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Ambient air pollution and Alzheimer's disease and other dementias: a global study between 1990 and 2019

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Abstract

Background Emerging research found air pollution may be associated with incident Alzheimer's disease (AD) and other dementias. However, few studies have examined these associations at the global scale. This study aimed to assess the dynamic associations between ambient air pollution and the burden of AD and other dementias worldwide.

Methods This study synthesised 149 countries/territories between 1990 and 2019. These data include age-standardised mortality rate (ASMR) and disability-adjusted life-years (DALYs) of AD and other dementias, ambient air pollution (fine particulate matter [$PM_{2.5}$], NO_2 and O_3 concentration) and a series of covariates were from various source. Average annual percentage changes (AAPCs) were calculated to investigate the temporal variations. Linear mixed models were adopted to assess the associations with single- and multi-pollutant separately. The associations between air pollution changes and the AD and other dementias were also examined using linear regression models. Stratified analyses by Global North–South divide and human development index were performed to explore the potential inequity in air pollution impacts.

Results During 1990–2019, the global ASMR, DALYs and O_3 increased by 0.11%, 0.09%, and 0.17% per year, respectively. In contrast, $PM_{2.5}$ and NO_2 decreased by 0.33% and 0.14% per year, respectively. Each 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 0.118 (95% confidence interval [CI]: 0.060 – 0.175) higher ASMR and 0.966 (95%CI: 0.321 – 1.611) higher DALYs after adjusting for all the covariates. The ASMR increased by 0.112 and the DALYs increased by 1.068 for each 10 μg/m^3 increase in O_3. The NO_2–dementia associations were relatively weak. Stronger O_3–dementia associations were found in the Global South than those in the Global North.

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Conclusions The burden of dementia is expected to increase globally, given the continuously expansion of the ageing population. Air pollution was found to be significantly associated with a higher burden of AD and dementia. As a persistent challenge in urban cities, air pollution demands strict regulatory control.

Keywords Air pollution, Alzheimer's disease and other dementias, Global burden of Disease study, Inequity, Healthy ageing cities

Background

Alzheimer's disease (AD) and other dementias have gradually become a global challenge over the past decades. Evidence shows that since 1990, the prevalence of AD and other dementias has increased by 80.4% and the associated deaths have doubled, reaching 1.6 million worldwide in 2019 [1]. Approximately 46 – 51 million adults are living with AD and other dementias globally [2]. This number is expected to reach 131.5 million by the end of 2050, given the continuously expanding ageing population worldwide [3]. Patients with AD and other dementias tend to have higher risks of infection, falls, and depression and a lower quality of life than healthy individuals [4]. Thus, a substantial burden of AD and other dementias may further aggravate the healthcare, economic, and social burdens on both families and countries.

Multifaceted factors collectively drive the risk and burden of AD and other dementias; these include but are not limited to genetic, ageing-related, lifestyle, and environmental factors [4]. Among these factors, air pollution has increasingly become a crucial determinant of the occurrence and development of AD and other dementias. Given that 99% of the global population is living in areas with substandard air quality [5], the burden of dementia attributable to air pollution is enormous and needs to be investigated further.

The associations between air pollution and AD and other dementias have not been well documented. Although the biological mechanism underlying the neurological effects of air pollution remain unclear, previous studies have proposed the possibilities of impairment of blood – brain barrier, protein aggregation, brain inflammation, and oxidative stress in the neurological system [6, 7]. Previous studies investigating the associations between air pollution and AD and other dementias have mainly been based in a specific country or city [8]. Notably, the literature is geographically biased towards developed areas. Therefore, investigating the disparities in the air pollution-neurology associations in areas with different socioeconomic status will provide a new direction to fully investigate the global landscape of air pollution signature in relation to AD and other dementias. A few Global Burden of Disease (GBD) studies have examined the risk factors (including overall air pollution) for dementia [9, 10] and other neurological disorders [11]. However, information on the associations between specific air pollutants and AD and other dementias is limited, and their concentration – response (C-R) associations remain unknown. These studies have assessed the overall disease burdens or their simple correlations with possible risk factors [9, 12], but the dynamic associations between different air pollutants and the burden of dementia over the past few decades remain to be elucidated. In addition, research findings on the impacts of ambient O_3 on neurological health are limited and inconsistent, and more relevant studies are warranted [8].

This study aimed to examine the associations between long-term exposure to ambient air pollution and the burden of AD and other dementias across 149 countries/territories between 1990 and 2019. We examined three major ambient air pollutants that are well-recognised leading risk factors for mortality: namely, particulate matter that has a diameter of 2.5 micrometre or less ($PM_{2.5}$), nitrogen dioxide (NO_2, an important indicator of nitrogen oxides group), and ozone (O_3). We further investigated disparities in the air pollution – dementia associations across the Global North (i.e., the northern regions of Brandt Line) and Global South (i.e., the southern regions of Brandt Line).

Methods

Study design and health outcomes

This was a repeated cross-sectional study at the global scale. Information from various databases was collected, and Table S1 shows the source of all databases included. In this study, health outcomes included the yearly age-standardised mortality rate (ASMR) and disability-adjusted life-years (DALYs) of AD and other dementias. DALYs, an important indicator of the total disease burden, is defined as the sum of years lived with disability and years of life loss due to deaths from AD and other dementias. The ASMRs and DALYs of AD and other dementias in 210 countries/territories from 1990 to 2019 were obtained from the Institute for Health Metrics and Evaluation [13]. Previous GBD studies have described the methods of estimating the burden of AD and other dementias in detail [14–16]. In brief, AD and other dementias were mainly defined using the following International Classification of Diseases (ICD) codes: ICD-10 (F00 – F02.0, F02.8 – F06.2, G30 – G31.1 and G31.8 – G32.89) and ICD-9 (290 – 290.9, 294.0 – 294.9, 331 – 331.7 and 331.82 – 331.9). Data on personal and aggregated diagnoses and deaths were calculated and estimated as the ASMR and DALYs for each country/

region. This was achieved using the Bayesian meta-regression tool (DisMod-MR 2.1) and spatiotemporal Gaussian process regression [1]. Finally, we included a total of 149 countries/territories in the main analyses after excluding those with missing information on various covariates. The descriptive characteristics of both included and excluded countries are presented in Table S2.

