The impacts of air pollution on mortality and hospital readmission among Medicare beneficiaries with Alzheimer's disease and Alzheimer's disease-related dementias: a national retrospective cohort study in the USA

Shuxin Dong, Danielle Braun, Xiao Wu, Maayan Yitshak-Sade, Deborah Blacker, Marianthi-Anna Kioumourtzoglou, Joel Schwartz, Daniel Mork, Francesca Dominici, Antonella Zanobetti

Summary

Background Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD) are prevalent neurodegenerative disorders, posing a critical worldwide public health challenge. Ambient air pollution has been identified as a potential risk factor for AD progression based on toxicological and epidemiological studies. We aimed to evaluate the impacts of air pollution—including fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), summer ozone (O_3), and oxidant—on readmission or death among Medicare enrollees previously hospitalised with an AD/ADRD diagnosis code.

Methods We constructed a population-based nationwide retrospective cohort including all Medicare fee-for-service beneficiaries (aged ≥65 years) in the contiguous USA (2000–16) hospitalised with AD/ADRD, and followed them up from the year after their first hospitalisation until (1) year of death (mortality cohort) and (2) year of second hospitalisation for any cause (readmission cohort). We calculated annual average $PM_{2.5}$, NO_2, summer O_3, and oxidant concentrations for each individual at their residential ZIP code in each year after their first hospitalisation with AD/ADRD. We applied Cox proportional hazard models for the mortality and readmission cohorts stratifying on individual risk factors and adjusting for socioeconomic status, seasonal temperatures, and relative humidity.

Findings Our cohort consisted of 5 544 118 individuals, of whom 4 543 759 (82·0%) died and 3 880 894 (70·0%) were readmitted to the hospital during the study period. The average follow-up times were 3·34 years (SD 2·60) for the mortality cohort and 1·98 years (SD 1·65) for the readmission cohort. In both the mortality and readmission cohorts we found significant associations with each pollutant. For an IQR increase in NO_2, we found a hazard ratio (HR) for mortality of 1·012 (95% CI 1·009–1·015) and an HR for readmission of 1·110 (1·104–1·117). In the readmission cohort, we found an HR of 1·084 (1·079–1·089) for an IQR increase (3·87 μg/m³) in $PM_{2.5}$. The results slightly decreased in multi-pollutant models. The results of effect modification for mortality and readmission varied by pollutant, but higher risks were found among Black males and among those eligible for Medicaid in general.

Interpretation We provide new evidence that among a susceptible population with previous AD/ADRD-related hospitalisations, annual air pollution exposure since first hospitalisation is associated with risk of readmission and death.

Funding National Institute on Aging.

Copyright © 2025 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY-NC-ND 4.0 license.

Lancet Planet Health 2025; 9: e114–23

Department of Environmental Health (S Dong SM, Prof J Schwartz PhD, A Zanobetti PhD), **Department of Biostatistics** (D Mork PhD, D Braun PhD, Prof F Dominici PhD), **and Department of Epidemiology** (Prof D Blacker PhD, Prof J Schwartz), **Harvard T.H. Chan School of Public Health, Boston, MA, USA; Department of Data Science, Dana-Farber Cancer Institute, Boston, MA, USA** (D Braun); **Department of Biostatistics** (X Wu PhD) **and Department of Environmental Health Sciences** (M-A Kioumourtzoglou PhD), **Mailman School of Public Health, Columbia University, New York, NY, USA; Department of Environmental Medicine and Climate Science, Icahn School of Medicine at Mount Sinai, New York, MA, USA** (M Yitshak-Sade PhD); **Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA** (Prof D Blacker)

Correspondence to: Shuxin Dong, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA 02215, USA **shuxindong@hsph.harvard.edu**

Introduction

Neurodegenerative disorders are a major cause of death and disability globally, posing a critical worldwide public health challenge. Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD) are the most prevalent neurodegenerative disorders, with an estimated 5·8 million cases in 2020.[1] Without major advances in treatment and prevention, cases are projected to almost triple to 13·8 million by 2050.[1] The lack of effective treatments for AD/ADRD underscores the importance of identifying modifiable risk factors for AD/ADRD progression.

Long-term air pollution exposure is associated with increased mortality and other health outcomes.[2,3] Research suggests that air pollution, by triggering mechanisms such as oxidative stress and neuroinflammation,[4] might hasten the onset of neurodegenerative diseases, leading to earlier hospital admissions.[4–6] Oxidative stress and inflammatory processes might play a key pathogenic role in AD,[7] and exposure to air pollution has repeatedly been linked to oxidative stress,[8] elevated inflammatory biomarkers, and atherosclerosis, both in animal and epidemiologic studies.[9,10] Therefore, air pollution could be an important risk factor in AD progression.

Research in context

Evidence before this study

The number of people diagnosed with neurodegenerative disorders has increased across the world, and there is an urgent need to understand the potential modifiable risk factors that exacerbate neurodegenerative disorders and especially Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD). Recently, there has been an increased interest in studying the impact of air pollution, a ubiquitous yet modifiable risk factor, on neurodegenerative disorders. We searched PubMed for studies examining associations of air pollution exposure with neurological disorders published until November, 2024. We used the keywords: ("PM2.5" OR "fine particulate matter" OR "fine particles" OR "air pollution" OR "air pollutants") AND ("neurological" OR "neurodegeneration" OR "neurodegenerative" OR "cognitive" OR "Alzheimer's disease" OR "dementia"). Toxicological studies provided evidence that through biological pathways such as oxidative stress and neuroinflammation, ambient air pollution could exacerbate disease progression. Epidemiological studies have provided evidence of the association between air pollution exposure and neurodegeneration. A recent review found that long-term exposure to $PM_{2.5}$ can increase the risk of dementia and AD/ADRD, while other reviews focused on dementia and cognitive decline with unclear findings. Some papers examined the effect of air pollution and AD/ADRD among people receiving Medicare. No studies focused on the susceptible population of people hospitalised with AD/ADRD to examine whether air pollution exacerbates the need for a subsequent readmission or death.

