daily maximum 8-hour average O_3 concentrations in Jiangsu province during 2015–2019 were obtained from the long-term, full-coverage, high-resolution, and high-quality near-surface air pollutants dataset for China (i.e., ChinaHighAirPollutants, CHAP, available at https://weijing-rs.github.io/product.html). The CHAP dataset was generated from our proposed artificial intelligence models combining with big data including ground

Table 1
Characteristics of the study population, 2015–2019.

Characteristic	No. (%)	
	Dementia (n = 47,108)	AD (n = 14,942)
Case days	47,108	14,942
Control days	159,852	50,723
Sex		
Male	18,255 (38.8)	5477 (36.7)
Female	28,853 (61.2)	9465 (63.3)
Age, mean (SD), years	84.1 (9.2)	84.4 (7.5)
<85	22,188 (47.1)	7231 (48.4)
≥85	24,920 (52.9)	7711 (51.6)
Race		
Han	47,034 (99.8)	14,914 (99.8)
Other	74 (0.2)	28 (0.2)
Marital status		
Unmarried	841 (1.8)	252 (1.7)
Married	20,025 (42.5)	5956 (39.9)
Divorced	345 (0.7)	122 (0.8)
Widowed	25,757 (54.7)	8575 (57.4)
Unknown	140 (0.3)	37 (0.2)
Season at death[a]		
Cool	24,243 (51.5)	7743 (51.8)
Warm	22,865 (48.5)	7199 (48.2)
Year of death		
2015	9076 (19.3)	2280 (15.3)
2016	9423 (20.0)	2707 (18.1)
2017	9217 (19.6)	2770 (18.5)
2018	9538 (20.2)	3145 (21.0)
2019	9854 (20.9)	4040 (27.0)

AD: Alzheimer's disease; SD: standardized deviation.
[a] Cool season was defined as November to March, while warm season was defined as April to October.

measurements, satellite remote sensing products, atmospheric reanalysis, and model simulations (Wei et al., 2021a, 2021b, 2022a, 2022b). The cross-validation coefficient of determination (R^2) for $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was 0.91, 0.88, 0.84, 0.84, 0.80, and 0.87, respectively. For each subject, we assessed daily exposure to each air pollutant on the case day and control days by extracting their concentrations from the CHAP dataset at his or her geocoded residential address, which could be the home address or the location of the clinic or nursing home where the subject was cared for before death. In addition to exposure on the same day of death (lag 0), we also considered single-day lag exposures (lag 1 to lag 6) and moving average day exposures (lag 01 to lag 06), which refers to exposure on a given previous day, and the mean exposure on the same day and given previous days prior, respectively (Myung et al., 2019).

2.4. Covariates

We retrieved daily grid (resolution: 0.0625° × 0.0625°) data on meteorological conditions in Jiangsu province during 2015–2019 from the China Meteorological Administration Land Data Assimilation System (CLDAS version 2.0) (Liu et al., 2020). Daily exposure to meteorological conditions was estimated by extracting 24-hour average temperature and relative humidity at each subject's residential address (Zhou et al., 2020). We did not consider individual-level covariates including sex, age, race, genetics, and lifestyle as confounders because they were unlikely to change materially within the case and corresponding control days (Carracedo-Martinez et al., 2010).

2.5. Outcomes

In China, based on medical records and information collected from the household, each death was given a death certificate by attending doctors or health center staffs to provide the chain of events leading to death (including immediate cause, intervening cause, and underlying cause) and the approximate interval between disease onset. According to the death certificate, doctors or investigators further code the underlying cause according to the International Statistical Classification of Diseases and Related Health Problems Tenth Revision (ICD-10) (Liu et al., 2016; World Health Organization, 2015; Yang et al., 2005). The outcome of this

