Associations between life course exposure to ambient air pollution with cognition and later-life brain structure: a population-based study of the 1946 British Birth Cohort

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Summary

Background Previous research has linked higher exposure to air pollution to increased cognitive impairment at older ages. We aimed to extend the existing evidence in this area by incorporating exposures across the life course in addition to measures of cognition and brain structural imaging in participants at midlife to older age.

Methods For this population-based study, we used data from the Medical Research Council National Survey of Health and Development (NSHD; also known as the 1946 British Birth Cohort) and a neuroimaging substudy of the NSHD known as Insight 46. Participants were recruited after birth in a single week during March, 1946. Our objectives were to assess whether exposure to air pollutants in midlife (age 45–64 years) was associated with poorer processing speed and poorer verbal memory between the ages of 43 years and 69 years, and whether exposures were associated with poorer cognitive state and brain structure outcomes at age 69–71 years. Air pollution exposure data were available for nitrogen dioxide (NO_2; ages 45–64 years); particulate matter with diameter less than 10 μm (PM_{10}; ages 55–64 years); and nitrogen oxides (NO_x) and particulate matter with diameters less than 2·5 μm ($PM_{2·5}$) and between 2·5 μm and less than 10 μm (PM_{coarse}) and particulate matter absorbance ($PM_{2·5}$abs) as a measure of black carbon absorption (ages 60–64 years), with adjustments for early-life exposures to black smoke and sulphur dioxide. Verbal memory was tested with a 15-item recall task and processing speed with a visual search task at ages 43, 53, 60–64, and 69 years. The Addenbrooke's Cognitive Examination III (ACE-III), a measure of cognitive state, was conducted at age 69 years. Whole-brain, ventricular, hippocampal, and white matter hyperintensity volumes were assessed by MRI at age 69–71 years. Generalised linear models and generalised mixed linear models were used to explore associations between pollution exposure, cognitive measures, and brain structural outcomes, adjusted for sociodemographic factors including smoking status and neighbourhood deprivation.

Findings Between the ages of 43 years and 69 years, we included 1534 NSHD participants in the verbal memory and processing speed analysis. Of 2148 participants who underwent testing during the wave of follow-up in 2015–16, at age 69 years, 1761 were included in the ACE-III analysis. Of the 502 NSHD participants recruited into the Insight 46 substudy, 453 were included in the analysis. Higher exposure to NO_2 and PM_{10} was associated with slower processing speed between the ages of 43 years and 69 years (NO_2 β −8·121 [95% CI −10·338 to −5·905 per IQR increase in exposure]; PM_{10} β −4·518 [−6·680 to −2·357]). Higher exposure to all tested pollutants was associated with lower ACE-III score at age 69 years (eg, NO_2 β −0·589 [−0·921 to −0·257]). Higher exposure to NO_x was associated with smaller hippocampal volume (β −0·088 [−0·172 to −0·004]) and higher exposure to NO_2 and PM_{10} was associated with larger ventricular volume (NO_2 β 2·259 [0·457 to 4·061]; PM_{10} β 1·841 [0·013 to 3·669]) at age 69–71 years.

Interpretation Acknowledging the probable effects of exposure early in life, higher exposure to nitrogen dioxide, nitrogen oxides, and coarse particulate matter in midlife to older age was associated with poorer cognition, processing speed, and brain structural outcomes, strengthening evidence for the adverse effects of air pollution on brain function in older age.

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Introduction

Dementia and cognitive decline in older adults (age ≥65 years) are key global health priorities, with up to 153 million people predicted to be living with dementia by 2050.[1] Preventive interventions are therefore urgently needed. For older adults, higher exposure to some pollutants—notably particulate matter (eg, with a diameter of <2·5 μm, known as $PM_{2·5}$) and gaseous pollutants such as

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Research in context

Evidence before this study

Exposure to particulate matter and gaseous air pollutants has been associated with a range of health problems across the life course, including dementia and cognitive decline. We searched PubMed from database inception to March 10, 2025, with no language restrictions, using different terms for air pollution as the exposure ("air pollut*" or "environment* pollut*" or "particulate matter" or "$PM_{2·5}$" or "PM_{10}" or "nitrogen dioxide" or "NO_2") and cognition as the outcome measure ("cognition" or "cognitive decline" or "memory" or "executive function" or "attention" or "processing speed"), considering brain structural outcomes ("MRI" or "magnetic resonance spectroscopy" or "neuroimaging" or "imaging" or "PET"), and limiting the search to studies carried out in adult populations ("adult*"). We found a growing evidence base linking higher exposure to a range of pollutants to poorer cognitive state and to brain structural outcomes. However, results regarding associations with specific cognitive domains vary considerably—particularly those from studies with long-term longitudinal, repeated measures designs and from studies investigating gaseous pollutants and particulate matter of different sizes. Furthermore, there is very little evidence addressing the effects of cumulative exposure over the life course on cognition in older adults (age ≥65 years). Finally, few studies compare the effects of different pollutant exposures on cognition and brain structure among participants within the same cohort.

Added value of this study

This study in older adults has one of the longest follow-up periods among studies addressing the effect of air pollution on a broad range of cognitive outcomes and brain structural measures. Our findings suggest a reduction in general cognitive performance over time, related to higher long-term exposures to air pollutants. We expand on the existing evidence base to examine the association between exposures to different air pollutants, including nitrogen dioxide (NO_2) and particulate matter with a diameter of less than 2·5 μm ($PM_{2·5}$), and cognitive state and neuroimaging outcomes over a 26-year period. Unlike previous work, we adjusted for lifetime exposure to a range of pollutants while also adjusting for an extensive range of clinical and sociodemographic factors, including childhood cognition. We show that, even after adjusting for early-life exposure to air pollution and childhood cognition, exposures over the midlife (age 45–64 years) period to NO_2, nitrogen oxides (NO_x), and particulate matter—with diameters less than 2·5 μm (ie, $PM_{2·5}$), less than 10 μm (PM_{10}), and between 2·5 μm and 10 μm (PM_{coarse}), and particulate matter absorbance ($PM_{2·5}$abs) as a measure of black carbon absorption—are all associated with poorer general cognitive state, and PM_{10} and NO_2 are associated with poorer processing speed but not poorer verbal memory. We observed parallel changes in ventricular and hippocampal volume in individuals with higher exposure to NO_2, NO_x, and PM_{10}.