Added value of this study

To the best of our knowledge, this is the first national study to investigate the relationship between long-term exposure to air pollution and time to any readmission or death among the more susceptible population of Medicare enrollees with a previous hospitalisation with a diagnostic code for AD/ADRD. Our results provide evidence that exposure to air pollution accelerates readmission for any cause and to a lesser extent accelerates death. In addition, the effects of air pollution on both mortality and any readmission were found in both single-pollutant and multi-pollutants models and varied by sex, race or ethnicity, Medicaid eligibility, and age, with Black individuals found to be more at risk compared with White individuals, Hispanic individuals, and those of other races. Key features of this study are that we accounted for the competing risk of death in the readmission cohort and index event bias to address several sources of bias. We examined a large US population of over 5·5 million patients with AD/ADRD, with 17 years of follow-up, and used high-resolution spatiotemporal model air pollution predictions to assign exposures to each individual during the follow-up time.

Implications of all the available evidence

In this more susceptible population, exposure to air pollution exacerbates the risk of rehospitalisation for any cause and death. Our study adds to the small but emerging evidence that long-term air pollution might increase the risk of hospitalisation for neurodegenerative disorders, and that the risk remains elevated in the subgroup of the population who is at higher risk due to a previous hospitalisation. In addition, the greatest risk is not due to one pollutant alone; traffic-related pollutants together are the most dangerous to people with neurodegenerative disorders. This evidence suggests that a re-evaluation of the existing air quality standards is necessary as further reductions in ambient air pollution could benefit people with AD/ADRD and the ageing US population more broadly.

Studies on AD/ADRD using Medicare[11,12] found that annual $PM_{2.5}$ exposure level was significantly associated with an increased hazard of first hospitalisation with AD/ADRD. A review[13] found that long-term $PM_{2.5}$ exposure might increase the risk of dementia and ADRD. However, most previous studies have focused primarily on a single pollutant, and to the best of our knowledge, there is an absence of evidence on the effect of air pollution on the more susceptible population of people already living with AD/ADRD.

In this study, we focused on Medicare enrollees admitted with an AD/ADRD diagnosis code. We followed them up until a second hospitalisation for any cause, including AD/ADRD (hereafter referred to as readmission), or until death, and examined the link between air pollution exposure ($PM_{2.5}$, nitrogen dioxide [NO_2], summer ozone [O_3], oxidant) and health outcomes, as death and readmission, in the contiguous USA during 2000–16. We applied Cox proportional hazard models, and we adjusted for competing risk of death using an inverse probability weighting (IPW) approach in the readmission cohort. In both readmission and death analyses, we considered single-pollutant and multi-pollutant models while adjusting for individual-level factors and ZIP code-level socioeconomic and demographic covariates. We also compared our results on individuals with AD/ADRD with a comparison group consisting of the Medicare population with a previous hospitalisation for any cause. Finally, we examined potential effect modifications by sex, race or ethnicity, age, population density, and Medicaid eligibility.

Methods

Study population

We obtained Medicare Part A claims data from the Centers for Medicare and Medicaid Services and selected all Medicare fee-for-service beneficiaries aged 65 years or older who entered the cohort between Jan 1, 2000, and Dec 31, 2016. Each individual has a unique identifier for

tracking over time. The Medicare master beneficiary file contains annually updated individual information, including age, sex, race or ethnicity, date of death, Medicaid eligibility (a proxy for low socioeconomic status), and residential ZIP code.

Medicare Part A data are required to identify the AD/ADRD cohort used throughout our analyses. We defined an AD/ADRD-related hospitalisation (or a hospitalisation with AD/ADRD) as a claim where any AD/ADRD codes appeared among the first ten diagnosis billing codes using ICD-9 and ICD-10, following the codes used in the Chronic Conditions Data Warehouse algorithm for "Alzheimer's disease, related disorders, or senile dementia" (appendix p 4), which include indicators for chronic conditions.

We constructed two open cohorts for each health outcome: a mortality cohort and a readmission cohort. Starting from the year of their first AD/ADRD-related hospitalisation, participants were followed up by calendar year (January–December) until death or end of the study period (Dec 31, 2016) for the mortality cohort; individuals were followed up until readmission, death, or the study's end for the readmission cohort. Because individuals were in both cohorts, we treated mortality as a censoring event in the readmission cohort and as an outcome in the mortality cohort. We excluded individuals without complete follow-up information on individual-level variables in both sub-cohorts.

This study was conducted under IRB 21-0032 approved by the Harvard T.H. Chan School of Public Health Human Subjects Committee.

Exposures: $PM_{2·5}$, NO_2, summer O_3, oxidant

We obtained annual ambient $PM_{2·5}$, O_3, and NO_2 concentrations from validated ensemble models for the years 2000–16.[14–16] To account for complex atmospheric mechanisms, generalised additive models were fit by integrating three machine learning models (neural networks, random forest, and gradient boosting), allowing for spatially varying weights among them. The models relied on monitoring data and were calibrated using satellite data, meteorological variables, land-use variables, elevation, chemical transport model predictions, several reanalysis datasets, and other predictors to obtain predicted daily $PM_{2·5}$, daily NO_2, and daily maximum 8-h O_3 concentrations at 1 km² grid cells across the contiguous USA. The ensemble models showed good predictive performance, with cross-validated R^2=0·89 for annual $PM_{2·5}$ predictions[14] and 0·788 for NO_2.[16] For O_3, the model had the best performance during summer, with an R^2 of 0·88.[15]

We averaged the grid cell predictions by ZIP code and calculated the annual average $PM_{2·5}$ and NO_2 concentrations for each ZIP code. For O_3, we computed summer (June–August) ZIP code averages. The average annual exposures were calculated in each year after an individual's first hospitalisation with AD/ADRD. To investigate the effect of oxidative capacity of air pollution, we calculated oxidant exposure level based on NO_2 and O_3:

$$\text{Oxidant exposure level} = \frac{1·07 \times NO_2 + 2·075 \times O_3}{3·145}$$

We assigned predicted annual $PM_{2·5}$, NO_2, summer O_3, and oxidant to every person-year by ZIP code of residence and calendar year.

Meteorological information and other potential confounders

We obtained daily maximum temperature and relative humidity at 4 km² grid cells for the contiguous USA from gridMET via Google Earth Engine. We averaged daily maximum temperature and relative humidity by season, defined as winter (December–February) and summer (June–August). These averages were included in the models to represent yearly weather exposure.

See Online for appendix

Other potential confounders that have been associated with ambient air pollution and implicated in neurological health[17] are socioeconomic status and general life habits including: (1) average BMI and smoking rate from the Behavioral Risk Factor Surveillance System; and (2) median household income, median value of housing units, proportion of residents below the poverty line, proportion of residents with a high-school diploma, proportion of Hispanic residents, proportion of Black residents, population density, and proportion of occupants who owned their house, from the US census. Missing yearly data were added using linear interpolation. Further details are described in the appendix (p 3).