Standard protocol approvals, registrations, and patient consents

As this study only utilized country- or region-level data and did not include any individual-level information, it was exempt from ethical approval. Consequently, informed consent was not required.

Assessment of three air pollutants

The GBD data and satellite-based estimates were synthesised to assess long-term exposure to ambient $PM_{2.5}$. The GBD estimates of $PM_{2.5}$ air pollution were assessed using Bayesian hierarchical calibration model by combining different data source, and details has been introduced previously [1]. For the satellite-based estimates, hybrid models were used to estimate monthly $PM_{2.5}$ concentration at a resolution of 1 km [2] between 1998 and 2019, as described previously [17]. The original data sources were detailed in previous studies [1, 17]. In brief, satellite-derived aerosol optical depth data, $PM_{2.5}$ observations from ground-level monitoring stations, a chemical transport model, and geographically weighted regression were utilised to estimate the monthly $PM_{2.5}$ concentration worldwide. The estimates have been adjusted and validated before [17]. Annual average $PM_{2.5}$ was then calculated by averaging the monthly concentration in the same year. The pixel-level estimates of $PM_{2.5}$ were then aggregated into country-level concentration [1].

An updated GEOS-Chem chemical transport model was used to estimate daily NO_2 concentration at a resolution of 1 km [2] between 2005 and 2019 [18]. NO_2 columns from TROPOspheric Monitoring Instrument, ground-level monitoring data and spatiotemporal ancillary data were assimilated into the model. The corresponding data sources were presented in previous study [18]. The NO_2 estimates were then validated and adjusted. Daily NO_2 estimates within the same year were averaged to calculate annual average NO_2. The pixel-level NO_2 estimates were then aggregated into country-level concentration. Annual O_3 concentration for each country/territory between 1990 and 2019 were obtained from the GBD 2019 study, which also provides a detailed listing of the original data sources [1]. Briefly, a Bayesian maximum entropy model was used to estimate ground-level O_3 concentration. The summer (the 6 months with the highest level of O_3 air pollution) averages of 8-h daily maximum values were calculated as an indicator of annual O_3 concentration. The air pollutant assessment models demonstrated strong cross-validation performance (R^2 ranging from 0.92 to 0.99) and high consistency with pollutant measurements from monitoring stations (correlation coefficients ranging from 0.71 to 0.74).

Covariates

The covariates were selected empirically, guided by findings from previous studies [2, 3]. The following country-level covariates were included: household air pollution (i.e., proportion of using solid fuels: high [≥50%] vs. low [<50%]), annual ambient temperature (°C), gross domestic product (GDP; USD per capita), vegetable and fruit intake (high [≥250 g/day] vs. low [<250 g/day]), alcohol consumption (litres of pure alcohol per capita), age-standardised rate of cigarette smoking (%), age-standardised rate of physical inactivity (i.e., < 150 min of moderate intensity, or <75 min of vigorous intensity of physical activity each week; %), age-standardised rate of raised blood pressure (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; %), age-standardised rate of raised fasting blood glucose (≥7.0 mmol/L; %), and mean total cholesterol (mmol/L). Table S1 shows the data source in detail. Covariates were matched with health outcomes based on the corresponding year and country/region.

Statistical analyses

Average annual percent changes (AAPCs) with 95% confidence intervals (CIs) were estimated to assess the temporal trends in the air pollutants concentrations and the ASMRs and DALYs of AD and other dementias for each country/territory, continent, and worldwide. Joinpoint regression analyses were performed to estimate the AAPCs between 1990 and 2019 [19]. Logarithmic transformations of air pollution, ASMRs and DALYs, and ordinary least squares fitting with constant variance were performed. The maximum number of join points was pre-defined as three [19].

Linear mixed models were used to investigate the associations between air pollution and AD and other dementias. A country/territory-level random intercept was included to consider the clustering effects within a country/territory. All the abovementioned covariates were included as time-dependent factors in statistical models. Annual average concentration of ambient $PM_{2.5}$, NO_2 and O_3 was included as continuous variable (per 10 μg/m^3). Air pollution quartiles (with the first quartile as the reference group) were adopted to evaluate the non-linear associations between air pollution and AD and other dementias. Coefficients with 95% CIs were calculated to assess the associations. Both single and multiple pollutant models were evaluated. A Chi-square test was performed to examine whether the association between air pollution and AD and other dementias was linear. C-R curves were plotted using natural cubic spline functions.

We conducted a linear model to examine the associations between the AAPCs of air pollution and the ASMRs and DALYs of AD and other dementias. We included all the abovementioned covariates in the models. AAPC tertiles were used with the second tertile as the reference group. Both the reduced (first tertile) and increased (third tertile) level of air pollution were examined. Trend tests were also performed by treating the AAPC tertiles as a continuous variable.

To assess the robustness of air pollution–dementia associations, the following sensitivity analyses were conducted: (1) 2-year average air pollution was examined to minimise the delayed impacts; (2) multiple pollutants were examined using Bayesian kernel machine regression to account for potential collinearity; (3) $PM_{2.5}$ data from the GBD 2019 study (1990–1997) and the satellite-based $PM_{2.5}$ estimates (1998–2019) were examined simultaneously to determine whether different source may affect the main findings; and (4) excluding the data before 2005, when NO_2 concentration was unavailable. We further performed stratified analyses by the Global North–South divide (Global North vs. Global South) and human development index (HDI; very high and high vs. medium and low) were performed to assess heterogeneity and inequity in air pollution–dementia associations between different regions.