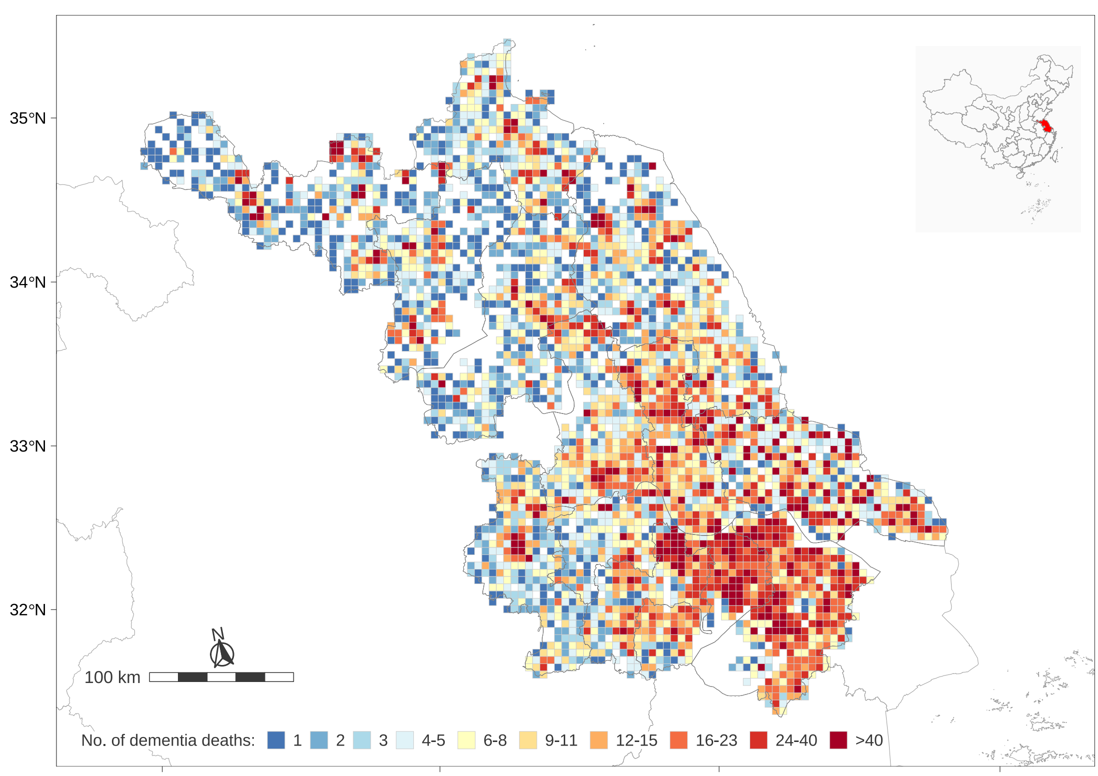

Fig. 1. Spatial distribution of the study population in Jiangsu province, China, 2015–2019. The grids with different colors indicate the number of dementia deaths at a 5 km × 5 km spatial resolution.

Table 2
Distribution of exposure to ambient air pollutants and meteorological conditions on the date of dementia death.

	Percentile					Mean (SD)
	5th	25th	50th	75th	95th	
Air pollutant						
$PM_{2.5}$, μg/m^3	18.9	30.9	44.7	65.7	113.6	52.6 (30.7)
PM_{10}, μg/m^3	34.9	53.5	76.1	106.9	167.7	85.3 (42.9)
SO_2, μg/m^3	6.9	11.0	15.2	21.2	35.3	17.4 (9.5)
NO_2, μg/m^3	17.7	25.9	34.2	46.2	69.0	37.6 (16.2)
CO, mg/m^3	0.55	0.71	0.85	1.06	1.50	0.91 (0.30)
O_3, μg/m^3	44.6	67.8	90.7	126.1	181.2	99.7 (42.8)
Meteorological condition						
Temperature, °C	1.1	6.5	14.4	23.2	30.4	14.9 (9.5)
Relative humidity, %	50.2	65.6	75.7	84.7	92.6	74.3 (13.1)

CO: carbon monoxide; NO_2: nitrogen dioxide; O_3: ozone; $PM_{2.5}$: particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}: particulate matter with an aerodynamic diameter ≤ 10 μm; SD: standardized deviation; SO_2: sulfur dioxide.

study was mortality from dementia (ICD-10 codes: F01, F03, G30, and G31) as the underlying cause. The subjects were previously diagnosed as dementia (including vascular dementia, unspecified dementia, Alzheimer's disease, and other degenerative diseases of nervous system, not elsewhere classified), and died from dementia itself or from diseases/symptoms induced by dementia.

2.6. Statistical analysis

We employed conditional logistic regression models to assess exposure-response associations. In single-pollutant models, exposure to each air pollutant with different lag periods was separately included in the model to estimate the percent change in odds ([odds ratio − 1] × 100%) of dementia mortality and its 95 % confidence interval (CI) per 10 μg/m^3 increase of exposure. Because the linear assumption between air pollutant exposure and dementia mortality may not hold, we further included the exposure as a natural cubic spline function (degree of freedom [*df*] = 3) in the model and performed likelihood ratio tests to examine potential nonlinear associations. In addition, we fitted 2-pollutant models by including each of the other pollutants in the single-pollutant model. The difference between the single- and its nested 2-pollutant models was tested using the likelihood ratio test. To adjust for meteorological conditions, we included a natural cubic spline function of daily temperature (lag 03-day; *df* = 6) and relative humidity (lag 03-day; *df* = 3) in all models (Liu et al., 2019a). We conducted stratified analyses by sex, age and season, and compared the associations across each stratification using a 2-sample z test (Altman and Bland, 2003).