Statistical analysis

To examine the association between air pollutants and time to readmission (in the readmission cohort) or mortality (in the mortality cohort) separately, we applied Cox proportional hazard models with the Andersen–Gill formulation[18] to allow time-varying covariates. The model stratified the baseline hazard by individual risk factors and adjusted for potential confounding by socioeconomic and meteorological variables. Additionally, we accounted for regional variability by including intercepts that represented a baseline hazard for each US census region (Northeast, South, Midwest, and West) and addressed unmeasured temporal confounding with calendar year indicators.

For each outcome we fit single-pollutant and multi-pollutant models (two-pollutant model for $PM_{2·5}$ + oxidant; three-pollutant model for $PM_{2·5}$ + NO_2 + summer O_3) to consider effects of one pollutant while controlling for simultaneous effects of correlated exposures (appendix p 2).

We examined effect modification by including interaction terms between each pollutant and the following risk factors: sex, Medicaid eligibility, urban versus rural areas (below *vs* above median population

density), median poverty rate (below *vs* above median), entry age (≤85 *vs* >85 years), and race or ethnicity (White, Black, Hispanic, or other) to identify more susceptible subgroups. We further examined the effects by race or ethnicity stratified by patients' Medicaid eligibility.

ZIP code-level random effects were considered but were computationally infeasible due to the large number of ZIP codes. To account for potential spatial correlation in the observations, robust standard errors were estimated using an m-out-of-n bootstrap procedure[19] applied to residential ZIP code. We reported results as hazard ratios (HRs) for an IQR increase in exposures with 95% CIs. All statistical analyses were performed using R 4.3.1, and the code is available online.

For the **code** see https://github.com/ShuxinD/pm-no2-o3-hospitalization-death-ADRD-coxph

We used IPWs to account for the competing risk of death in time-to-readmission analyses. Since the study population is older, death is a substantial competing risk when analysing time to readmission as some individuals might die before a subsequent hospitalisation. We used stabilised weights to account for possible outlier weights that might give undue importance to certain observations (appendix p 2).

The study population includes enrollees who have had an AD/ADRD-related hospitalisation. This sub-population of Medicare enrollees might be more or less prone to having other risk factors for AD/ADRD, leading to the potential for index event bias, where the exposure–response relationship can be distorted by the collider bias (see directed acyclic graph in appendix p 17). We used IPWs to correct for this index event bias in single-pollutant models as a sensitivity analysis in both the mortality and readmission cohorts (appendix p 2). To test whether the census regions were confounders, we excluded these from the single-pollutant models. Additionally, we followed up Medicare enrollees from their first any-cause hospitalisation until their subsequent any cause rehospitalisation (readmission) or death (mortality) and replicated the previous analyses as a comparison group analysis.

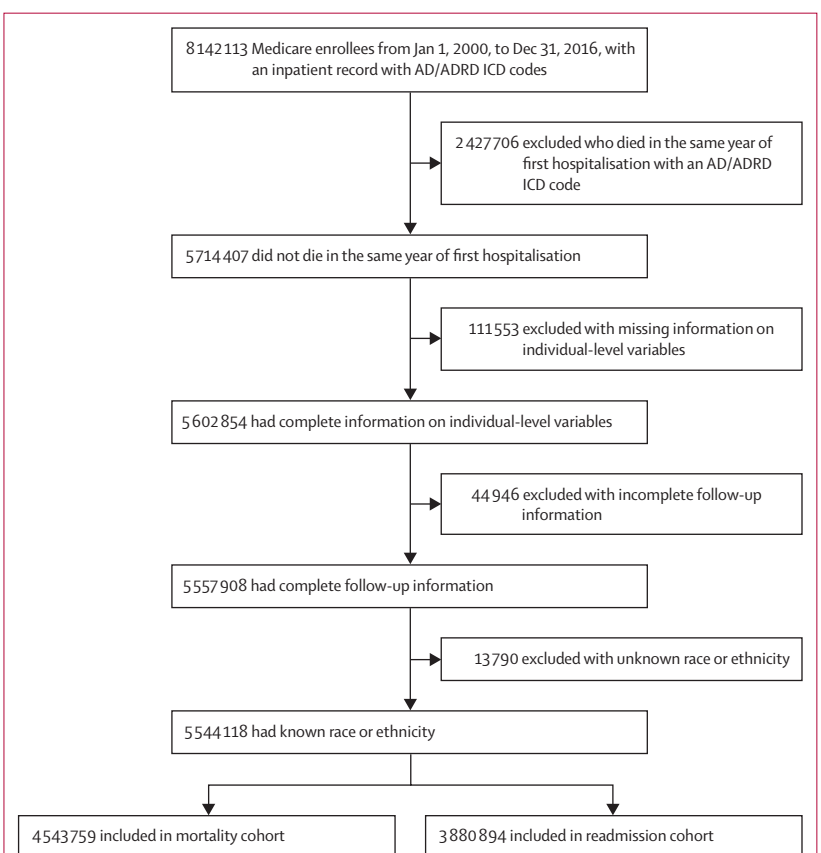

Figure 1: **Flow chart describing the process of constructing the cohorts**
AD/ADRD=Alzheimer's disease and Alzheimer's disease-related dementias.

	Overall (n=5 544 118)
Sex	
Women	3 661 634 (66·0%)
Men	1 882 484 (34·0%)
Race	
White	4 715 117 (85·0%)
Black	610 799 (11·0%)
Hispanic	108 539 (2·0%)
Other*	109 663 (2·0%)
Entry age, years	82·93 (7·30)
Entry age in categories, years	
≥65 to <70	337 328 (6·1%)
≥70 to <75	581 754 (10·5%)
≥75 to <80	1 027 373 (18·5%)
≥80 to <85	1 425 412 (25·7%)
≥85 to <90	1 316 379 (23·7%)
≥90 to <95	669 743 (12·1%)
≥95 to <100	178 085 (3·2%)
≥100 to <105	7610 (0·1%)
≥105 to <115	434 (<0·1%)
Medicaid eligibility	
Eligible	1 653 271 (29·8%)
Ineligible	3 890 847 (70·2%)
Region	
Midwest	1 316 419 (23·7%)
Northeast	1 172 506 (21·1%)
South	2 292 843 (41·4%)
West	762 350 (13·8%)
Death	4 543 759 (82·0%)
Readmission	3 880 894 (70·0%)
Average follow-up time, years	
Mortality cohort	3·34 (2·60)
Readmission cohort	1·98 (1·65)

Data are n (%) or mean (SD). AD/ADRD=Alzheimer's disease and Alzheimer's disease-related dementias. *Other includes Asian, American Indian, and Alaskan Native.