The AAPCs were estimated using the Joinpoint Regression Programme (version 5.0, National Cancer Institute). Statistical analyses of air pollution–dementia associations were performed using R language (Version 4.0.2, Vienna, Austria). Statistical significance was defined as a two-tailed *p* value of <0.05.

Results

This study synthesised data from 149 countries/territories between 1990 and 2019. Globally, the median estimates (interquartile range) of the ASMR and DALYs of AD and other dementias were 22.93 (21.38–24.97) and 332.04 (309.71–350.15) per 100,000 persons, respectively (Table S3). The global ASMR and DALYs of AD and other dementias increased over the 30 years, with AAPCs of 0.11% (95%CI: 0.11–0.12%) and DALYs of 0.09% (95%CI: 0.09–0.09%) (Table 1, Figure S1). This temporal dynamic pattern was consistent across most continents. Detailed descriptions of AD and other dementias, and their AAPC values in 149 countries/territories, five continents and two regions are shown in Tables S3 and S4, and Figures S2 and S3. Of note, Fig. 1A and S4 shows the geospatial distribution of the ASMRs and DALYs, respectively in 2019. The Global South, especially African countries/territories, generally had a greater burden of AD and other dementias than the Global North.

During the study period, the overall mean (standardised deviation) concentration of ambient $PM_{2.5}$, NO_2 and O_3 were 27.67 μg/m^3 (16.87 μg/m^3), 1.87 μg/m^3 (3.68 μg/m^3) and 78.88 μg/m^3 (19.41 μg/m^3), respectively (Table S3). The global ambient $PM_{2.5}$ and NO_2 concentration showed a decreasing trend between 1990 and 2019, and the corresponding AAPC was −0.33% (95%CI: -0.49% to -0.17%) for $PM_{2.5}$ and −0.14% (95%CI: -0.23% to -0.05%) for NO_2 (Table 1, Figure S5). In contrast, the global ambient O_3 concentration increased gradually during the study period, with an AAPC of 0.17% (95%CI: 0.07–0.28%) (Table 1, Figure S5). Descriptive statistics and AAPC values of the three air pollutants in 149 countries/territories and five continents are shown in Table S3 and Figures S6–S8. Table S4 illustrates the description of covariates in the world and by countries/territories and continents. Figure 1B and S9 show the geospatial distributions of ambient $PM_{2.5}$, NO_2 and O_3 in 2019. Notably, the Global South generally had higher $PM_{2.5}$ and O_3 concentration than the Global North. Hot spots of NO_2 were mainly European countries and areas around the Yellow Sea and East Sea (Figure S9).

We found that $PM_{2.5}$ and O_3 were positively associated with the ASMR and DALYs of AD and other dementias (Table 2, Figures S10–S15). In the single-pollutant models, every 10 μg/m^3 increase in ambient $PM_{2.5}$ was

Table 1 Average annual percent changes in Alzheimer's disease and other dementias and air pollution globally and in the five continents between 1990 and 2019

	Mortality rate	DALYs	$PM_{2.5}$	NO_2	O_3
Global	0.11 (0.11, 0.12)	0.09 (0.09, 0.09)	-0.33 (-0.49, -0.17)	-0.14 (-0.23, -0.05)	0.17 (0.07, 0.28)
Global North	0.02 (0.01, 0.03)	0.02 (0.02, 0.03)	-1.31 (-01.51, -1.10)	-0.16 (-0.33, 0.01)	-0.12 (-0.16, -0.01)
Global South	0.16 (0.15, 0.16)	0.12 (0.11, 0.12)	-0.07 (-0.27, 1.12)	0.15 (-0.04, 0.35)	0.34 (0.20, 0.50)
Africa	0.23 (0.22, 0.24)	0.17 (0.16, 0.18)	0.08 (-0.18, 0.34)	-0.42 (-0.78, -0.11)	0.53 (0.38, 0.71)
America	0.03 (0.02, 0.03)	0.04 (0.03, 0.05)	-0.83 (-0.98, -0.69)	0.86 (0.70, 0.99)	-0.32 (-0.38, −0.22)
Asia	0.17 (0.16, 0.19)	0.13 (0.12, 0.13)	0.11 (-0.13, 0.34)	0.39 (0.16, 0.62)	0.40 (0.34, 0.46)
Europe	-0.04 (-0.04, -0.03)	-0.02 (-0.03, -0.01)	-1.83 (-2.02, -1.64)	-0.28 (-0.39, -0.17)	-0.26 (-0.40, -0.11)
Oceania	0.08 (0.07, 0.09)	0.01 (0.01, 0.02)	0.47 (0.23, 0.64)	0.19 (-1.40, 1.77)	0.17 (0.08, 0.27)

Mortality rate refers to the age-standardised mortality rate per 100,000 persons. DALYs refers to age-standardised disability-adjusted life-years per 100,000 persons