To estimate the excess mortality from dementia associated with short-term exposure to ambient air pollution, we calculated the excess fraction of mortality from dementia as (Xu et al., 2022; Fu et al., 2018):

$$\text{Excess fraction} = \frac{\sum_{i=1}^{N} 1 - \frac{1}{e^{\beta \times (C_i - C_0)}}}{N} \times 100\%$$

where β refers to the point estimate (ln odds ratio) of air pollutant exposure in the conditional logistic regression model; C_i refers to air pollutant exposure for each subject on the date of death; C_0 refers to a counterfactual scenario of theoretical minimum risk exposure level (GBD 2019 Risk Factors Collaborators, 2020), or the referent air pollutant concentration according to the 2005, 2021 World Health Organization (WHO) air quality guidelines

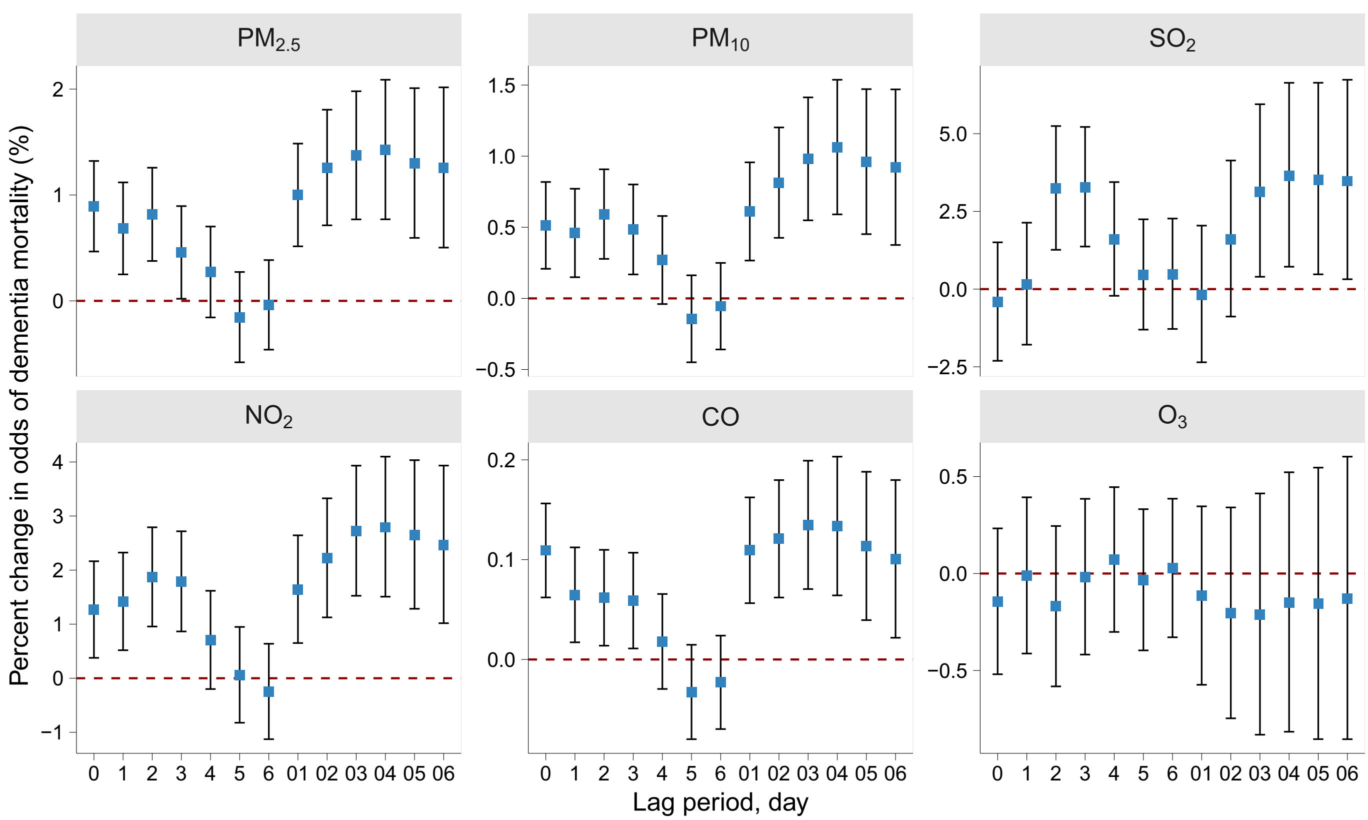

Fig. 2. Percent change (95 % CI) in odds of dementia mortality associated with each 10 μg/m^3 increase of exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 with different lag periods. Lag 0-day exposure refers to air pollutant exposure on the same day of death; lag 1-day (2 to 6-day) exposure refers to the daily exposure at 1 day (2 to 6 days) before death; while lag 01-day (02 to 06-day) exposure refers to the mean of daily exposure on the day of death and 1 day (2 to 6 days) prior. CI: confidence interval; CO: carbon monoxide; NO_2: nitrogen dioxide; O_3: ozone; $PM_{2.5}$: particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}: particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2: sulfur dioxide.

(AQGs) (World Health Organization, 2006, 2021) and the ambient air quality standards in China (Ministry of Environmental Protection of the People's Republic of China, 2012); N refers to the number of dementia deaths. The number of excess deaths from dementia was calculated as excess fraction × N. We further estimated the excess fraction by sex, age, season and performed the 2-sample z test to compare the estimates across each stratification.