Table 1: **Cohort characteristics of Medicare fee-for-service Part A beneficiaries hospitalised with an AD/ADRD diagnosis code in the contiguous USA from 2000 to 2016 followed up from the first such hospitalisation until the event (death or readmission) or the study's end**

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Our study population consisted of 5 544 118 Medicare beneficiaries hospitalised with an AD/ADRD diagnosis code (figure 1). Among all individuals, 4 543 759 (82·0%) died and 3 880 894 (70·0%) were readmitted to the hospital for any cause during follow-up. The average follow-up times were 3·34 years (SD 2·60) for the mortality cohort and 1·98 years (SD 1·65) for the readmission cohort. The average entry age was 82·9 years (SD 7·3). More than one-quarter (29·8%) were eligible for Medicaid and the most common race (85·0%) was White (table 1).

Table 2 summarises the spatial distribution of exposures and other covariates at the ZIP code level. The spatial variation was calculated by averaging over calendar years on a one-row-per-ZIP code dataset. Correlations between pollutants varied between 0·15 and 0·42 (appendix pp 11–12). The annual average $PM_{2·5}$ (10·1 μg/m³, IQR 3·68 μg/m³) and NO_2 exposures (19·2 parts per billion [ppb], IQR 13·84 ppb) were calculated based on all measured values. NO_2 was below the National Ambient Air Quality Standard (53 ppb), whereas $PM_{2·5}$ was above the newly updated standard of 9·0 μg/m³. Air pollution distributions in the readmission cohort were similar to those in the mortality cohort.

Exploratory analyses based on smoothing functions indicated exposure–response relationships were approximated by a linear function (appendix pp 13–14). We found significantly increased hazard for mortality and readmission across single-pollutant and multi-pollutant models (table 3), except for summer O_3. An IQR increase in average annual NO_2 was associated with an increased hazard for mortality of 1·012 (95% CI 1·009–1·015), equivalent to 45 853 deaths attributable to an IQR increase in NO_2. The effect sizes of $PM_{2·5}$, NO_2, summer O_3, and

	Mortality cohort					Readmission cohort				
	Mean	SD	25th percentile	Median	75th percentile	Mean	SD	25th percentile	Median	75th percentile
Exposures										
$PM_{2·5}$ (μg/m³)	10·1	2·8	8·2	9·9	11·9	10·2	2·9	8·2	10·0	12·1
NO_2 (ppb)	19·2	9·7	11·6	17·4	25·4	19·4	9·8	11·7	17·5	25·6
Summer O_3 (ppb)	44·7	5·7	41·7	44·7	48·0	44·8	5·7	41·8	44·8	48·3
Oxidant (ppb)	32·1	3·8	29·5	31·8	34·3	32·1	3·8	29·5	31·8	34·4
Meteorological covariates										
Summer average maximum temperature (°C)	31·0	3·4	28·6	30·8	33·3	30·9	3·4	28·5	30·7	32·2
Winter average maximum temperature (°C)	9·9	7·3	4·2	8·7	15·4	9·8	7·3	4·1	8·7	14·3
Summer average maximum relative humidity (%)	88·0	10·6	85·0	90·3	94·7	88·0	10·8	85·1	90·4	94·8
Winter average maximum relative humidity (%)	84·6	7·4	80·7	85·6	89·7	84·8	7·5	80·9	85·8	90·0
BRFSS covariates										
BMI (kg/m²)	27·5	1·0	26·9	27·5	28·1	27·4	1·0	26·8	27·4	28·0
Smoking rate	0·46	0·07	0·42	0·46	0·50	0·47	0·07	0·42	0·47	0·51
Census covariates										
Median household income (×$1000)	53·8	22·8	38·0	48·3	64·3	53·4	22·5	37·8	48·0	63·5
Median value of housing units (×$1000)	203·2	160·6	100·6	152·3	245·9	198·4	156·6	98·8	149·1	238·5
Proportion of residents below the poverty line (%)	9·9	6·8	5·4	8·1	12·4	9·7	6·7	5·4	8·0	12·1
Proportion of residents with a high-school diploma (%)	25·0	14·2	14·4	22·5	33·2	25·3	14·3	14·5	22·8	33·7
Proportion of occupants who owned a house (%)	66·9	16·5	58·5	69·7	78·4	67·2	16·2	59·0	70·0	78·6
Proportion of Hispanic residents (%)	11·8	17·0	2·1	5·1	13·2	11·4	16·6	2·0	4·9	12·8
Proportion of Black residents (%)	13·4	19·7	1·5	4·9	15·9	12·8	19·2	1·4	4·6	15·0
Population density (1000 people per square mile)	3·6	9·6	0·2	1·1	3·4	3·4	9·1	0·2	1·0	3·3

BRFSS=Behavioral Risk Factor Surveillance System. ppb=parts per billion.

Table 2: **Distribution of annual air pollution exposure ($PM_{2·5}$, NO_2, summer O_3, oxidant), meteorological variables, census variables, and BRFSS variables**

oxidant decreased slightly in multi-pollutant models compared with single-pollutant models, and summer O_3 became non-significant. We also found significant associations between each pollutant and readmissions while accounting for competing risk of death, with effect sizes higher than the mortality associations. In single-pollutant models, we found an HR of 1·110 (95% CI 1·104–1·117) for an IQR increase of 13·92 ppb in NO_2, and an HR of 1·084 (1·079–1·089) for an IQR increase of 3·87 μg/m³ in $PM_{2·5}$. In multi-pollutant models, these effect sizes slightly decreased but remained significant. The numbers of readmissions attributable to an IQR increase in $PM_{2·5}$ and NO_2 were 164 203 and 255 577, respectively. Oxidant was also associated with readmissions in single-pollutant and multi-pollutant models, while summer O_3 was not significant when adjusting for $PM_{2·5}$ and NO_2. Results were unchanged when excluding competing risk IPWs (appendix p 5).