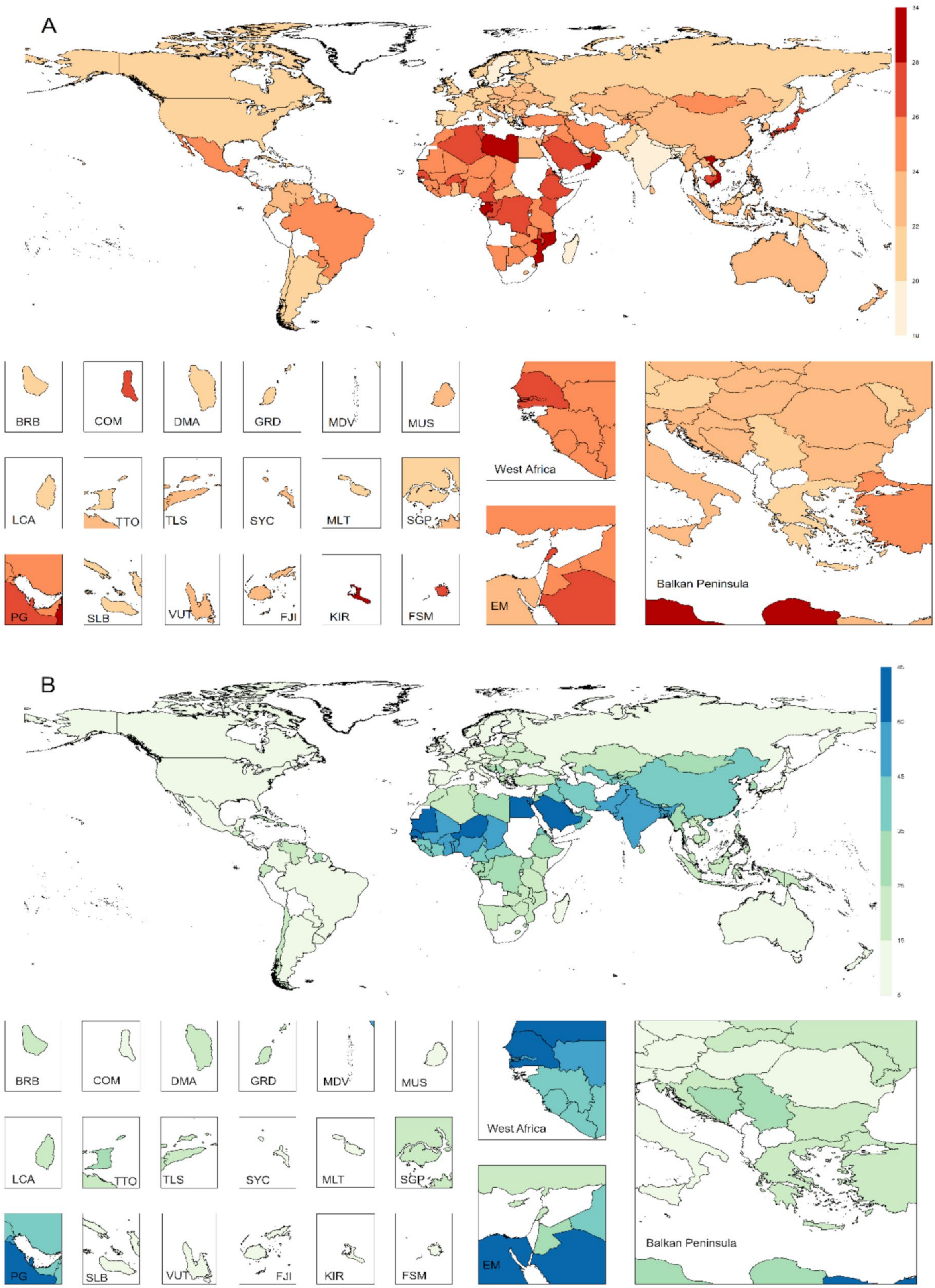

Fig. 1 Spatial distributions of the age-standardised mortality rates of Alzheimer's disease and other dementias and the annual $PM_{2.5}$ concentration in 149 countries/territories in 2019

Panel **A** refers to the age-standardised mortality rates of Alzheimer's disease and other dementias (per 100,000 persons). Panel **B** refers to the annual average $PM_{2.5}$ (μg/m^3)

Table 2 Associations between air pollution and age-standardised mortality rates and disability-adjusted life-years of Alzheimer's disease and other dementias

	Mortality rate	*P* value	Disability-adjusted life-years	*P* value
	Coefficients (95%CI)		Coefficients (95%CI)	
Single pollutant models				
$PM_{2.5}$				
First quartile	Ref	—	Ref	—
Second quartile	0.088 (-0.025, 0.201)	0.128	0.496 (-0.770, 1.761)	0.443
Third quartile	0.033 (-0.105, 0.171)	0.641	-0.484 (-2.029, 1.061)	0.539
Fourth quartile	0.347 (0.151, 0.543)	0.001	2.498 (0.301, 4.696)	0.026
Per 10 μg/m^3	0.118 (0.060, 0.175)	< 0.001	0.966 (0.321, 1.611)	0.003
NO_2				
First quartile	Ref	—	Ref	—
Second quartile	-0.148 (-0.289, -0.008)	0.038	-1.387 (-2.956, 0.183)	0.083
Third quartile	-0.036 (-0.214, 0.142)	0.691	0.230 (-1.760, 2.221)	0.821
Fourth quartile	0.069 (-0.155, 0.293)	0.546	2.892 (0.381, 5.403)	0.024
Per 10 μg/m^3	-0.160 (-0.408, 0.088)	0.206	-2.379 (-5.171, 0.414)	0.095
O_3				
First quartile	Ref	—	Ref	—
Second quartile	0.092 (0.003, 0.180)	0.043	1.468 (0.476, 2.459)	0.004
Third quartile	0.184 (0.070, 0.297)	0.002	2.218 (0.945, 3.490)	0.001
Fourth quartile	0.371 (0.226, 0.516)	< 0.001	3.950 (2.322, 5.578)	< 0.001
Per 10 μg/m^3	0.112 (0.076, 0.149)	< 0.001	1.068 (0.657, 1.479)	< 0.001
Multiple pollutant models*				
$PM_{2.5}$				
First quartile	Ref	—	Ref	—
Second quartile	0.078 (-0.035, 0.191)	0.174	0.432 (-0.833, 1.697)	0.503
Third quartile	0.010 (-0.128, 0.147)	0.890	-0.683 (-2.227, 0.861)	0.386
Fourth quartile	0.295 (0.099, 0.490)	0.003	2.022 (-0.178, 4.222)	0.072
Per 10 μg/m^3	0.092 (0.034, 0.150)	0.002	0.725 (0.074, 1.376)	0.029
NO_2				
First quartile	Ref	—	Ref	—
Second quartile	-0.119 (-0.259, 0.021)	0.095	-1.105 (-2.674, 0.464)	0.168
Third quartile	0.001 (-0.176, 0.178)	0.991	0.597 (-1.394, 2.588)	0.557
Fourth quartile	0.122 (-0.101, 0.346)	0.284	3.410 (0.896, 5.925)	0.008
Per 10 μg/m^3	-0.126 (-0.373, 0.121)	0.316	-2.052 (-4.839, 0.735)	0.149
O_3				
First quartile	Ref	—	Ref	—
Second quartile	0.090 (0.002, 0.179)	0.046	1.461 (0.470, 2.452)	0.004
Third quartile	0.171 (0.057, 0.285)	0.003	2.108 (0.834, 3.381)	0.001
Fourth quartile	0.346 (0.200, 0.492)	< 0.001	3.723 (2.090, 5.357)	< 0.001
Per 10 μg/m^3	0.102 (0.065, 0.139)	< 0.001	0.984 (0.569, 1.400)	< 0.001