The robustness of our results was evaluated by several sensitivity analyses, including: 1) restricting the analyses to AD deaths (ICD-10 code: G30); 2) restricting the analyses to subjects ≥ 65 years; and 3) adjusting for temperature using a *df* of 3. All statistical analyses were performed using R version 4.1.2 (R Core Team, 2021). All statistical tests were 2-sided and $p < 0.05$ was considered statistically significant.

3. Results

During 2015–2019, we identified 47,108 deaths from dementia, including 14,942 deaths from AD (Table 1) and there were 47,108 case days and 159,852 control days. The spatial distribution of these dementia deaths is demonstrated in Fig. 1. The daily concentration of ambient air pollutants and daily number of dementia deaths in Jiangsu province, China during the study period are presented in Fig. S1. Among the dementia deaths, 61.2 % were female, 52.9 % died at 85 years or older, and 51.5 % died in cool season. Mean exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was 52.6 μg/m^3, 85.3 μg/m^3, 17.4 μg/m^3, 37.6 μg/m^3, 0.91 mg/m^3, and 99.7 μg/m^3, respectively (Table 2). Exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO was positively correlated (all $p < 0.05$), while O_3 exposure was negatively correlated with exposure to other pollutants (Table S1).

In single-pollutant models, we observed significant associations between $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO exposures and dementia mortality, with overall the strongest association pronounced at lag 04-day exposure. Each 10 μg/m^3 increase of lag 04-day exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO was significantly associated with a 1.43 % (95 % CI: 0.77, 2.09 %), 1.06 % (95 % CI: 0.59, 1.54 %), 3.64 % (95 % CI: 0.72, 6.64 %), 2.80 % (95 % CI: 1.51, 4.10 %), and 0.13 % (95 % CI: 0.06, 0.20 %) increase in odds of dementia mortality, respectively (Fig. 2 and Table S2). We did not observe any departure from linearity for $PM_{2.5}$, PM_{10}, NO_2, or CO (all p for nonlinear trend > 0.05); in contrast, the odds of dementia mortality increased monotonically with increasing SO_2 exposure at lower levels but attenuated at higher levels (p for nonlinear trend = 0.02; Fig. 3). In 2-pollutant models, the association of exposure to $PM_{2.5}$, PM_{10}, and NO_2 did not significantly change (all p for difference > 0.05; Table 3), while the associations for SO_2 and CO became insignificant (p for difference < 0.05; Table 3 and Fig. S2). We did not observe any significant association between O_3 exposure and dementia mortality.

Table 4 presents the excess mortality from dementia associated with lag 04-day exposure to $PM_{2.5}$, PM_{10}, and NO_2 in Jiangsu province, China during 2015–2019. Overall, the excess deaths associated with exposure to $PM_{2.5}$, PM_{10}, and NO_2 accounted for 4.87 % (95 % CI: 2.69, 6.97 %), 5.50 % (95 % CI: 3.13, 7.79 %), and 6.43 % (95 % CI: 3.57, 9.16 %) of dementia deaths, corresponding to 2813 (95 % CI: 1552, 4029), 3180 (95 % CI: 1806, 4502), and 3716 (95 % CI: 2064, 5295) deaths, respectively. We estimated that 3.10 % (95 % CI: 1.71, 4.46 %) and 3.03 % (95 % CI: 1.71, 4.31 %) of dementia deaths would be avoid if the exposure to $PM_{2.5}$ and PM_{10} was reduced to the 2005 WHO AQGs. According to the 2021 WHO AQGs, the avoidable excess fraction of mortality from dementia associated with exposure to $PM_{2.5}$, PM_{10}, and NO_2 was 4.17 % (95 % CI: 2.30, 5.98 %), 3.39 % (95 % CI: 1.92, 4.82 %), and 2.90 % (95 % CI: 1.60, 4.16 %),