Figure 2 and figure 3 show the results of effect modification for mortality and readmission, and these results varied by pollutant. We found that the risk of mortality was significantly higher among people older than 85 years, among Black individuals (although not for O_3), and among those eligible for Medicaid (for NO_2 and oxidant). Moreover, the risk of readmission associated with increased exposure was significantly higher among those eligible for Medicaid, and among Black individuals (only for NO_2). The results by race or ethnicity stratified by dual eligibility varied by pollutant and outcome (appendix pp 15–16), with pollution effects on mortality

	IQR	Hazard ratio (95% CI)		
		Single-pollutant model	$PM_{2·5}$ + NO_2 + summer O_3 model	$PM_{2·5}$ + oxidant model
Mortality				
$PM_{2·5}$	3·68 μg/m³	1·007 (1·005–1·009)	1·003 (1·001–1·005)	1·006 (1·003–1·008)
NO_2	13·84 ppb	1·012 (1·009–1·015)	1·010 (1·007–1·014)	NA
Summer O_3	6·28 ppb	1·002 (1·000–1·004)	1·001 (0·998–1·003)	NA
Oxidant	4·75 ppb	1·006 (1·004–1·008)	NA	1·004 (1·001–1·006)
Readmission (with competing risk)				
$PM_{2·5}$	3·87 μg/m³	1·084 (1·079–1·089)	1·053 (1·048–1·059)	1·070 (1·065–1·075)
NO_2	13·92 ppb	1·110 (1·104–1·117)	1·085 (1·079–1·092)	NA
Summer O_3	6·51 ppb	1·020 (1·016–1·024)	0·999 (0·997–1·001)	NA
Oxidant	4·82 ppb	1·055 (1·050–1·059)	NA	1·031 (1·027–1·036)

NA=not applicable. ppb=parts per billion.

Table 3: **Estimated hazard ratios for an IQR increase in single-pollutant models and multi-pollutant models**

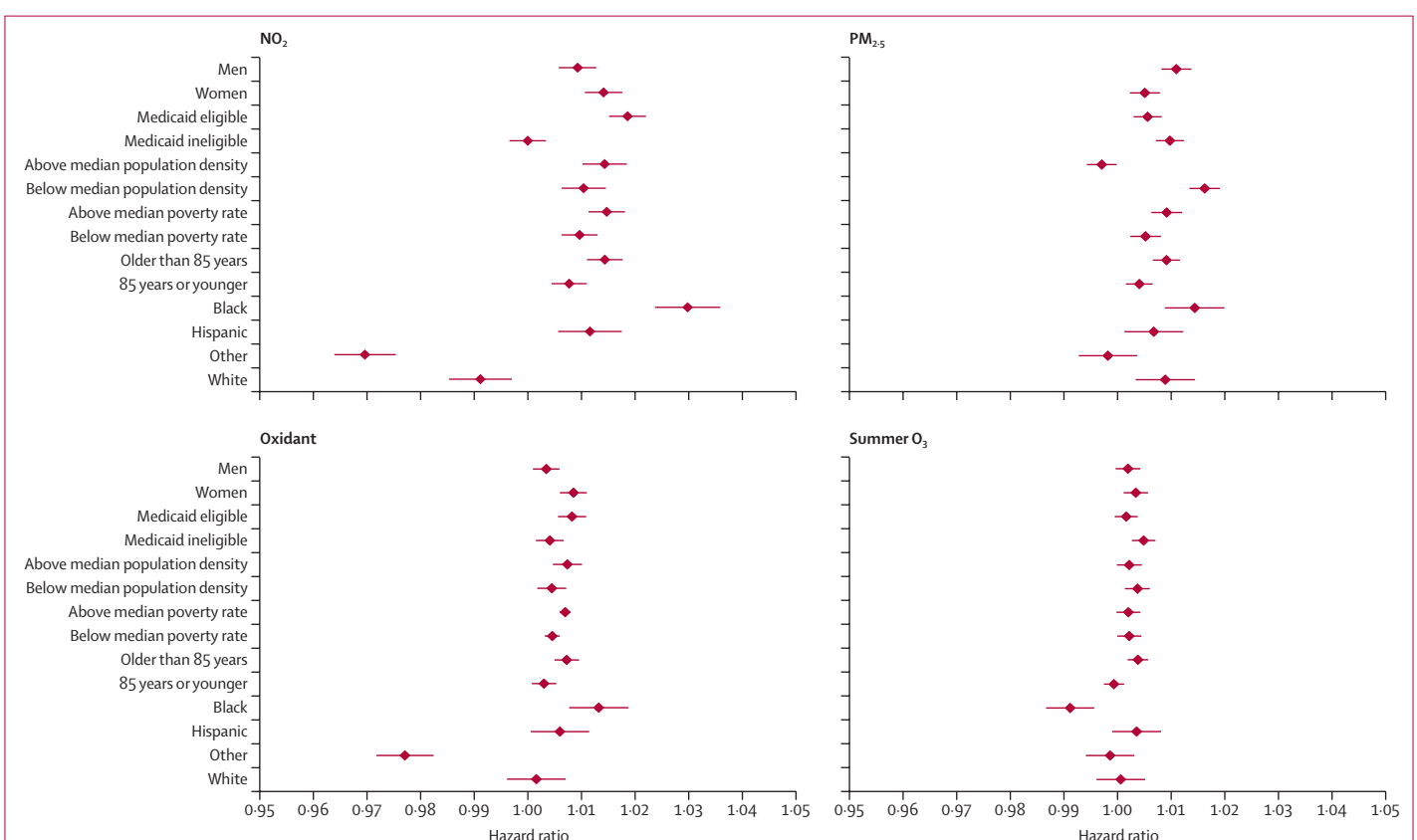

Figure 2: **Estimated hazard ratios of mortality for an IQR increase in $PM_{2·5}$, NO_2, summer O_3, and oxidant in single-pollutant models by sex, entry age, Medicaid eligibility, population density and poverty rate at the residential address, and race or ethnicity**
Error bars show 95% CIs.