Implications of all the available evidence

This study not only reinforces the existing evidence of associations between higher exposure to a range of air pollutants and poorer general cognitive state in mid-to-late life (age 43–69 years), but also strengthens the evidence by showing that these associations are robust to the inclusion of participants' previous exposure and childhood cognitive performance. However, these findings should be considered in the context of the effects of exposure to air pollution earlier in life and the complex interactions of environmental and genetic factors with cognition and brain structure, which start in utero and are cumulative over the life course. Despite the possible heterogeneity in air pollutant profiles and exposures, the differing associations with cognitive domains and brain regions potentially suggest specific vulnerabilities after exposure to associated primary pollutants. The findings further support that air pollution is harmful, with potentially irreversible changes to the human brain, and that actions to reduce air pollution, including in midlife, could potentially provide benefits to people later in life, conserving cognitive and brain structure into older age.

nitrogen dioxide (NO_2)—has been associated with poorer cognitive state,[2] cognitive impairment,[3] and a higher risk of dementia,[4] with a population attributable fraction of risk for exposure in older age estimated at 3%.[5]

Disease processes underlying dementia and cognitive decline arise decades before the onset of symptoms,[5] and for air pollution exposure this may begin in the in-utero and postnatal stages.[6] These stages could be key periods for universal and targeted prevention of air pollution exposure, alongside interventions in midlife (age 40–64 years) and beyond to ensure healthy ageing and brain health. Current studies investigating pollution and cognitive impairment are often limited by age range, including studies investigating mixed-age cohorts,[2] and by the availability of lifetime pollutant exposures and outcomes for older-age cohorts, in which cumulative exposures within the cohort might have been different.[7] To our knowledge, cognitive outcomes resulting from air pollution exposure across the life course have been examined by only one study, which was limited to one pollutant ($PM_{2·5}$) and a single outcome (intelligence quotient).[8] Furthermore, evidence for the effects of exposure on a range of cognitive domains is conflicting, especially for gaseous pollutants (eg, NO_2) in comparison with $PM_{2·5}$.[2] In the UK, few studies have examined longitudinal associations with cognition across repeated timepoints, and those that have found mixed results.[3,9] Because these pollutants have different sources and potential mechanisms of action, identifying which is contributing to poorer cognition is important for developing informed policy.

Several putative mechanisms through which air pollution could negatively affect brain structure have been proposed, including the induction of neuroinflammation and oxidative stress, potentially as an indirect result of long-term cardiopulmonary effects.[3] In animal models, exposure to

pollutants—including NO_2—has been shown to promote neuroinflammation and neurodegeneration, including in hippocampal regions (eg, via cycloxygenase-2-mediated inflammatory pathways).[10] Little evidence is available in humans; however, findings suggest that the long-term consequences of neuroinflammation, oxidative stress, and neuronal cell death can manifest as neuroimaging differences, including in brain volume,[3] and in differences in early-life post-mortem examinations.[6] Studies combining pollutant exposure and cognitive and neuroimaging outcomes could provide mechanistic insights into how pollution is linked to dementia, particularly if participants are studied at an age younger than the common clinical onset of dementia and cognitive impairment but at which pathology and poor brain health is expected to accumulate. Studies such as this are much more scarce than those providing evidence for cognitive outcomes alone, and examine short exposure windows[11] and few exposures.[12]

To address these issues, we used data from the Medical Research Council (MRC) National Survey of Health and Development (NSHD; also known as the 1946 British Birth Cohort), a prospective population-based birth cohort, to examine associations between long-term exposure to outdoor air pollution and longitudinal cognition and in-depth neuroimaging measures of brain health. Notably, we address challenges in assessing temporality between exposure and outcomes across the life course by controlling for childhood cognition and historical air-pollution measures. Our two objectives were to assess whether higher long-term exposure to NO_2, nitrogen oxides (NO_x), and particulate matter ($PM_{2.5}$, particulate matter with diameters of <10 μm [PM_{10}] and between 2·5 μm and 10 μm [PM_{coarse}], and particulate matter absorbance [$PM_{2.5}$abs] as a measure of black carbon absorption fraction) in midlife to older age was associated with poorer processing speed and poorer verbal memory between the ages of 43 years and 69 years, and to assess whether these exposures were associated with poorer cognitive state and brain structure outcomes at age 69–71 years. We hypothesised that higher exposure would be associated with poorer performance in processing speed and verbal memory tests between the ages of 43 years and 69 years, and poorer cognitive state and brain structure outcomes at age 69–71 years.

Methods

Study design and participants

For this population-based study, we used data from the MRC NSHD. During one week in March, 1946, the mothers of 13 687 babies—encompassing 91% of births recorded in England, Scotland, and Wales that week—were initially interviewed and 5362 singleton babies, selected to contain roughly the same number of babies from each social class, were recruited to the NSHD cohort for follow-up (appendix p 4). Written informed consent was obtained from participants at all follow-up visits during adulthood and was retrospectively obtained for development data collected at younger ages. The most recent ethical approval for the NSHD was granted in 2014 by the National Research Ethics Service Committee London Queen Square and by the Scotland Research Ethics Committee (REC; 14/LO/1073) and Scotland A REC (14/SS/1009). Ethical approval for the neuroscience substudy, Insight 46, was granted by the National Research Ethics Service Committee London (14/LO/1173). A STROBE checklist is available in the appendix (pp 17–21).

Measures

Air pollution

We aimed to estimate exposure across the life course using several air pollution models constructed with contemporaneous monitoring data since 1946, although data availability varied between and within models over this time period. NO_2 exposure was modelled at ages 45, 55, and 64 years, with three land-use regression models;[13–15] PM_{10} exposure was modelled at ages 55 years and 64 years;[14,16] exposures to NO_x, $PM_{2.5}$, PM_{coarse}, and $PM_{2.5}$abs were modelled at age 64 years.[15,16] All models had a resolution of 100 metres × 100 metres, apart from that modelling NO_2 exposure at age 45 years, which had a resolution of 200 metres × 200 metres. Validation R^2 values reported by models varied depending on year and exposure, but most were 0·5 or greater. A description of the models and model selection is available in the appendix (pp 4–6). The concentrations of all pollutants were measured in $\mu g/m^3$, apart from $PM_{2.5}$abs, for which the unit was 10^{-5} m^{-1}. We further adjusted for previous exposure to mean concentrations of black smoke (a measure of particulates in the air) and sulphur dioxide (SO_2) at ages 16, 25, 36, and 45 years.[17] We used the Douglas–Waller Index to estimate coal consumption in the participants' county borough at birth, reported as low, medium, or high.