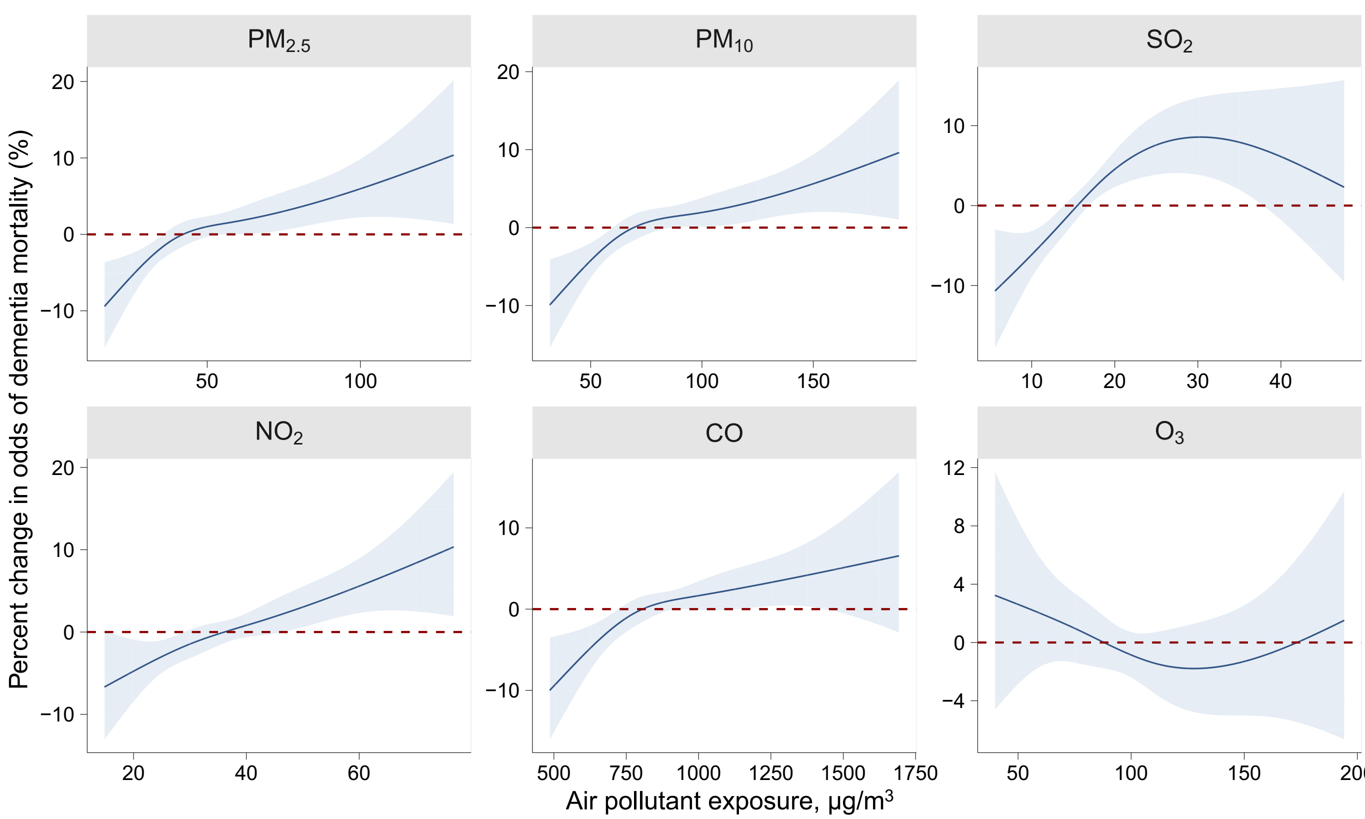

Fig. 3. Exposure-response curves of lag 04-day exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 with mortality from dementia. Lag 04-day exposure refers to the mean of daily exposure on the day of death and 4 days prior. The blue solid lines with shaded regions represent percent changes in odds of mortality from dementia and their corresponding 95 % CIs. The red horizontal line in each panel indicates the referent percent change of 0. CI: confidence interval; CO: carbon monoxide; NO_2: nitrogen dioxide; O_3: ozone; $PM_{2.5}$: particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}: particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2: sulfur dioxide.

Table 3
Percent change (95 % CI) in odds of dementia mortality associated with each 10 μg/m^3 increase of lag 04-day exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 estimated by single- and 2-pollutant models.

Air pollutant	Model	Percent change (95 % CI)	*p* value for difference[a]
$PM_{2.5}$[b]	Single	1.43 (0.77, 2.09)	
	Adjusted for SO_2	1.18 (0.32, 2.05)	0.48
	Adjusted for NO_2	0.80 (−0.18, 1.80)	0.10
	Adjusted for CO	1.25 (0.04, 2.47)	0.74
	Adjusted for O_3	1.54 (0.86, 2.22)	0.15
PM_{10}[b]	Single	1.06 (0.59, 1.54)	
	Adjusted for SO_2	0.90 (0.29, 1.51)	0.51
	Adjusted for NO_2	0.66 (−0.03, 1.36)	0.12
	Adjusted for CO	0.93 (0.15, 1.71)	0.67
	Adjusted for O_3	1.12 (0.64, 1.60)	0.21
SO_2	Single	3.64 (0.72, 6.64)	
	Adjusted for $PM_{2.5}$	0.03 (−3.39, 3.57)	<0.001
	Adjusted for PM_{10}	0.06 (−3.30, 3.53)	<0.001
	Adjusted for NO_2	−0.74 (−4.38, 3.03)	<0.001
	Adjusted for CO	0.75 (−2.65, 4.27)	0.004
	Adjusted for O_3	3.66 (0.74, 6.66)	0.62
NO_2	Single	2.80 (1.51, 4.10)	
	Adjusted for $PM_{2.5}$	1.61 (−0.31, 3.56)	0.11
	Adjusted for PM_{10}	1.47 (−0.40, 3.37)	0.06
	Adjusted for SO_2	2.48 (0.57, 4.42)	0.67
	Adjusted for CO	2.13 (0.27, 4.02)	0.34
	Adjusted for O_3	2.83 (1.54, 4.13)	0.48
CO	Single	0.13 (0.06, 0.20)	
	Adjusted for $PM_{2.5}$	0.02 (−0.11, 0.15)	0.04
	Adjusted for PM_{10}	0.03 (−0.09, 0.14)	0.02
	Adjusted for SO_2	0.10 (0.01, 0.18)	0.31
	Adjusted for NO_2	0.05 (−0.05, 0.15)	0.02
	Adjusted for O_3	0.14 (0.07, 0.21)	0.27
O_3	Single	−0.15 (−0.82, 0.52)	
	Adjusted for $PM_{2.5}$	−0.50 (−1.18, 0.19)	<0.001
	Adjusted for PM_{10}	−0.43 (−1.11, 0.25)	<0.001
	Adjusted for SO_2	−0.35 (−1.03, 0.34)	0.003
	Adjusted for NO_2	−0.24 (−0.91, 0.43)	<0.001
	Adjusted for CO	−0.38 (−1.05, 0.30)	<0.001