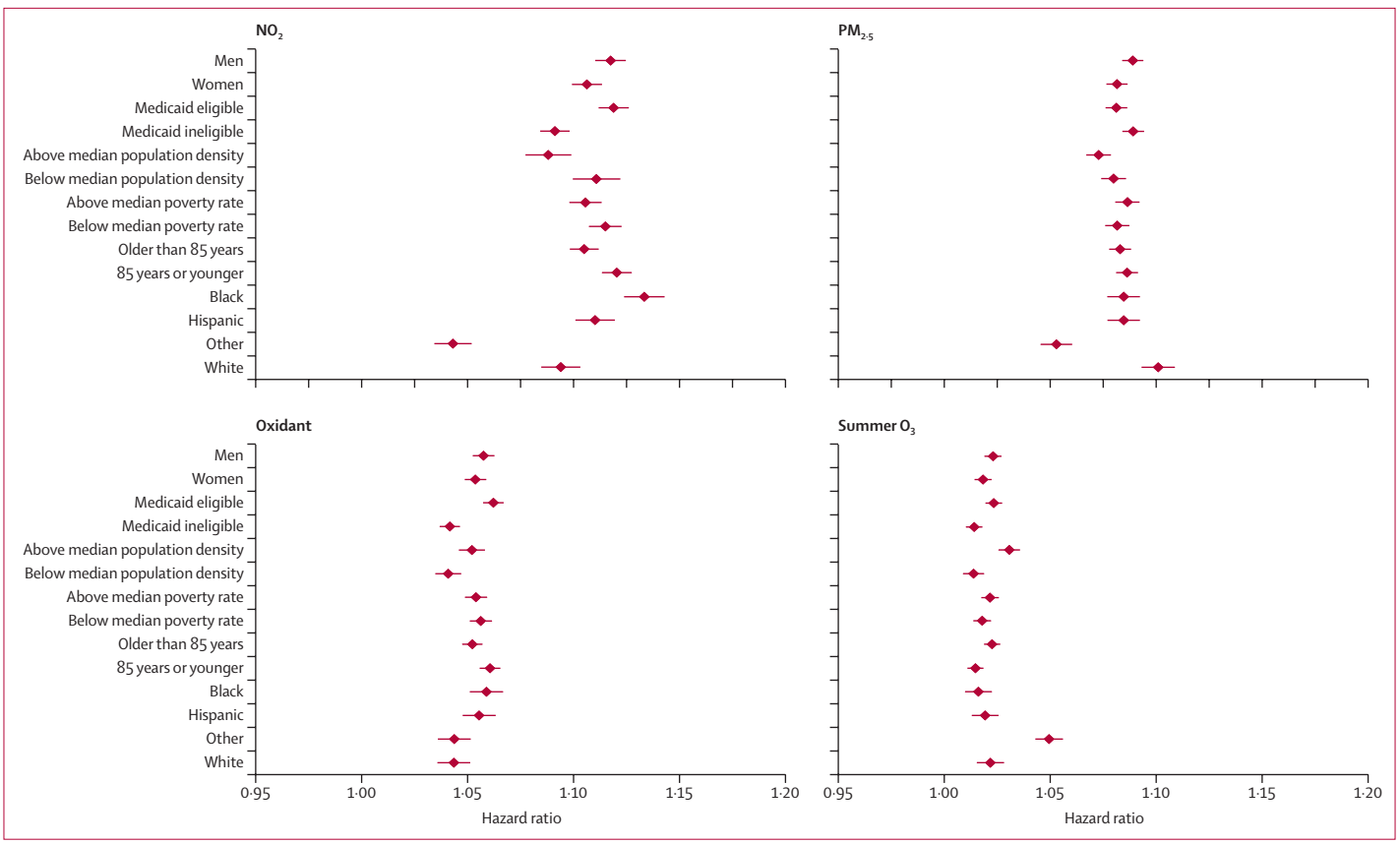

Figure 3: **Estimated hazard ratios of readmission for an IQR increase in $PM_{2.5}$, NO_2, summer O_3, and oxidant in single-pollutant models modified by sex, entry age, Medicaid eligibility, population density and poverty rate at the residential address, and race or ethnicity**
Error bars show 95% CIs.

mostly higher among Black people and Hispanic people with dual eligibility for Medicaid compared with non-dual-eligible White people.

In sensitivity analyses, when adjusting for the index event bias (appendix p 6), the effect size decreased except for $PM_{2·5}$ and summer O_3 with mortality. When we excluded the census region variables in the single-pollutant models (appendix p 10), the point estimates shifted up and down, which implies potential confounding by regions. Additionally, when comparing with the Medicare population with a previous hospitalisation (cohort size of 31 102 086), we found larger effects of air pollution on readmission and smaller effects on mortality in the patients with AD/ADRD (appendix p 7).

We also present the results of all potential confounders without bootstrapping from the multi-pollutant model for mortality (appendix p 8) and readmission (appendix p 9). We observed that higher BMI and higher smoking rate at the neighbourhood level are harmful for both health outcomes while controlling for other covariates.

Discussion

This is the first study to investigate the effects of long-term exposure to air pollution on readmission and death among Medicare enrollees with a previous hospitalisation with a diagnostic code of AD/ADRD. We found that exposure to air pollution is associated with an increased hazard of readmission for any cause, as well as death, and that the effects of air pollution on both mortality and any readmission varied by sex, race or ethnicity, Medicaid eligibility, and age.

Given the high percentage of deaths in the cohort, we addressed bias due to possible death of individuals before readmission by accounting for the competing risk of death. We included IPWs in the model, assuming that those who died would have had a similar risk of readmissions as those who survived and had the same covariates value. In a sensitivity analysis, we adjusted for index event bias induced by restricting our study to individuals with an initial hospitalisation with an AD/ADRD diagnosis code. The results after adjusting for index event bias were attenuated within the mortality analysis but retained statistical significance.

We examined the relationship between death or readmission and each pollutant separately and in multi-pollutant models. The multi-pollutant model allows us to consider the effect of a single pollutant while controlling for simultaneous effects of correlated exposures, which

were moderate in our data. We continued to find significant results (except for O_3), although with smaller effect sizes compared with the single-pollutant models. Our findings strengthen the evidence that individual exposures are related to the outcome of interest and suggest that the contribution to accelerate death or readmission was not solely dependent on one pollutant. Specifically, NO_2 and $PM_{2·5}$ had the highest HRs, suggesting that traffic-related pollutants together are the most dangerous to people with neurodegenerative disorders. Some studies[20–22] support the relationship between proximity to roadways and AD/ADRD, which is consistent with our findings.[23] The finding that air pollution has a larger effect on rehospitalisation compared with mortality among people admitted with AD/ADRD suggests that individuals who are readmitted to the hospital for any cause are more susceptible to air pollution effects. In sensitivity analyses, patients with a previous hospitalisation for AD/ADRD were more susceptible to the effects of air pollution on readmission compared with those with any-cause previous hospitalisation.