Abbreviation: CI refers to confidence interval

Associations were estimated by adjusting for household air pollution, calendar year, gross domestic product, cigarette smoking, alcohol drinking, physical inactivity, hypertension, diabetes, total cholesterol, vegetable and fruit intake, and ambient temperature

The cut points are 16.51, 22.74 and 33.36 μg/m^3 for $PM_{2.5}$ quartiles; 0.30, 0.62 and 1.55 μg/m^3 for NO_2 quartiles; and 65.73, 77.73 and 93.62 μg/m^3 for O_3 quartiles

* Refers to the estimated associations after mutually adjusting for other air pollutants

associated with a 0.118 (95%CI: 0.060 to 0.175) higher ASMR and 0.966 (95%CI: 0.321 to 1.611) higher DALYs of AD and other dementias, after adjusting for all the covariates. When the annual average $PM_{2.5}$ concentration dropped below the WHO air quality guideline (AQG; 10 μg/m^3), the ASMR and DALYs decreased by 0.270 (95%CI: 0.113 to 0.428) and 3.033 (95%CI: 1.272 to 4.795), respectively (data not shown). Non-linear C-R curves were observed between ambient $PM_{2.5}$ and the ASMR and DALYs (Chi-square = 8.76 and 3.53; *p* value = 0.003 and 0.060) (Fig. 2). Both the ASMs and DALYs increased rapidly when the $PM_{2.5}$ concentration was lower than 20 μg/m^3, and the trend remained relatively stable as the concentration increased further. Similar associations were observed when considering delayed impacts (Table S5), correlations with other air pollutants

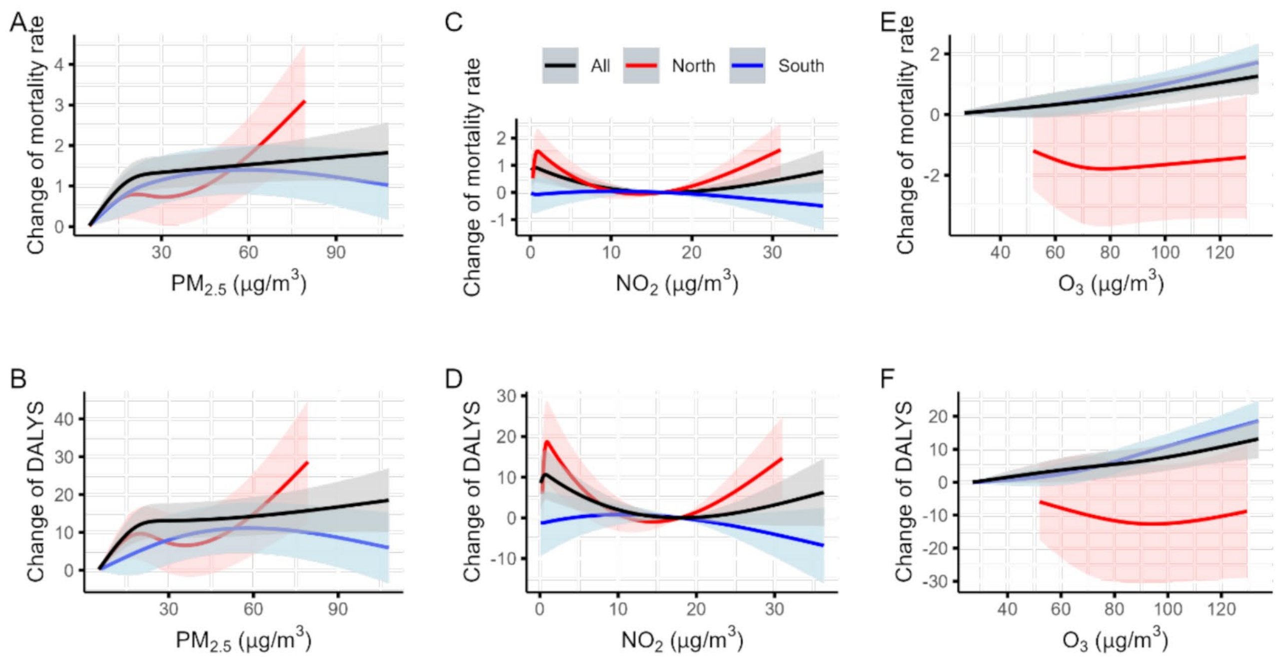

Fig. 2 Concentration-response associations between ambient air pollution and age-standardised mortality rates and disability-adjusted life-years of Alzheimer's disease and other dementias