Verbal memory and processing speed

At ages 43, 53, 60–64, and 69 years, verbal memory was assessed with a 15-item recall task, after each word was presented for 2 s. The total score over three identical trials was used as a continuous measure, scored out of 45, with higher scores indicating better verbal memory. Different word lists were used at each follow-up visit to minimise practice effects.[18] Processing speed was assessed through a visual search task. The task involved crossing out two target letters among a block of text of individual letters in 1 min. Search speed was represented by the position reached at the end of this interval (maximum 600 at age 53–69 years and 450 at age 43 years), with a higher score indicating faster processing speed.[18]

Cognitive state and verbal fluency

Cognitive state at age 69 years was assessed using the Addenbrooke's Cognitive Examination-III (ACE-III; appendix p 6).[19] This test consists of 19 items, with a total score ranging between 0 and 100 points, in which higher

See Online for appendix

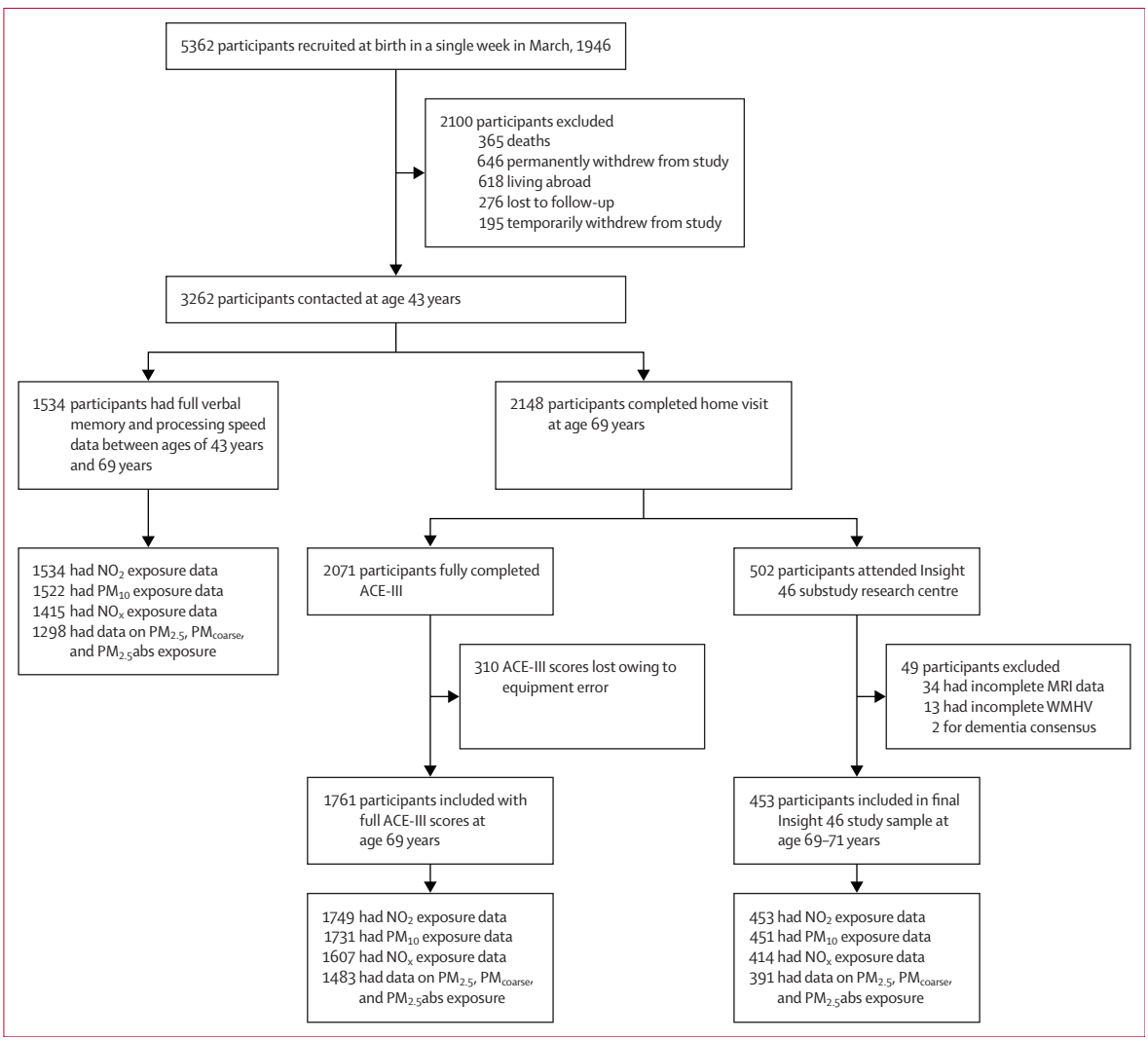

Figure 1: **Participant flowchart**
ACE-III=Addenbrooke's Cognitive Examination-III. NO_2=nitrogen dioxide. NO_X=nitrogen oxides. PM_{10}=particulate matter of diameter less than 10 μm. $PM_{2·5}$=particulate matter of diameter less than 2·5 μm. $PM_{2·5}$abs=particulate matter absorbance as a measure of black carbon absorption. PM_{coarse}=particulate matter with diameter between 2·5 μm and 10 μm. WMHV=white matter hyperintensity volume.

scores are indicative of better cognitive functioning. We also tested verbal fluency, one of the subscales of ACE-III, scored between 0 and 14 points. Both the total score and the verbal fluency subscale have a quasi-normal distribution—a normal distribution with a left skew.

Neuroimaging

A sample of NSHD participants were invited to the Insight 46 substudy and had a brain scan between the ages of 69 years and 71 years on a Biograph mMR 3 T PET/MRI scanner. Full details of the methods are provided elsewhere.[20] In brief, whole brain volume, left and right hippocampal volume (summed to give total hippocampal volume), and ventricular volume were quantified from T1-weighted MRI using automated techniques.[21,22] White matter hyperintensity volume (WMHV)—a marker of presumed cerebral small vessel disease—was assessed from T1-weighted and fluid-attenuated inversion recovery MRI using the segmentation algorithm Bayesian model selection.[23] Total intracranial volume was determined using statistical parametric mapping.[24] All volumes are reported in cm^3.

Covariates

Covariates were assigned sex at birth, educational attainment, occupational social class (of the participant's father when the participant was aged 4 years and of the participant themselves when they were aged 43 years and 53 years), neighbourhood deprivation (assessed at age 53 years and 60 years), cigarette smoking (measured in pack-years up

to age 63 years), childhood cognition (at age 15 years), and internalising and externalising symptoms at age 13–15 years. Covariates are described in full in the appendix (pp 6–7).

Statistical analysis

All analyses were carried out in Stata Version 18.0 MP. A description of all objectives and models and a timeline of measures is provided in the appendix (pp 23–25, 50). NO_2, PM_{10}, NO_x, $PM_{2.5}$, PM_{coarse}, and $PM_{2.5}$abs were included as continuous variables rescaled by IQR to enable comparison between pollutants on different concentration scales. All covariate measures were included from the closest available timepoint to each exposure.

We compared sociodemographic and clinical characteristics between participants who did not have an available ACE-III score at age 69 years and those who did, and between participants with an ACE-III score and those from the Insight 46 substudy. These comparisons were conducted using χ^2 tests, *t* tests, or Mann–Whitney *U* tests as appropriate.

For each objective, the final sample was derived from the complete data for outcome and exposure measures. To address missing data in covariates, multiple imputation models using chained equations were used under a missing-at-random assumption (appendix p 7). The main results reported are from models using this imputed data.

To address the first objective—assessing whether exposure in midlife to older age was associated with poorer processing speed and poorer verbal memory between the ages of 43 years and 69 years—we examined longitudinal associations between each pollutant (NO_2, modelled at ages 45, 55, and 60–64 years; and PM_{10}, modelled at ages 55 years and 60–64 years) and verbal memory and processing speed between the ages of 43 years and 69 years with the use of random intercept models, with participant for level 2 and repeated measures of cognition within each participant at level 1. Associations between exposure to NO_x, $PM_{2.5}$, PM_{coarse}, and $PM_{2.5}$abs (modelled at age 60–64 years) and verbal memory and processing speed at age 69 years were examined using linear regression models.