CI: confidence interval; CO: carbon monoxide; NO_2: nitrogen dioxide; O_3: ozone; $PM_{2.5}$: particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}: particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2: sulfur dioxide.

[a] *p* value for difference was compared with each single-pollutant model.

[b] To avoid collinearity, the exposure to $PM_{2.5}$ and PM_{10} were not included in the same model due to their strong correlation.

respectively. Using the ambient air quality standards in China, the avoidable excess fraction was 0.39 % (95 % CI: 0.21, 0.56 %), 0.11 % (95 % CI: 0.06, 0.15 %), and 0.0090 % (95 % CI: 0.0050, 0.010 %), respectively.

In the stratified analyses, the associations and the corresponding excess fractions for all pollutants did not significantly vary across sex, age, or season (all *p* for difference > 0.05; Tables 5 and S3). All the sensitivity analyses yielded similar results (Figs. S3–S5).

4. Discussion

In this large case-crossover study, we found that short-term exposure to $PM_{2.5}$, PM_{10}, and NO_2 was consistently associated with increased odds of mortality from dementia including AD, and these associations did not vary across sex, age, or season. Our findings indicate a considerable excess mortality associated with short-term exposure to ambient air pollution in Jiangsu province, China during 2015–2019. In addition, our results suggest that reducing pollutant exposure to the 2021 WHO AQGs would avoid up to 4.17 % of the dementia deaths, while the ambient air quality standards in China would only help avoid up to 0.39 %.

To date, the association between short-term exposure to air pollution and dementia mortality has rarely been investigated. One possible reason is that mortality from dementia as the underlying cause of death accounts for a relatively small proportion (2.87 % in 2019 estimated by the GBD study) of the total deaths, which may hinder studies to achieve statistical power due to insufficient sample size. The US study estimated that each 10 μg/m^3 increase in lag 01-day exposure to $PM_{2.5}$ was significantly associated with a 0.94 % and 1.04 % increase in odds of all-cause mortality among subjects with previous hospital admissions for dementia and AD, respectively, which was close to our estimates (1.00 %; lag 01-day exposure) (Zanobetti et al., 2014). It should be noted that the all-cause mortality among subjects with previous hospital admissions for dementia in the US study was unnecessarily equivalent to mortality from dementia as the underlying cause, which was typically used in epidemiological studies investigating the acute effects of air pollution on mortality (Chen et al., 2017c; Liu et al., 2019a); therefore, the results may be incomparable with our estimates and need to be interpreted with caution. In the Hong Kong study, Ho et al. implemented a cross-sectional design and reported that each 10 μg/m^3 increase of lag 0-day exposure to PM_{10}, NO_x, and O_3 was respectively associated with a −3.1 %, −1.2 %, 3.4 % change in odds of dementia mortality, which was inconsistent with our findings (Ho et al., 2020). However, the cross-sectional study design with analyses using an unconditional logistic regression model did not account for time and season trends of air pollutant concentrations, which may have resulted in biased estimates.

The consistent associations identified in our study provide strong evidence that ambient air pollution may trigger deaths from dementia. The underlying biological mechanisms on the adverse effects of air pollution on the neurological system remain to be elucidated. Accumulating evidence suggests that ambient air pollutants may penetrate and be deposited in the brain, which can cause brain damage by provoking inflammatory response, inducing oxidative stress, altering glia cell levels, and precipitating Aβ peptides (Block et al., 2004; Block and Calderon-Garciduenas, 2009; Calderon-Garciduenas et al., 2008; Levesque et al., 2011). Air pollutants

Table 4
Excess fraction and number of excess deaths from dementia associated with lag 04-day exposure to $PM_{2.5}$, PM_{10}, and NO_2 in Jiangsu province, China during 2015–2019.