Solid lines represent the estimated associations between air pollution and Alzheimer's disease and other dementias, and grey bands represent the corresponding 95% confidence intervals

(Table 2 and S6), and different source of $PM_{2.5}$ air pollution (Table S7). Table 3 shows the associations between the AAPC in $PM_{2.5}$ and AD and other dementias. Compared to the second tertile of the AAPC in $PM_{2.5}$ (-1.12–0.14%), reduced $PM_{2.5}$ was associated with a lower ASMR of 0.062 (95%CI: -1.272 to 1.149) per 100,000 persons and fewer DALYs by 3.116 (95%CI: -19.917 to 13.686) per 100,000 persons.

Table 2 shows that each 10 μg/m^3 increase in ambient O_3 was associated with a 0.112 (95%CI: 0.076 to 0.149) higher ASMR and 1.068 (95%CI: 0.657 to 1.479) higher DALYs of AD and other dementias. When the annual average O_3 dropped below < the AQG (70 μg/m^3), the ASMR and DALYs decreased by 0.149 (95%CI: 0.069 to 0.229) and 1.796 (95%CI: 0.903 to 2.688), respectively (data not shown). Linear C-R associations were found between ambient O_3 and the ASMR and DALYs (*p* value for the linearity tests was 0.345 and 0.461, respectively) (Fig. 2E and F). Similar associations were observed when examining 2-year average O_3 alone (Table S5) and together with other air pollutants (Table 2 and S6). Compared with the second tertile of AAPC in O_3 (-0.08–0.46%), reduced O_3 was associated with a lower ASMR of 0.933 (95%CI: -1.847 to -0.019) per 100,000 persons and fewer DALYs by 12.793 (95%CI: -25.565 to -0.021) per 100,000 persons (Table 3).

Figure 2C and D illustrates the U-shaped associations between ambient NO_2 and AD and other dementias. The minimum ASMR and DALYs were observed when the NO_2 was approximately 16–17 μg/m^3. Overall associations between NO_2 (AAPC) and AD and other dementias were relatively weak (Tables 2 and 3). The associations remained stable after controlling for other air pollutants (Table 2 and S6) and excluding missing data before 2005 (Table S8).

Table S9 shows that air pollution–dementia associations were probably different in the Global North and Global South. Compared with the Global North, the Global South showed a significantly stronger association between ambient O_3 and AD and other dementias (Table S9, Figure S16). The difference in the associations was 0.127 (95%CI: 0.041 to 0.213) for the ASMR and 2.275 (95%CI: 1.298 to 3.252) for DALYs. In addition, the associations between AD and other dementias and air pollution were found to be stronger in countries/territories with low or medium HDI values than those with high or very high HDI values, although the differences in the associations were not always statistically significant (Table S10, Figure S17).

Discussion

This large-scale study evaluated the associations between ambient air pollution and the burden of AD and other dementias from 1990 to 2019 across 149 countries/territories. The results revealed that long-term exposure to ambient air pollution was associated with higher ASMR

Table 3 Associations between average annual percentage changes in air pollution and age-standardised mortality rates and disability-adjusted life-years of Alzheimer's disease and other dementias

	Mortality rate	*P* value	Disability-adjusted life-years	*P* value
	Coefficients (95%CI)		Coefficients (95%CI)	
Single pollutant models				
$PM_{2.5}$				
First tertile	-0.062 (-1.272, 1.149)	0.920	-3.116 (-19.917, 13.686)	0.717
Second tertile	Ref	–	Ref	–
Third tertile	0.070 (-0.830, 0.970)	0.879	2.007 (-10.485, 14.500)	0.753
Trend test	0.067 (-0.527, 0.661)	0.826	2.440 (-5.804, 10.683)	0.563
NO_2				
First tertile	-0.454 (-1.385, 0.478)	0.341	-7.008 (-19.939, 5.923)	0.288
Second tertile	Ref	–	Ref	–
Third tertile	-0.296 (-1.225, 0.633)	0.533	-4.710 (-17.611, 8.191)	0.474
Trend test	0.078 (-0.418, 0.575)	0.758	1.139 (-5.760, 8.038)	0.746
O_3				
First tertile	-0.933 (-1.847, -0.019)	0.047	-12.793 (-25.565, -0.021)	0.052
Second tertile	Ref	–	Ref	–
Third tertile	0.401 (-0.570, 1.372)	0.420	1.511 (-12.065, 15.086)	0.828
Trend test	0.679 (0.138, 1.220)	0.015	7.409 (-0.175, 14.993)	0.058
Multi-pollutant models*				
$PM_{2.5}$				
First tertile	-0.052 (-1.273, 1.169)	0.934	-3.328 (-20.263, 13.607)	0.701
Second tertile	Ref	–	Ref	–
Third tertile	0.070 (-0.843, 0.983)	0.880	2.455 (-10.21, 15.119)	0.705
Trend test	0.063 (-0.544, 0.670)	0.839	2.796 (-5.621, 11.213)	0.516
NO_2				
First tertile	-0.459 (-1.396, 0.477)	0.338	-6.711 (-19.592, 6.17)	0.309
Second tertile	Ref	–	Ref	–
Third tertile	-0.382 (-1.328, 0.564)	0.430	-6.161 (-19.176, 6.853)	0.355
Trend test	0.042 (-0.462, 0.545)	0.872	0.321 (-6.611, 7.254)	0.928
O_3				
First tertile	-0.952 (-1.868, -0.036)	0.044	-12.901 (-25.587, -0.216)	0.048
Second tertile	Ref	–	Ref	–
Third tertile	0.504 (-0.492, 1.500)	0.323	2.760 (-11.033, 16.553)	0.696
Trend test	0.742 (0.185, 1.300)	0.010	8.153 (0.417, 15.890)	0.041