To address the second objective—assessing whether exposures were associated with poorer cognitive state and brain structure outcomes at age 69–71 years—we used generalised linear regression models to examine prospective associations between the mean exposure to NO_2, PM_{10}, NO_x, $PM_{2.5}$, PM_{coarse}, and $PM_{2.5}$abs and ACE-III total score and fluency, in addition to whole brain, ventricular, and total hippocampal volumes at ages 69–71 years. Owing to the non-normal distribution of WMHV, we fit a model using the gamma distribution and log link, with coefficients exponentiated.

All models were fitted separately for each outcome and air pollutant. Model 1 was an unadjusted model, including only outcome and exposure. Model 2 adjusted for sex assigned at birth, father's social class, internalising and externalising symptoms at age 13–15 years, educational attainment,

	ACE-III cohort (N=1761)	Insight 46 subcohort (N=453)
Assigned sex at birth		
Male	848 (48·2%)	233 (51·4%)
Female	913 (51·8%)	220 (48·6%)
Social class of father at participant age 4 years		
Professional or intermediate	426/1623 (26·3%)	144/437 (33·0%)
Non-manual skilled	343/1623 (21·1%)	100/437 (22·9%)
Manual skilled	482/1623 (29·7%)	108/437 (24·7%)
Partly skilled or unskilled	372/1623 (22·9%)	85/437 (19·5%)
Social class of participant at age 43 years		
Professional or intermediate	792/1591 (49·8%)	280/427 (65·6%)
Non-manual skilled	373/1591 (23·4%)	84/427 (19·7%)
Manual skilled	244/1591 (15·3%)	39/427 (9·1%)
Partly skilled or unskilled	182/1591 (11·4%)	24/427 (5·6%)
Social class of participant at age 53 years		
Professional or intermediate	790/1597 (49·5%)	283/439 (64·5%)
Non-manual skilled	391/1597 (24·5%)	90/439 (20·5%)
Manual skilled	225/1597 (14·1%)	39/439 (8·9%)
Partly skilled or unskilled	191/1597 (12·0%)	27/439 (6·2%)
Highest education attained by age 26 years		
No qualifications	500/1675 (29·9%)	72/440 (16·4%)
Up to O Level or equivalent	489/1675 (29·2%)	129/440 (29·3%)
A Level or equivalent and higher	686/1675 (41·0%)	239/440 (54·3%)
Exposure to air pollution at birth		
1 (low pollution)	281/1561 (18·0%)	66/415 (15·9%)
2	508/1561 (32·5%)	151/415 (36·4%)
3	418/1561 (26·8%)	109/415 (26·3%)
4 (high pollution)	354/1561 (22·7%)	89/415 (21·4%)
Smoking status (pack-years up to age 63 years), median (IQR)	3·8 (0 to 16·5)	1·5 (0 to 10)
Neighbourhood deprivation at age 53 years, median (IQR)	19·4 (17·5 to 21·4)	18·8 (17·1 to 20·8)
Neighbourhood deprivation at age 60 years, median (IQR)	15·4 (12·7 to 17·9)	14·6 (12·2 to 17·3)
Cognition score at age 15 years, median (IQR)	0·3 (−0·3 to 0·8)	0·5 (0·0 to 1·0)
Internalising symptoms at age 13–15 years		
Absent	816/1583 (51·5%)	242/433 (55·9%)
Mild	603/1583 (38·1%)	160/433 (37·0%)
Severe	164/1583 (10·4%)	31/433 (7·2%)
Externalising symptoms at age 13–15 years		
Absent	1232/1583 (77·8%)	361/433 (83·4%)
Mild	265/1583 (16·7%)	56/433 (12·9%)
Severe	86/1583 (5·4%)	16/433 (3·7%)
Verbal memory scores (points), median (IQR)		
Age 43 years	26 (22 to 30)	27 (23 to 31)
Age 53 years	25 (21 to 29)	26 (23 to 31)
Age 60–64 years	25 (21 to 29)	26 (22 to 30)
Age 69 years	22 (18 to 27)	24 (20 to 27)
Processing speed scores (points), median (IQR)		
Age 43 years	350 (297 to 415)	349 (301 to 408)
Age 53 years	288 (239 to 329)	288 (239 to 329)
Age 60–64 years	239 (231 to 307)	283 (239 to 307)
Age 69 years	239 (222 to 307)	239 (222 to 307)
ACE-III scores at age 69 years (points), median (IQR)		
Total score	93 (88 to 96)	94 (91 to 97)
Fluency score	11 (10 to 13)	12 (10 to 13)

(Table 1 continues on next page)

	ACE-III cohort (N=1761)	Insight 46 subcohort (N=453)
(Continued from previous page)		
Pollutant exposures (μg/m^3), median (IQR)		
NO_2 (age 45 years)	29·5 (25·5 to 35·3)	29·2 (25·5 to 35·6)
NO_2 (age 55 years)	26·8 (24·2 to 31·0)	26·9 (24·2 to 31·1)
NO_2 (age 60–64 years)	22·2 (17·5 to 26·7)	21·9 (17·3 to 26·9)
PM_{10} (age 55 years)	20·3 (18·9 to 21·8)	20·3 (19·0 to 21·8)
PM_{10} (age 60–64 years)	15·7 (14·8 to 16·6)	15·7 (14·8 to 16·6)
NO_x (age 60–64 years)	36·7 (29·0 to 45·1)	35·8 (27·4 to 44·3)
$PM_{2·5}$ (age 60–64 years)	9·6 (8·9 to 10·2)	9·5 (8·8 to 10·1)
PM_{coarse} (age 60–64 years)	6·1 (5·8 to 6·6)	6·1 (5·8 to 6·6)
$PM_{2·5}$abs (age 60–64 years; 10^{-5} m^{-1})	1·0 (0·9 to 1·2)	1·0 (0·9 to 1·2)
Mean SO_2 (age 16–45 years)	62·3 (47·2 to 81·3)	62·7 (47·6 to 81·7)
Mean black smoke (age 16–45 years)	38·2 (25·4 to 55·9)	37·4 (25·4 to 54·1)
Mean NO_2 (age 45 years to 60–64 years)	26·5 (23·2 to 31·1)	26·1 (23·0 to 30·3)
Mean PM_{10} (age 55 years to 60–64 years)	18·3 (17·1 to 19·7)	18·3 (17·0 to 19·7)
Age at scan date (years), median (IQR)	—	70·7 (70·1 to 71·2)
Volume by MRI (cm^3), median (IQR)		
Whole brain volume	—	1100·6 (1036·5 to 1163·3)
Ventricular volume	—	27·1 (19·9 to 37·4)
Hippocampal total volume	—	6·2 (5·9 to 6·7)
White matter hyperintensity volume	—	3·1 (1·6 to 6·8)

Data are n (%) unless otherwise stated. Percentages might not total 100 owing to rounding. ACE-III=Addenbrooke's Cognitive Examination-III. A level=Advanced Level. NO_2=nitrogen dioxide. NO_x=nitrogen oxides. O Level=Ordinary Level. PM_{10}=particulate matter of diameter less than 10 μm. $PM_{2·5}$=particulate matter of diameter less than 2·5 μm. $PM_{2·5}$abs=particulate matter absorbance as a measure of black carbon absorption. PM_{coarse}=particulate matter with diameter between 2·5 μm and 10 μm. SO_2=sulphur dioxide.