	Above theoretical minimal risk exposure level[a]	Above 2005 WHO AQGs[b]	Above 2021 WHO AQGs[c]	Above China standard[d]
Excess fraction (%)				
$PM_{2.5}$	4.87 (2.69, 6.97)	3.10 (1.71, 4.46)	4.17 (2.30, 5.98)	0.39 (0.21, 0.56)
PM_{10}	5.50 (3.13, 7.79)	3.03 (1.71, 4.31)	3.39 (1.92, 4.82)	0.11 (0.06, 0.15)
NO_2	6.43 (3.57, 9.16)	–	2.90 (1.60, 4.16)	0.0090 (0.0050, 0.010)
Excess deaths				
$PM_{2.5}$	2813 (1552, 4029)	1793 (986, 2575)	2408 (1327, 3453)	225 (124, 325)
PM_{10}	3180 (1806, 4502)	1752 (991, 2490)	1961 (1110, 2786)	61 (35, 88)
NO_2	3716 (2064, 5295)	–	1674 (924, 2401)	5 (3, 8)

AQGs: air quality guidelines; NO_2: nitrogen dioxide; $PM_{2.5}$: particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}: particulate matter with an aerodynamic diameter ≤ 10 μm; WHO: World Health Organization.

[a] The theoretical minimum risk exposure level for 24-hour average $PM_{2.5}$, PM_{10}, and NO_2 was 8.6 μg/m^3, 18.5 μg/m^3, and 7.5 μg/m^3, respectively.

[b] The 2005 WHO AQGs for 24-hour average $PM_{2.5}$ and PM_{10} concentration was 25 μg/m^3 and 50 μg/m^3, respectively.

[c] The 2021 WHO AQGs for 24-hour average $PM_{2.5}$, PM_{10}, and NO_2 concentration was 15 μg/m^3, 45 μg/m^3, and 25 μg/m^3, respectively.

[d] The Grade 2 values in ambient air quality standards in China (GB 3095-2012) for 24-hour average $PM_{2.5}$, PM_{10}, and NO_2 concentration was 75 μg/m^3, 150 μg/m^3, and 80 μg/m^3, respectively.

Table 5
Percent change (95 % CI) in odds of dementia mortality associated with each 10 μg/m^3 increase of lag 04-day exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 stratified by sex, age, and season.

Stratification	Percent change (95 % CI)					
	$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	O_3
Sex						
Male	0.82 (−0.23, 1.88)	0.75 (−0.01, 1.51)	0.19 (−4.34, 4.95)	1.64 (−0.41, 3.73)	0.06 (−0.05, 0.17)	0.53 (−0.56, 1.62)
Female	1.80 (0.96, 2.65)	1.26 (0.65, 1.87)	5.75 (1.99, 9.65)	3.51 (1.86, 5.19)	0.18 (0.09, 0.27)	−0.57 (−1.41, 0.28)
p value for difference[a]	0.15	0.30	0.07	0.17	0.11	0.12
Age						
<85	0.96 (0.00, 1.93)	0.73 (0.04, 1.43)	1.57 (−2.59, 5.91)	2.3 (0.43, 4.20)	0.11 (0.01, 0.21)	−0.12 (−1.09, 0.85)
≥85	1.82 (0.92, 2.73)	1.34 (0.70, 1.99)	5.46 (1.42, 9.66)	3.22 (1.45, 5.02)	0.15 (0.06, 0.25)	−0.16 (−1.08, 0.76)
p value for difference[a]	0.20	0.21	0.20	0.49	0.55	0.95
Season[b]						
Cool	1.31 (0.59, 2.04)	0.96 (0.42, 1.51)	3.66 (0.30, 7.14)	2.69 (1.24, 4.16)	0.12 (0.04, 0.20)	−1.89 (−3.28, −0.49)
Warm	1.57 (−0.06, 3.23)	1.30 (0.29, 2.31)	5.90 (−0.32, 12.51)	3.97 (1.06, 6.97)	0.13 (−0.02, 0.27)	−0.47 (−1.28, 0.35)
p value for difference[a]	0.78	0.57	0.54	0.45	0.94	0.09

CI: confidence interval; CO: carbon monoxide; NO_2: nitrogen dioxide; O_3: ozone; $PM_{2.5}$: particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}: particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2: sulfur dioxide.
[a] *p* value for difference was compared with another stratified group.
[b] Cool season was defined as November to March, while warm season was defined as April to October.

can also change the permeability of brain-blood barrier, which may lead to accumulation of metals or neurotoxic substances in the brain and cause adverse effects on patients (Delgado-Saborit et al., 2021; Kilian and Kitazawa, 2018; Oppenheim et al., 2013).