Abbreviations: AAPC refers to average annual percentage change; CI refers to confidence interval

Associations were estimated by adjusting for household air pollution, calendar year, gross domestic product, cigarette smoking, alcohol drinking, physical inactivity, hypertension, diabetes, total cholesterol, vegetable and fruit intake, and ambient temperature

The cut points were – 1.12% and 0.14% for the tertiles of $PM_{2.5}$ AAPC; -0.29% and 0.72% for the tertiles of NO_2 AAPC; and – 0.08% and 0.46% for the tertiles of O_3 AAPC

* Refers to the estimated associations after mutually adjusting for other air pollutants

and DALYs of AD and other dementias globally. Reducing air pollution has the potential to attenuate the global burden of AD and other dementias. We further found spatial disparities in the O_3–dementia associations, with stronger associations observed in the Global South than in the Global North. Notably, countries/territories with low or medium HDI values generally exhibited a greater burden of AD and other dementias attributable to ambient air pollution than those with high HDI.

Global spatial and temporal trend

Between 1990 and 2019, the ASMR and DALYs of AD and other dementias increased by an average of 0.11% and 0.09% each year, respectively. Consistent with a previous study [12], we observed an overall increasing trend of ASMR and DALYs of AD and other dementias during the study period. Such an increasing trend may be partially attributable to the ageing population and the improvement in diagnostic tests for neurological diseases, in addition to potential risk factors [20]. We also observed consistently higher ASMR and DALYs in the Global South than in the Global North (median value: 23.65 vs. 22.08 per 100,000 persons for ASMR and 326.60 vs. 335.09 per 100,000 persons for DALYs). Particularly, in Africa, the AAPC in the ASMR was more than twice that in the global ASMR (Table 1). This disparity between the Global South and Global North can be explained by the well-established health systems, developed economics, and better living environments in the Global North. Despite the decreasing trend observed in a few developed countries (Figures S2 and S3), extra efforts are still required to combat the burden of AD and other dementias, especially in the Global South.

We observed a generally decreasing trend of ambient $PM_{2.5}$ worldwide (0.46% each year), whereas ambient O_3 increased in most countries/territories (0.17% per year), especially in Africa and Asia during the study period. The formation of O_3 is complex and mainly involves interaction between solar ultraviolet radiation and other air pollutants (including volatile organic compound and NO_X). Therefore, future air pollution control strategies should focus more on O_3 air pollution and the combination of the three studied air pollutants. Our results also revealed variations in the spatial distributions of the three air pollutants. $PM_{2.5}$ pollution was mainly clustered in North Africa, NO_2 pollution in Central Europe, and O_3 pollution in Middle East and Southern Asia (Fig. 1B and S9). Local source of air pollution, culture, and climate may partially explain these heterogeneities.

$PM_{2.5}$ and Alzheimer's disease and other dementias

We found that each 10 μg/m^3 increase in the annual average $PM_{2.5}$ was associated with a 0.118 higher ASMR and 0.966 higher DALYs, respectively, worldwide (Table 2). A few reviews and global studies have examined their associations [9–11], but only one depicted their C-R associations [10]. The negative associations between long-term exposure to ambient $PM_{2.5}$ and AD or other dementias have also been found in previous cohort studies with information on personal characteristics [21–23]. It should be noted that the overall benefits of $PM_{2.5}$ reduction on AD and other dementias were statistically significant (Table 3). This is possibly because the large variations of $PM_{2.5}$ pollution in different countries and adopting different AQGs may have practically meaning. However, air pollution control still has different levels of benefits on the alleviation of the burden of AD and dementias. The potential mechanism underlying this link is considered to mainly involve brain inflammation, brain connectome damage, and increased levels of microglia-derived brain extracellular vesicles [7].

To the best of our knowledge, no study has investigated the differences in the air pollution–dementia associations between the Global North and Global South. We found that compared with the Global South, air pollution–dementia associations were relatively stronger in the Global North where ambient $PM_{2.5}$ concentration was higher, although the differences were not statistically significant (Figure S16 A and B). The weaker associations in the Global South possibly because the population living in that region is better adapted to the health impact of high $PM_{2.5}$ air pollution. Further studies in the Global South, especially in Africa, are required to confirm our findings.

O_3 and Alzheimer's disease and other dementias

To date, no relevant global study has examined the O_3–dementia associations. Our study found consistent and linear associations between ambient O_3 and AD and other dementias at the global scale (Fig. 2). We also found that a reduced O_3 concentration is linked to a reduced ASMR and DALYs of AD and other dementias (Table 3). In addition, a few cohort studies with information on personal characteristics have observed the adverse impacts of long-term exposure to O_3 on AD, neurological diseases and cognitive decline [24–26].