Table 1: **Characteristics and outcome scores of the ACE-III analysis cohort and Insight 46 subcohort**

neighbourhood deprivation (at whichever age was closest to the first exposure timepoint [53 years or 60 years], or time-varying for the first objective), social class in adulthood (at whichever age was closest to the first exposure timepoint [43 years or 53 years], or time-varying for the first objective), and smoking pack-years up to the age of 63 years. Fully adjusted models (model 3) also included previous air pollution exposure at birth and between the ages of 16 years and 45 years, as well as cognition at age 15 years, to address possible reverse directionality due to participants with poorer cognition in childhood potentially being more likely to live somewhere with higher pollution in adulthood. For neuroimaging outcomes, all models were adjusted for total intracranial volume and models 2 and 3 were adjusted for age at brain scan. Beta coefficients (β) and 95% CIs are presented for the difference in mean score (for ACE-III, processing speed, and verbal memory), and difference in volume (for brain structure) per IQR increase in exposure. Exponentiated beta coefficients are presented for WMHV, which represents change in WMHV (eg, 1·04=4% change) per IQR increase in exposure.

As a sensitivity analysis, we first assessed the effects of extreme exposure by repeating analyses to compare participants in the highest exposure quartile with those in the lowest three exposure quartiles. Second, to examine co-pollutant confounding, we ran two-pollutant models (appendix p 10). Third, we conducted a complete case analysis to assess any discrepancies with our imputed analysis. Finally, we used generalised additive models to account for possible non-linearity between pollutant–outcome associations (appendix pp 10–14).

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The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

At age 69 years, 2638 (49·2%) of the initial 5362 participants remained in the NSHD cohort. Of these, 2148 (81·4%) underwent a home visit during this wave of follow-up between March, 2015 and March, 2016 (figure 1),[25] of whom 1761 (81·9%) had ACE-III scores available and were included in the analyses (table 1). The median total score for the ACE-III was 93 points (IQR 88–96). Air pollution exposures at ages 45, 55, and 60–64 years were highly correlated within and across each wave with mean exposure to NO_2 and PM_{10} (correlation coefficients 0·18–0·84; appendix p 26). Correlations with previous exposure (to black smoke and SO_2) were low to moderate (range 0·05–0·57). Participants whose ACE-III scores were missing for any reason (eg, death, living abroad, withdrawal from the study, or loss to follow-up) were more likely than those with available ACE-III scores to have lower childhood cognition (p=0·0052), no qualifications (p=0·023), and slightly lower NO_2 exposure (p<0·0001) between the ages of 43 years and 60–64 years (appendix pp 27–28).

502 participants from within the NSHD cohort joined the Insight 46 neuroimaging substudy at ages 69–71 years (March, 2015–March, 2018; figure 1), of whom 453 were included in the analysis.[20] These participants had similar exposure levels to the ACE-III cohort (eg, median NO_2 exposure 26·5 [IQR 23·2–31·1] in the ACE-III cohort *vs* 26·3 [23·0–30·3] in the Insight 46 cohort; p=0·31), but had slightly higher total scores in the ACE-III (93 points [IQR 88–96] *vs* 94 [91–97]; p<0·0001), and were generally healthier[26] and lived in areas of lower deprivation (appendix p 28). A comparison of characteristics between participants with available ACE-III scores and those with available verbal memory and processing speed scores is available in the appendix (p 29).

No association was found between exposure to NO_2 or PM_{10} and verbal memory decline between the ages of 43 years and 69 years in fully adjusted models (NO_2 β –0·123 [95% CI –0·261 to 0·015]; PM_{10} β –0·011 [–0·167 to 0·145]). Higher exposure to NO_2 (between the ages of 45 years and 60–64 years) and PM_{10} (between the ages of 55 years to 60–64 years) was associated with slower processing speed between the ages of 43 years and 69 years (NO_2 β –8·121 [–10·338 to –5·905]; PM_{10} β –4·518 [–6.680 to –2.357]; table 2). We observed no associations between exposure to NO_x, $PM_{2·5}$, PM_{coarse}, or $PM_{2·5}$abs at age 60–64 years and verbal memory or processing speed at age 69 years

	Model 1, β (95% CI)	p value	Model 2, β (95% CI)	p value	Model 3, β (95% CI)	p value	VIF*
NO_2 (N=1534)							
Verbal memory	0·070 (−0·053 to 0·192)	0·27	−0·088 (−0·222 to 0·046)	0·20	−0·123 (−0·261 to 0·015)	0·080	1·68
Processing speed	1·886 (−0·129 to 3·901)	0·077	−6·162 (−8·257 to −4·067)	<0·0001	−8·121 (−10·338 to −5·905)	<0·0001	1·68
PM_{10} (N=1522)							
Verbal memory	−0·077 (−0·215 to 0·061)	0·28	−0·018 (−0·175 to 0·139)	0·83	−0·011 (−0·167 to 0·145)	0·90	1·65
Processing speed	−6·302 (−8·112 to −4·493)	<0·0001	−4·728 (−6·657 to −2·598)	<0·0001	−4·518 (−6·680 to −2·357)	<0·0001	1·65

NO_2 exposure was estimated at ages 45 years to 60–64 years and PM_{10} exposure at ages 53 years to 60–64 years. Continuous verbal memory was assessed at ages 43, 53, 60–64, and 69 years and processing speed at ages 43, 53, 60–64, and 69 years. β and 95% CIs represent the mean difference in verbal memory score or processing speed score per IQR (μg/m^3) increase in air pollutant levels. Model 1 is an unadjusted model including only outcome and exposure. Model 2 adjusted for sex assigned at birth, father's social class, internalising and externalising problems at age 13–15 years, educational attainment, neighbourhood deprivation at ages 53 years and 60 years, social class at ages 43 years and 53 years, and smoking pack-years up to age 63 years. Model 3 is a fully adjusted model that also adjusts for coal use in the local area at birth and previous exposure to sulphur dioxide and black smoke between the ages of 16 years and 45 years, as well as cognition at age 15 years. NO_2=nitrogen dioxide. PM_{10}=particulate matter of diameter less than 10 μm. VIF=mean variance inflation factor. *VIF is reported for the model 3 fixed effects only.