This is the first study to examine the association between exposure to air pollution and AD/ADRD progression to readmission or death; therefore, we are unable to directly compare our results with other studies. Some studies examined the effects of air pollution in the Medicare population. A nationwide Medicare analysis[11] found a significant association between $PM_{2·5}$ and first hospital admission with AD/ADRD. Another nationwide analysis[12] reported an association of $PM_{2·5}$ and NO_2 with incident dementia. Another nationwide Medicare population study found significant associations between mortality and both $PM_{2·5}$ and O_3.[2] A study using five distinct approaches supported that a 10 μg/m³ decrease in $PM_{2·5}$ led to a statistically significant 6–7% decrease in mortality risk.[24] A more recent analysis restricted to people never exposed to $PM_{2·5}$ concentrations above 12 μg/m³ reported a higher effect size at the lower concentration. We defined long-term exposure over the course of a previous year, but there is evidence that time-lagged exposure over a decade or more could be related to increased risk of AD/ADRD health outcomes.[23]

Few studies investigated multi-pollutant exposure and AD/ADRD risk. A prospective population-based cohort study showed a positive exposure–response relationship between dementia and $PM_{2·5}$, NO_2, and noise, but not O_3.[25] Another population-based cohort study suggested that long-term exposures to O_3 and $PM_{2·5}$ above the current national standards were associated with increased risk of AD.[26] One hospital-based cohort study reported a positive association between NOx and O_3 and hospitalisation for dementia and a negative association for NO_2.[27] These studies examining several pollutants revealed contradictory results for NO_2 and O_3 in AD/ADRD epidemiological studies but agreed in their findings on the effects of $PM_{2·5}$, whereas we concluded that NO_2 is more important than or similar to $PM_{2·5}$.

In general, Black individuals in our analysis were more susceptible to all pollutants than White individuals, Hispanic individuals, and people of other races. Shi and colleagues[12] found similar results where the association between $PM_{2·5}$ or NO_2 and risk of AD/ADRD was greater among Black individuals. Likewise, Younan and colleagues[28] observed a two times greater risk of AD due to $PM_{2·5}$ exposure for Black women compared with White women. There is also an indication that Black individuals are diagnosed with AD/ADRD at higher rates than their White counterparts[29] and that Black individuals are more susceptible to negative effects of air pollution when considering outcomes such as mortality.[2]

Toxicological studies have shown that particles inhaled into the lungs can enter the bloodstream, cross the blood–brain barrier, and influence the central nervous system,[4] inducing inflammation through the production of reactive oxygen species.[4–6] The biological mechanisms of oxidative stress and neuroinflammation by which air pollution impacts cardiovascular disease provide a pathway for the effect of air pollution on AD/ADRD as well. Therefore, our findings suggest that long-term air pollution might not only exacerbate the risk of hospitalisation for people with neurodegenerative disorders but also further elevate the risk of recurrent hospitalisation in the subgroup of the population who is at higher risk due to a previous hospitalisation. In addition, we show that traffic-related pollutants together are the most dangerous to people with neurodegenerative disorders.

Our study has several strengths. First, we provided new evidence that among those with a hospital diagnosis code of AD/ADRD, air pollution is associated with mortality and any readmission. Instead of focusing on AD/ADRD incidence in the general population, we hypothesised that the AD/ADRD population is more susceptible to air pollution and that higher exposure to air pollution would exacerbate readmission and mortality. Second, we used a large US-based sample of over 5·5 million patients with AD/ADRD, with 17 years of follow-up. We used high-resolution spatiotemporal model predictions to assign exposures to each individual during the follow-up time. All models have excellent predictive accuracy, reducing the potential for exposure measurement error. Our analysis addressed several sources of bias including competing risks and index event bias. Finally, we control for a variety of individual-level and area-level covariates to adjust for a range of factors possibly related to the likelihood of readmission and death.

Our study has several limitations. Acknowledging that unmeasured confounding exists, we adjusted all models for multiple demographic and socioeconomic neighbourhood-level socioeconomic variables that could act as a surrogate for some unmeasured individual-level data, and expected the potential residual bias to be small. Individual-level risk factors for AD/ADRD, such as smoking, are not available in Medicare data. However,

similar studies[2,30] have previously assessed the sensitivity of results to the lack of these risk factors by comparing results using the Medicare population and the Medicare Current Beneficiary Survey with detailed individual-level information, and found that adjusting for these individual-level risk factors did not change the results. We did not examine the role of comorbidities, but future work should investigate how comorbidities exacerbate the effects of air pollution on health. We only included fee-for-service beneficiaries because hospitalisation data for Medicare Advantage enrollees are not available. Given that fee-for-service Medicare covered 76% of the population in 2010,[31] we believe that our results are generalisable to the population older than 65 years. Adjustment for additional covariates, such as greenspace, might be warranted but were not available for our study.

Another limitation is the use of administrative data, which has the potential for misclassification of AD/ADRD diagnoses. Dementia is in general underdiagnosed; it is poorly documented in medical records and death certificates, and rarely the primary cause of hospitalisation.[32] Therefore, the use of health system records, such as Medicare data, can result in outcome misclassification. Our use of Chronic Conditions Data Warehouse ICD codes has been compared against a known AD/ADRD cohort, and a previous study[32] found reasonable specificity in classifying cases but relative low sensitivity, which will bias our results towards the null. However, future studies might benefit from methods accounting for potential discrepancies in AD/ADRD diagnosis definitions. Using ZIP code aggregated air pollution data,[2,11,24,33,34] despite the excellent predictive accuracy of the air pollution models, has the potential for exposure measurement error. However, this is likely independent of health outcomes, resulting in bias towards the null.[35]

In conclusion, our study provides strong evidence that long-term exposure to air pollution is significantly associated with a higher risk of any readmissions and mortality among individuals hospitalised with AD/ADRD. This is the first long-term study that investigated people discharged after hospitalisation with AD/ADRD, and showed that, in this more susceptible population, exposure to pollutants such as $PM_{2.5}$ and NO_2 accelerates rehospitalisation and death. Our findings suggest that further reduction in ambient air pollution could benefit the AD/ADRD population.

Contributors

MY-S, DBl, M-AK, FD, and AZ contributed to the conceptualisation. SD and DBr curated the dataset. SD, DBr, XW, JS, and AZ contributed to the methodology. SD, DBr, and AZ administered the analyses. SD did the formal analyses and visualisation, and wrote the original draft. SD accessed and verified the dataset. All authors had full access to all the data in the study and final responsibility for the decision to submit for publication. All authors contributed to the revision of the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

All hospitalisation data used in our study were obtained from the Centers for Medicare & Medicaid Services under a data sharing agreement and we are not permitted to directly share the third-party raw data used in the analyses.