This is the first study to quantitatively estimate the excess mortality from dementia associated with short-term exposure to ambient air pollution. We found that a considerable excess mortality from dementia (up to 6.43 % of all dementia deaths) was attributable to short-term exposure to ambient air pollution. This is of critical public health significance, given the global number of people living with dementia is currently over 50 million and expected to almost triple by 2050. Our findings suggest that up to 4.17 % of the deaths from dementia would be avoided if the particulate matter pollution level is reduced to the 2021 WHO air quality guidelines, indicating that reducing ambient air pollution level may be an effective approach to help prevent deaths from dementia. Our results also suggest that the current ambient air quality standards in China may be insufficient to prevent premature deaths from dementia. It may be helpful for the government to further reduce the level of ambient air pollutants including $PM_{2.5}$, PM_{10} and NO_2, and for dementia patients to reduce individual exposure to these air pollutants. In clinical practices, potential health benefits can be achieved if clinical practitioners and caregivers take air pollution prevention into consideration during the treatments and daily care for dementia patients.

The unique strength of our study was the study population with a large sample size and a wide range of pollutant exposures. The included dementia deaths came from a base population of over 80 million during a 5-year period, which was considerably large to help obtain a sufficient statistical power for modeling and stratified analyses. Because Jiangsu province was experiencing critical air pollution issues during the study period, the range of air pollutant exposure was wide and offered us the possibility to quantitatively investigate detailed exposure-response associations, especially at high exposure levels. Second, we took advantage of the case-crossover design to accurately assess individual level exposures to air pollutants using the CHAP dataset, which had a relatively high spatiotemporal resolution and a full coverage both spatially and temporally, and therefore enabled us to include all dementia deaths in Jiangsu province during the study period. In addition, this design accounted for long-term trends, known or unknown time-invariant individual-level covariates, and time-varying meteorological conditions. Third, we included six criteria ambient air pollutants in China within a single study, which allowed us to estimate the effect of each pollutant on dementia mortality with consideration of other pollutants.

Our study also has several limitations. First, we assessed the individual-level exposure by retrieving pollutant concentrations from a gridded dataset at the residential address. This may introduce exposure misclassification because we did not consider factors including personal indoor air pollution exposure and time-activity pattern. However, the high correlation between exposures to ambient and indoor air pollution (Krebs et al., 2021), and the nature of case-crossover design (the time-activity pattern was unlikely to change materially within one month) may in part alleviate the exposure misclassification. In addition, the misclassification tended to be nondifferential and the results were generally biased towards the null (Whitcomb and Naimi, 2020). Second, it was reported that dementia-related deaths were typically underestimated globally due to the misclassification in the death certificates and high rates of undiagnosed cases (Stokes et al., 2020). Although the mortality data in our study was under strict quality control with a considerably low misclassification rate (< 3 %), potential misdiagnosis or coding errors for dementia may still exist given the large sample size. Possible spatial and disease variations of misclassification rate can also lead to slightly biased results; however, we were unable to identify these discrepancies due to the lack of data. Third, although we used 2-pollutant models to consider co-exposure to other pollutants as proposed by most previous studies, it was difficult for us to distinguish the respective effect of each air pollutant on dementia mortality due to moderate or high correlation between air pollutant exposures. Fourth, we used the case-crossover study design to control the time-invariant factors and time-varying meteorological conditions in the model; however, there might still be certain residual confounders. Finally, this study was based on dementia deaths from a single province in China. Although the sample size was considerably large, cautions should be made to generalize our results to other populations.

5. Conclusion

We found that short-term exposure to $PM_{2.5}$, PM_{10}, and NO_2 was consistently associated with increased odds of mortality from dementia, which may result in a considerable excess mortality. Our findings highlight a potential approach to prevent deaths from dementia by reducing exposure to ambient air pollution, especially in areas with high ambient air pollution. Future studies are warranted to confirm our results in other populations and to elucidate the underlying biological mechanisms.

CRediT authorship contribution statement

Tingting Liu: Investigation, Formal analysis, Writing – original draft. **Yun Zhou:** Investigation, Formal analysis, Writing – original draft. **Jing Wei:** Data curation. **Qi Chen:** Writing – review & editing. **Ruijun Xu:** Writing – review & editing. **Jingju Pan:** Writing – review & editing. **Wenfeng Lu:** Writing – review & editing. **Yaqi Wang:** Writing – review & editing. **Zhaoyu Fan:** Writing – review & editing. **Yingxin Li:** Writing – review & editing. **Luxi Xu:** Writing – review & editing. **Xiuqing Cui:**

Writing – review & editing. **Chunxiang Shi:** Data curation. **Lan Zhang:** Writing – review & editing. **Xi Chen:** Writing – review & editing, Funding acquisition. **Wei Bao:** Writing – review & editing. **Hong Sun:** Conceptualization, Data curation, Supervision, Validation, Writing – review & editing, Funding acquisition. **Yuewei Liu:** Conceptualization, Data curation, Supervision, Validation, Project administration, Funding acquisition, Writing - review & editing.

Data availability

The air pollution data are available at https://weijing-rs.github.io/product.html. The data on meteorological conditions and dementia mortality are confidential.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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