Table 2: **Longitudinal associations between exposure to NO_2 and PM_{10} and continuous verbal memory and processing speed**

	Model 1, β (95% CI)	p value	Model 2, β (95% CI)	p value	Model 3, β (95% CI)	p value	VIF*
NO_x (N=1415)							
Verbal memory	−0·188 (−0·552 to 0·177)	0·31	−0·055 (−0·386 to 0·276)	0·75	−0·165 (−0·493 to 0·163)	0·32	1·64
Processing speed	0·686 (−3·694 to 5·067)	0·76	1·940 (−2·430 to 6·311)	0·38	0·623 (−3·922 to 5·168)	0·79	1·64
$PM_{2·5}$ (N=1298)							
Verbal memory	−0·121 (−0·563 to 0·321)	0·59	0·102 (−0·305 to 0·508)	0·62	−0·012 (−0·413 to 0·389)	0·95	1·66
Processing speed	0·282 (−5·031 to 5·595)	0·92	1·304 (−4·014 to 6·622)	0·63	0·420 (−5·074 to 5·913)	0·88	1·66
PM_{coarse} (N=1298)							
Verbal memory	−0·197 (−0·465 to 0·072)	0·15	−0·143 (−0·388 to 0·102)	0·25	−0·100 (−0·336 to 0·137)	0·41	1·65
Processing speed	−1·225 (−4·451 to 2·000)	0·46	−0·823 (−4·027 to 2·381)	0·61	−1·195 (−4·408 to 2·017)	0·47	1·65
$PM_{2·5}$abs (N=1298)							
Verbal memory	0·049 (−0·289 to 0·387)	0·78	0·092 (−0·220 to 0·404)	0·56	0·040 (−0·279 to 0·359)	0·81	1·67
Processing speed	−0·193 (−4·259 to 3·872)	0·93	1·104 (−2·978 to 5·185)	0·60	−0·012 (−4·376 to 4·352)	1·00	1·67

Exposure to NO_x, $PM_{2·5}$, PM_{coarse}, and $PM_{2·5}$abs was estimated at age 60–64 years and continuous verbal memory and processing speed was assessed at age 69 years. β and 95% CIs represent the mean difference in verbal memory score or processing speed score per IQR (μg/m^3) increase in air pollutant levels. Model 1 is an unadjusted model including only outcome and exposure. Model 2 adjusted for sex assigned at birth, father's social class, internalising and externalising problems at age 13–15 years, educational attainment, neighbourhood deprivation at age 60 years, social class in adulthood at age 53 years, and smoking pack-years up to age 63 years. Model 3 is a fully adjusted model that also adjusts for coal use in the local area at birth and previous exposure to sulphur dioxide and black smoke between the ages of 16 years and 45 years, as well as cognition at age 15 years. NO_x=nitrogen oxides. $PM_{2·5}$=particulate matter of diameter less than 2·5 μm. $PM_{2·5}$abs=particulate matter absorbance as a measure of black carbon absorption. PM_{coarse}=particulate matter with diameter between 2·5 μm and 10 μm. VIF=mean variance inflation factor. *VIF is reported for model 3.

Table 3: **Prospective associations between exposure to NO_x, $PM_{2·5}$, PM_{coarse}, and $PM_{2·5}$abs and continuous verbal memory and processing speed**

(eg, $PM_{2.5}$ verbal memory β −0·012 [−0·413 to 0·389]; table 3).

We found evidence of a prospective association between higher exposure to all pollutants and lower total ACE-III scores at age 69 years (eg, NO_2 β −0·589 [95% CI −0·921 to −0·257]; figure 2, appendix pp 30–31). Associations were also observed between higher exposure to $PM_{2·5}$ and PM_{coarse} at age 60–64 years and lower scores on the ACE-III verbal fluency subscale at age 69 years ($PM_{2·5}$ β −0·137 [−0·273 to −0·002]; PM_{coarse} β −0·107 [−0·194 to −0·020]).

In fully adjusted models, higher exposure to NO_x at age 60–64 years was associated with smaller total hippocampal volumes at age 69–71 years (β −0·088 [95% CI −0·172 to −0·004]). Higher exposure to NO_2 and PM_{10} was associated with larger ventricular volume at age 69–71 years (NO_2 β 2·259 [0·457 to 4·061]; PM_{10} β 1·841 [0·013 to 3·669]; figure 3, appendix pp 32–33). No pollutants had an association with WMHV or whole brain volume (eg, for NO_2 and WMHV, β 1·023 [0·901 to 1·163]), and exposure to $PM_{2·5}$, PM_{coarse}, and $PM_{2·5}$abs had no association with any neuroimaging measure (appendix pp 32–33).

In sensitivity analyses comparing participants in the top quartile of pollutant exposure with those in the lower three quartiles, we saw slightly increased effect sizes between NO_2, PM_{10}, NO_x, and $PM_{2·5}$ exposure and total ACE-III score (appendix pp 36–37); for associations with neuroimaging measures, we observed more pronounced effect sizes between PM_{10} exposure and smaller hippocampal volume than in the main analyses (appendix pp 38–39). For two-pollutant models, findings were mixed (appendix pp 40–43), probably owing to high correlation between pollutants. Complete case analyses produced similar effect sizes and 95% CIs to the main findings, although the sample sizes were small (appendix pp 44–49). The addition of a non-linear term for pollutant–exposure associations did not improve the fit of any of the models we examined (appendix pp 10–14).

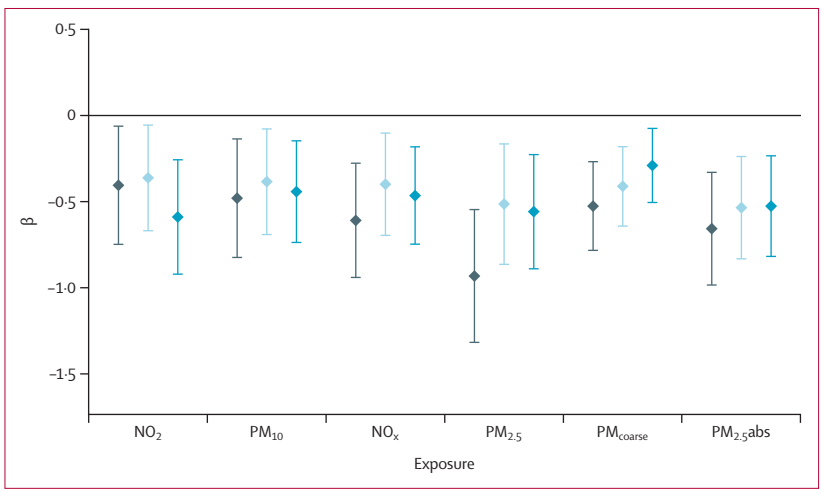

Figure 2: **Associations between exposure to air pollutants and ACE-III total score**
Bars show 95% CI; data in grey are from model 1, pale blue from model 2, and dark blue from model 3. Model 1 is an unadjusted model including only outcome and exposure. Model 2 adjusted for sex assigned at birth, father's social class, internalising and externalising problems at age 13–15 years, educational attainment, neighbourhood deprivation at the age of 53 years or 60 years, social class in adulthood at the age of 43 years or 53 years, and smoking pack-years up to the age of 63 years. Model 3 is a fully adjusted model that also adjusts for coal use in the local area at birth and previous exposure to sulphur dioxide and black smoke between the ages of 16 years and 45 years, as well as cognition at age 15 years. ACE-III=Addenbrooke's Cognitive Examination III. NO_2=nitrogen dioxide. NO_x=nitrogen oxides. PM_{10}=particulate matter of diameter less than 10 µm. $PM_{2·5}$=particulate matter of diameter less than 2·5 µm. $PM_{2·5}$abs=particulate matter absorbance as a measure of black carbon absorption. PM_{coarse}=particulate matter with diameter between 2·5 µm and 10 µm.