Acknowledgments

This study was supported by the National Institute on Aging (R01AG066793, RF1AG071024, 1RF1AG080948-01).

References

1 Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology* 2013; **80:** 1778–83.
2 Di Q, Wang Y, Zanobetti A, et al. Air pollution and mortality in the Medicare population. *N Engl J Med* 2017; **376:** 2513–22.
3 Chen J, Hoek G. Long-term exposure to PM and all-cause and cause-specific mortality: a systematic review and meta-analysis. *Environ Int* 2020; **143:** 105974.
4 Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci* 2009; **32:** 506–16.
5 Jayaraj RL, Rodriguez EA, Wang Y, Block ML. Outdoor ambient air pollution and neurodegenerative diseases: the neuroinflammation hypothesis. *Curr Environ Health Rep* 2017; **4:** 166–79.
6 Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid β-42 and α-synuclein in children and young adults. *Toxicol Pathol* 2008; **36:** 289–310.
7 Huang X, Moir RD, Tanzi RE, Bush AI, Rogers JT. Redox-active metals, oxidative stress, and Alzheimer's disease pathology. *Ann N Y Acad Sci* 2004; **1012:** 153–63.
8 Sørensen M, Daneshvar B, Hansen M, et al. Personal PM2.5 exposure and markers of oxidative stress in blood. *Environ Health Perspect* 2003; **111:** 161–66.
9 Dubowsky SD, Suh H, Schwartz J, Coull BA, Gold DR. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. *Environ Health Perspect* 2006; **114:** 992–98.
10 Araujo JA, Barajas B, Kleinman M, et al. Ambient particulate pollutants in the ultrafine range promote early atherosclerosis and systemic oxidative stress. *Circ Res* 2008; **102:** 589–96.
11 Shi L, Wu X, Danesh Yazdi M, et al. Long-term effects of $PM_{2.5}$ on neurological disorders in the American Medicare population: a longitudinal cohort study. *Lancet Planet Health* 2020; **4:** e557–65.
12 Shi L, Steenland K, Li H, et al. A national cohort study (2000–2018) of long-term air pollution exposure and incident dementia in older adults in the United States. *Nat Commun* 2021; **12:** 6754.
13 Cheng S, Jin Y, Dou Y, et al. Long-term particulate matter 2.5 exposure and dementia: a systematic review and meta-analysis. *Public Health* 2022; **212:** 33–41.
14 Di Q, Amini H, Shi L, et al. An ensemble-based model of $PM_{2.5}$ concentration across the contiguous United States with high spatiotemporal resolution. *Environ Int* 2019; **130:** 104909.
15 Requia WJ, Di Q, Silvern R, et al. An ensemble learning approach for estimating high spatiotemporal resolution of ground-level ozone in the contiguous United States. *Environ Sci Technol* 2020; **54:** 11037–47.
16 Di Q, Amini H, Shi L, et al. Assessing NO_2 concentration and model uncertainty with high spatiotemporal resolution across the contiguous United States using ensemble model averaging. *Environ Sci Technol* 2020; **54:** 1372–84.
17 Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement* 2015; **11:** 718–26.
18 Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Stat* 1982; **10:** 1100–20.
19 Ma X, Wang J. Robust inference using inverse probability weighting. *J Am Stat Assoc* 2019; **115:** 1–10.
20 Yuchi W, Sbihi H, Davies H, Tamburic L, Brauer M. Road proximity, air pollution, noise, green space and neurologic disease incidence: a population-based cohort study. *Environ Health* 2020; **19:** 8.

21 Calderón-Garcidueñas L, Villarreal-Ríos R. Living close to heavy traffic roads, air pollution, and dementia. *Lancet* 2017; **389:** 675–77.

22 Chen H, Kwong JC, Copes R, et al. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. *Lancet* 2017; **389:** 718–26.

23 Mork D, Braun D, Zanobetti A. Time-lagged relationships between a decade of air pollution exposure and first hospitalization with Alzheimer's disease and related dementias. *Environ Int* 2023; **171:** 107694.

24 Wu X, Braun D, Schwartz J, Kioumourtzoglou MA, Dominici F. Evaluating the impact of long-term exposure to fine particulate matter on mortality among the elderly. *Sci Adv* 2020; **6:** eaba5692.

25 Carey IM, Anderson HR, Atkinson RW, et al. Are noise and air pollution related to the incidence of dementia? A cohort study in London, England. *BMJ Open* 2018; **8:** e022404.

26 Jung CR, Lin YT, Hwang BF. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan. *J Alzheimers Dis* 2015; **44:** 573–84.

27 Cerza F, Renzi M, Gariazzo C, et al. Long-term exposure to air pollution and hospitalization for dementia in the Rome longitudinal study. *Environ Health* 2019; **18:** 72.

28 Younan D, Wang X, Gruenewald T, et al. Racial/ethnic disparities in Alzheimer's disease risk: role of exposure to ambient fine particles. *J Gerontol A Biol Sci Med Sci* 2022; **77:** 977–85.

29 Matthews KA, Xu W, Gaglioti AH, et al. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥65 years. *Alzheimers Dement* 2019; **15:** 17–24.

30 Makar M, Antonelli J, Di Q, Cutler D, Schwartz J, Dominici F. Estimating the causal effect of low levels of fine particulate matter on hospitalization. *Epidemiology* 2017; **28:** 627–34.

31 Neuman P, Jacobson GA. Medicare Advantage checkup. *N Engl J Med* 2018; **379:** 2163–72.

32 Taylor DH Jr, Østbye T, Langa KM, Weir D, Plassman BL. The accuracy of Medicare claims as an epidemiological tool: the case of dementia revisited. *J Alzheimers Dis* 2009; **17:** 807–15.

33 Kioumourtzoglou MA, Schwartz JD, Weisskopf MG, et al. Long-term PM2.5 exposure and neurological hospital admissions in the Northeastern United States. *Environ Health Perspect* 2016; **124:** 23–29.

34 Danesh Yazdi M, Wang Y, Di Q, Zanobetti A, Schwartz J. Long-term exposure to $PM_{2.5}$ and ozone and hospital admissions of Medicare participants in the Southeast USA. *Environ Int* 2019; **130:** 104879.

35 Josey KP, deSouza P, Wu X, Braun D, Nethery R. Estimating a causal exposure response function with a continuous error-prone exposure: a study of fine particulate matter and all-cause mortality. *J Agric Biol Environ Stat* 2023; **28:** 20–41.