Our study filled the knowledge gap regarding the differences in O_3–dementia associations between the Global North and South. We found significantly stronger associations in the Global South than in Global North, and the differences in the associations were 0.127 (95%CI: 0.041 to 0.213) for ASMR and 2.2745 (95%CI: 1.298 to 3.252) for DALYs. Notably, we observed weakly negative associations between ambient O_3 and AD and other dementias in the Global North (Table S9, Figure S16). Several cohort studies also observed protective or nonsignificant associations between O_3 and AD or dementia in a few countries in the Global North [27–29]. The relatively small sample size (*N* = 49 countries/territories) in the Global North, different climates, indoor air pollution level and range of O_3 may explain the differences in the health impacts of O_3 (Table S3). Contrast O_3–NO_2 correlations in the Global North (ρ = -0.11) and Global South (ρ = 0.18) may also explain the differences. In addition, compared with the Global South, countries/territories in the Global North had generally established control measurements of air pollution sooner and had a better health system to diagnose and treat AD and other dementias. Therefore, the health impacts of O_3 pollution in the Global North may be attenuated by the above factors.

NO_2 and Alzheimer's disease and other dementias

In this study, a higher NO_2 was generally associated with a greater burden of dementia, and reduced NO_2 air pollution may alleviate the disease burden. However, the NO_2–dementia associations were relatively weak (Tables 2 and 3). To date, no relevant global studies examined NO_2–dementia associations. Previous cohort studies have shown similar statistically nonsignificant [27] or significant [29, 30] negative associations between long-term exposure to ambient NO_2 and AD and/or other dementias in different countries. In addition, we found consistently stronger associations in the Global North than in the Global South, as well as in countries/territories with low/medium HDI values than in those with high HDI values. This finding suggests evident regional inequity in the health impact of ambient NO_2.

Strengths and limitations

First, by including 149 countries/territories, this study addressed the geographically biases of previous studies and provided evidence of potential disparities in air pollution–dementia associations across countries/territories and regions. This study synthesised data from regions with a variety of HDI levels, air pollution levels, climates, cultures, and overall medical conditions. Second, this study narrowed the knowledge gap regarding dynamic associations between air pollution and AD and other dementias across 30 years. Both improved and deteriorated air quality were considered in the study. This study also provided sufficient statistical power to detect air pollution–dementia associations and explore inequity in air pollution impacts between the Global North and Global South. Third, this study examined three main air pollutants, and both ambient and household air pollution were included. This study also controlled for a series of covariates. Therefore, the research findings were stable and reliable.

Our analyses are not without limitations. This study used population-level data, and the spatial resolution was relatively low. The findings might not be appliable to individuals. However, this was a global study mainly investigating the associations between long-term exposure to air pollution and the disease burden of AD and other dementias over three decades. Population-level information is sufficient and appropriate to assess long-term temporal trends and heterogeneity or inequity in countries/territories with different HDI levels. Our main findings are also supported by previous studies with individual information [31]. Second, a common limitation of the GBD studies is that the data on AD and other dementias were estimates instead of being derived from direct measurements or primary data. Therefore, cases of underestimation cannot be ruled out, especially in developing countries where relevant research on neurological diseases is scarce. Further individual-level studies within these regions are warranted to minimise the potential bias. Third, we did not distinguish the types and disease course of AD. The ASMR and DALYs in countries with different proportions of types and disease courses of dementia were different. This may have affected the estimated associations with air pollution. Further studies examining the associations of air pollution with types of dementia are required. However, differentiating the types/subtypes of dementias is difficult, even in studies with individual-level information. Thus, examining associations with different (sub)types of dementias at the global scale may be more challenging. Fourth, we did not investigate the air pollution–dementia associations separately in different age and gender groups due to the limitation of information on age- and sex-specific covariates. However, we controlled for age disparities by examining the age-standardised mortality rate and DALYs and including age-standardised covariates in this study. Further studies investigating gender sensitivity to the air pollution-dementia associations are required. Fifth, we employed a repeated cross-sectional study design. While yearly data for each country were collected repeatedly, this design inherently limited in its ability to examine the causal effects of air pollution on AD and other dimensions. Further longitudinal study designs are required to evaluate potential causal associations more effectively. Finally, this study integrated multiple data sources, including air pollution levels and covariates. These data were derived from various institutions, each potentially applying different methods and assessment standards, which could result in data inconsistency or bias. However, all datasets included in this study have been widely used and validated in previous studies. Moreover, the results of sensitivity analysis 3 indicate that different data sources did not significantly affect our main findings. Additionally, our other sensitivity analyses further confirm the robustness of our results. Therefore, we are confident that our research is reliable and free from significant bias.

Conclusions

This study found that increased concentration of $PM_{2.5}$ and O_3 was associated with an increased global burden of AD and other dementias, while NO_2 was marginally associated with these conditions. In general, the Global North demonstrated a greater disease burden of AD and other dementias linked to $PM_{2.5}$ and NO_2 than the Global South. Further studies in the Global South are required to address the inequity in air pollution impacts.

Abbreviations

AD	Alzheimer's disease
ASMR	Age-standardised mortality rate
DALYs	Disability-adjusted life-years
AAPCs	Average annual percentage changes
CI	Confidence interval
GBD	Global Burden of Disease
C-R	Concentration – response
$PM_{2.5}$	Particulate matter that has a diameter of 2.5 micrometre or less
NO_2	Nitrogen dioxide
O_3	Ozone
ICD	International Classification of Diseases
HDI	Human development index

Supplementary Information

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Supplementary Material 1

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Author contributions
Cui Guo and Dongze Wu conceptualized and designed the study. Cui Guo acquired the data. Cui Guo, Dongze Wu, and Ruiyun Li searched literature. Cui Guo and Dongze Wu analyzed data. Cui Guo, Jun Yang, Xingcheng Lu, Xiang Yan Chen, Jun Ma, Changqing Lin, Alexis K. H. Lau, Yingzhao Jin, Ruiyun Li, Shenjing He drafted the manuscript and produced the figures. All authors critically revised the manuscript. Cui Guo and Ruiyun Li obtained the funding and supervised this study.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors declare that they have no conflicting interests related to this manuscript.

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