Discussion

In this UK population-based cohort study, we used information on lifetime pollutant exposure and a range of covariates to examine associations between exposure and cognitive and brain structural outcomes in later life. We found that higher exposure to NO_2 and PM_{10} was associated with poorer processing speed, but not with poorer verbal memory, between the ages of 43 years and 69 years. Consistent with previous literature,[2,3] we found associations between exposure to all pollutants and lower total ACE-III scores at age 69 years, reflecting poorer overall cognitive state. In the Insight 46 substudy, we found that higher exposure to NO_2 and PM_{10} was associated with larger ventricular volume and higher exposure to NO_x was associated with smaller hippocampal volume. All analyses were robust to controlling for pollution exposure earlier in life and childhood cognition.

With the exception of $PM_{2·5}$ and episodic memory, for which supportive evidence of associations was found in a 2023 review,[2] evidence for links between exposure to air pollution and verbal memory and processing speed has been mixed and inconclusive.[2] We found no significant associations between exposure to any pollutant (from longitudinal NO_2 and PM_{10} or single-timepoint NO_x, $PM_{2·5}$, PM_{coarse}, or $PM_{2·5}$abs) and verbal memory. These findings differ from a 2024 analysis from the English Longitudinal Study of Ageing (ELSA), which reported associations between poorer composite memory and higher exposure to PM_{10} and NO_2 (PM_{10} β –0·02, 95% CI –0·04 to –0·01).[9] These associations were possibly confounded by differences in exposure before the study—particularly because cumulative exposure profiles could vary more in a mixed-age cohort such as ELSA than in participants of the same age, as in the NSHD. Additionally, the primary outcome in the ELSA study had a delayed-recall component, rather than the immediate recall test used by the NSHD. Such a delayed-recall test might recruit cognitive processes aligned with episodic memory, rather than working memory as in the case of immediate-recall tests, and it is possible that episodic memory is more vulnerable to the effects of pollution than is working memory. We did find associations between higher exposure to NO_2 and PM_{10} and poorer processing speed, for which existing evidence is again mixed in this domain.[2] In the USA, the Vietnam Era Twin Study of Aging found no association between exposure to NO_2 and $PM_{2·5}$ and processing speed in participants of a similar age group and with a similar exposure period.[27]

Extending our analysis to overall cognitive state at age 69 years, assessed using ACE-III, our findings were similar to those of other studies in this age group.[2,3,9,28] A reduction of one point in total ACE-III score in participants in the highest quartile of NO_2 exposure could be important across populations, particularly as a score of 88 is the upper cutoff for risk of dementia.[19] We included the verbal fluency subdomain to cover fluid cognitive function (with processing speed and verbal memory), similar to other studies.[27] We could not entirely rule out reverse directionality; however, we have attempted to control for this across the life course with measures of childhood cognitive state and multiple exposure measurements for different pollutants from birth. Although co-pollutant exposures could have introduced collinearity to our models, variance inflation factors were low, and correlation coefficients of the main pollutants of interest (NO_2, NO_x, PM_{10}, $PM_{2·5}$, PM_{coarse}, and $PM_{2·5}$abs) with black smoke and SO_2 were low to moderate.

We observed evidence of an association between PM_{10} and NO_2 and larger ventricular volume and between NO_x and smaller hippocampal volume, adding to evidence from the few studies examining the effects of pollution on brain structure.[12,29] Although we cannot infer from our current data whether our observations represent a change in volume over time, the differences in hippocampal volume equate to approximately 1 year of volume loss seen in normal ageing. In addition, hippocampal atrophy is not specific to, but has been associated with, the development of cognitive impairment and Alzheimer's disease.[30] It is possible that exposure to pollution could contribute to, lower the resilience to, or interact with the neuropathological processes that lead to dementia in later life. Exposure to NO_2 has been associated with proinflammatory responses both systemically and specifically in the brain, through factors such as TNF and IL-1β.[10] Experimental evidence suggests an upregulation of cyclooxygenase-2 dependent prostaglandin E_2, which can lead to increases in amyloid β, Alzheimer's disease-like progression, and potentially neuroinflammatory-related degeneration.[10] We did not find any associations between neuroimaging outcomes and $PM_{2·5}$;[29] this could be

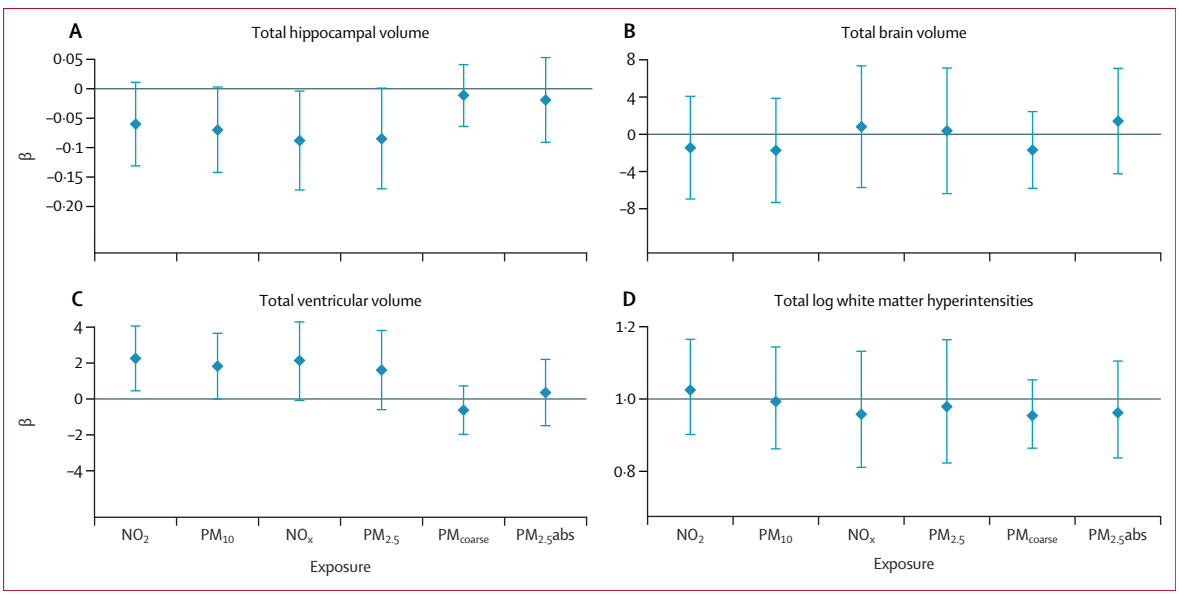

Figure 3: **Associations between exposure to air pollutants and brain structural outcome measures**
Bars show 95% CI. All results are fully adjusted for sex assigned at birth, father's social class, internalising and externalising problems at age 13–15 years, educational attainment, neighbourhood deprivation at age 53 years or 60 years, social class in adulthood at age 43 years or 53 years, smoking pack-years up to the age of 63 years, coal use in the local area at birth and previous exposure to sulphur dioxide and black smoke between the ages of 16 years and 45 years, as well as cognition at age 15 years. Models are also corrected for total intracranial volume and age at date of scan. NO_2=nitrogen dioxide. NO_X=nitrogen oxides. PM_{10}=particulate matter of diameter less than 10 μm. $PM_{2·5}$=particulate matter of diameter less than 2·5 μm. $PM_{2·5}$abs=particulate matter absorbance as a measure of black carbon absorption. PM_{coarse}=particulate matter with diameter between 2·5 μm and 10 μm.

because of a lack of power, as the study was not designed primarily to detect an association between air pollution and brain structural measures, or, feasibly, because other uncaptured characteristics of pollutants (eg, the composition of particulate matter) could alter toxicity. We also found no association between pollution exposure and WMHV, consistent with some studies,[31] despite a plausible link between exposure and cerebrovascular-related changes.[12]

There are some limitations to this study. Although we had data for measures of air pollution exposure from birth, the metrics changed over time in line with changing sources of air pollution in the UK, from primarily the burning of coal and fossil fuels during the early lives of participants in the cohort to, for example, transport sources in midlife to later life. Future research could examine smaller fractions of particulate matter, including ultrafine particles, which are of growing interest for both regulation[32] and research. We included residential measures of exposures from birth in this study. Further studies should include information on in-utero, indoor, and occupational exposures, where data are available. Although findings were consistent in terms of direction across models and pollutants, we also conducted multiple analyses that could increase the risk of type I error. We decided not to adjust for multiple comparisons as we had strong a-priori hypotheses, for which multiple testing correction can increase type II error. There was at least a 5-year gap between the final exposure measurements (at ages 60–64 years) and outcome measurements (at ages 69–71 years); we assumed that exposure was similar over this period, although this might not be the case, particularly within urban areas. There could also be residual confounding from other factors, including—but not limited to—humidity or temperature. Future work should look to incorporate other environmental metrics. Finally, the generalisability of the findings in this cohort could be limited owing to a healthy cohort effect and the fact that approximately 15% of ACE-III scores were lost during data collection at age 69 years. Because the results here reflect exposure in England, Scotland, and Wales, they might not be generalisable to other countries with different pollution profiles.

Overall, our study provides robust evidence linking exposure to air pollution to poorer cognition and shows that exposure during midlife is an important determinant of cognitive decline, and hence, potentially, the risk of incident dementia. We extend associations with cognition by drawing parallels with brain structure, specifically that participants with higher exposure to some outdoor air pollutants had smaller hippocampal and greater ventricular volumes. It is important to note that cognitive and brain structural changes in midlife to older age could result from decades of previous exposure to air pollution and the complex interactions between genetic and environmental risk factors that start in utero and are cumulative over the life course. We partially controlled for these factors by including air pollution exposures and cognitive functioning earlier in life in our models; however, more comprehensive investigations of all such factors are needed. Nonetheless, with large ageing populations, small reductions in exposure to air pollution—even in midlife—could lead to measurable improvements in

cognition and brain health, and could mitigate some risk of dementia in older adults.

Contributors

IB, TC, MR, JA-dlT, ISM, SLH, and HLF conceived and designed the study. ALH, JG, and RH developed the air quality models and linked the data. TC, IB, AR, and JA-dlT conducted and supported the statistical analysis. JMS is the principal investigator of the Insight46 substudy and JMS, MC, S-NJ, and SEK contributed to the collection and analysis of Insight 46 data. TC, JA-dlT, IB, and HLF wrote the first draft of the manuscript, on which all authors commented and provided intellectual input. TC and JA-dlT accessed and verified the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JMS received research funding from the National Institute for Health and Care Research (NIHR), the British Heart Foundation (PG/17/AQ20 90/33415), the LifeArc foundation, UK Dementia Research Institute, and Brain Research UK; received PET tracer from AVID Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly) and Alliance Medical; consulted for Roche, Eli Lilly, and Biogen; received royalties from Oxford University Press and Henry Stewart Talks; received support for attending meetings or travel expenses from Alzheimer's Association, the American Academy of Neurology, Alzheimer's Research UK, and Eli Lilly; and is Chief Medical Officer for Alzheimer's Research UK and a Senior Investigator at the UK NIHR. ALH received travel and subsistence for a conference from Health Data Research UK and is Chair of the Committee on the Medical Effects of Air Pollutants for the Department of Health and Social Care in the UK (unpaid role). ISM is a member of the Committee on the Medical Effects of Air Pollutants for the Department of Health and Social Care in the UK (unpaid role). RH is a member of the UK Biobank Strategic Oversight Committee and Our Future Health access board. SLH received consulting fees from the National Health Service (NHS) Race and Health Observatory and the Wellcome Trust; support for travel and accommodation from the Wellcome Trust; was a panel member for the UK Research and Innovation Mental Health Platform hub in 2023; a member of the Thrive London advisory board from 2019 to 2024; and is a member of the Core20PLUS Collaborative from NHS England, the MQ Mental Health Sciences Council, the Health Inequalities advisory board for NHS England and NHS Improvement, the Wellcome Trust Social Sciences (Discovery 9) shortlisting committee, the Foundation for the Sociology of Health and Illness as a Trustee, and the Adult Psychiatric Morbidity Survey steering group. SEK has received personal payment or honoria from M3 EU for educational materials. All other authors declare no competing interests.

Data sharing

Data are available to bona fide researchers on request to the NSHD Data Sharing Committee via a standard application procedure within the bounds of consent given previously by study members. Data cannot be shared publicly as sharing of the 1946 MRC NSHD data is dependent on the project being approved by the NSHD Data Sharing Committee, a data sharing agreement being in place between University College London and the academic institution that employs the researcher, and MRC Unit for Lifelong Health and Ageing resources being available to meet the requests for data sharing. Additionally, all proposals to use the NSHD data must support and adhere to the core principles of data sharing with the MRC. For more information on the NSHD and access to data and collaborations, see https://www.nshd.mrc.ac.uk/data/data-sharing/ or contact mrclha.enquiries@ucl.ac.uk. Further information can also be accessed at https://skylark.ucl.ac.uk, https://doi.org/10.5522/NSHD/Q101, https://doi.org/10.5522/NSHD/Q102, and https://doi.org/10.5522/NSHD/Q103.

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