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Longitudinal associations between air pollution and incident dementia as mediated by MRI-measured brain volumes in the UK Biobank

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ABSTRACT

Background: Although there is increasing evidence that environmental exposures are associated with the risk of neurodegenerative conditions, there is still limited mechanistic evidence evaluating potential mediators in human populations.

Methods: UK Biobank is a large long-term study of 500,000 adults enrolled from 2006 to 2010 age 40–69 years. ICD-10 classified reports of dementia cases up to 2022 (Alzheimer's disease, vascular dementia, dementia in other classified diseases, and unspecified dementia) were identified from health record linkage. Estimates of residential air pollution, traffic noise, and greenspace exposure have been modelled. Structural brain MRI was conducted from 2014 to 2022, with brain volumes relevant to dementia identified a priori. Associations between environmental exposures, brain volumes, and dementia cases (diagnosed post-MRI) were tested using linear and logistic regression and adjusted for age, sex, household income, ethnicity, education, smoking, and area-level deprivation. Mediation of exposure-outcome associations by plausible brain volumes (those associated with both environmental exposure and dementia outcomes) were modelled using the quasi-Bayesian Monte Carlo method (N = 34,817–39,772).

Results: Small but significant mediating effects (2%-8% of relationships mediated) were observed between $PM_{2.5abs}$ exposure and dementia risk by reduced total brain volume, NOx and Alzheimer's disease risk by reduced peripheral cortical grey matter, $PM_{2.5abs}$ and vascular dementia risk by reduced peripheral cortical grey matter, $PM_{2.5abs}$ and other dementia risk by reduced total grey matter, and PM_{10} and other dementia risk by reduced

Abbreviations: UK, United Kingdom; MRI, Magnetic Resonance Imaging; NHS, National Health Service; IMD, Indices of Multiple Deprivation; LSOA, Lower layer Super Output Areas; WIMD, Welsh IMD; SIMD, Scottish IMD; ESCAPE, European Study of Cohorts for Air Pollution Effects; LUR, Land Use Regression; COA, Census Output Area; CNOSSOS-EU, Common Noise Assessment Methods in Europe; NO_2, nitrogen dioxide; NOx, nitrogen oxides, nitrogen dioxide and nitric oxide; PM_{10}, Particulate Matter less than 10 μm; $PM_{2.5}$, Particulate Matter less than 2.5 μm; $PM_{2.5abs}$, $PM_{2.5}$ absorbance; PM_{coarse}, Particulate Matter between 2.5 and 10 micrometres; Lday, A-weighted average noise level between 7am-7 pm at residential address; Leve, A-weighted average noise level between 7 pm and 11 pm at residential address; Lnight, A-weighted average noise level between 11 pm and 7am at residential address; GS300m, percentage of land cover classed as greenspace within a 300 m buffer of the residential address; GS1000m, percentage of land cover classed as greenspace within a 1000 m buffer of the residential address; AD, Alzheimer's disease; VD, Vascular dementia; OD, Dementia in other diseases classified elsewhere; UD, Unspecified dementia; dB(A), A-weighted noise in decibels; GLUD, Generalised land use data base for England the; CEH, Centre for Ecology and Hydrology; AIC, Akaike information criteria; ACME, average causal mediating effect; SI, Supplementary Information.

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total grey matter. Greenspace and noise were not associated with dementia outcomes in the subset of the cohort providing brain imaging data.
Conclusions: This study adds to existing evidence of associations between environmental exposures and dementia outcomes. Our findings provide novel evidence that differences in brain volume may mediate these relationships. Future research is required to prove this mechanism and establish the other mechanisms through which exposure to air pollution might increase dementia risk.

1. Introduction

Dementia is the progressive loss of multiple cognitive abilities, such as memory, with significant impacts upon everyday functioning (Arvanitakis et al., 2019). Alzheimer's disease is the most common form of dementia, followed by vascular dementia, but dementia can also occur as a result of other conditions such as strokes or HIV (Arvanitakis et al., 2019; Prince et al., 2014). In most cases, it is a terminal disease that is irreversible and incurable, and usually occurs in persons aged 65 or older (Arvanitakis et al., 2019; Prince et al., 2014). As treatments for other diseases advance and populations age, the global burden of dementia is increasing. In 2015, 46.8 million people were living with dementia, expected to exceed to more than 130 million by 2050 (Prince et al., 2015).

There is growing epidemiological evidence that exposure to higher levels of air pollution and environmental noise may increase the risk of cognitive impairment, cognitive decline, and dementia, whereas exposure to greenspace may reduce the risk (Manuella Lech et al., 2021; Meng et al., 2022; Parra et al., 2022; Paul et al., 2019; Paul et al., 2020; Peters et al., 2019; Slawsky et al., 2022; Thompson et al., 2022; Thompson et al., 2023; Weuve et al., 2021; Wilker et al., 2023; Yu et al., 2020). However, in addition to observational evidence of such associations, it is important that research generates mechanistic evidence, to enhance the plausibility of causal inference and allow us to better understand how this occurs and, ultimately, how it can be prevented. In animal models, there is evidence that exposure to particulate matter (PM) can cause cerebral hypoperfusion, white matter injury and demyelination (Huuskonen et al., 2021; Liu et al., 2021). Although studies have found evidence for mediation between air pollution and general population cognitive decline or impairment by effects on the sleep cycle and brain structure (Lo et al., 2022), amyloid pathology (Ma et al., 2023), and atrophy of grey matter (Younan et al., 2020), only a small body of evidence has investigated whether plausible mechanisms such as structural (volumetric) brain changes mediate the relationships between environmental exposures and clinical presentation of dementia.

Previous studies in the UK Biobank have investigated the interrelationship between environmental exposures, brain volumes, and brain-related health outcomes. A recent study in the UK Biobank found that urban environmental profiles including air pollution and greenspace were associated with mental health symptoms and that these relationships were mediated by brain volume differences (Xu et al., 2023). Also in UK Biobank, shorter residential distance to major roads was associated with smaller brain structure volumes (peripheral cortical grey matter, grey matter, and total brain) and with increased risk of dementia risk, both mediated by traffic-related air pollution (NO_2 and $PM_{2.5}$) (Li et al., 2023). Although the harmful impacts of air pollution on the brain are hypothesised to help explain its impact on dementia risk, to the best of our knowledge, no studies have looked at structural volumes of the brain as a mediator of associations between environmental exposures and incident dementia in UK Biobank or any other large-scale prospective cohort.

Therefore, this study aimed to investigate whether associations between exposure to air pollution and incident dementia were mediated by MRI assessed brain volumes in the UK Biobank. Based on existing literature reporting associations with dementia and environmental exposures, volumes of areas of the brain were selected a priori as potential mediators. It was hypothesised that differences in brain volumes in these areas would significantly mediate associations between exposure to air pollution, noise, greenspace, and dementia.

2. Methods

2.1. Study participants and design

UK Biobank is a large multisite long term prospective cohort study of 500,000 adults who were enrolled from 2006 to 2010 at age 40–69. UK Biobank has approval from the North-West Multi-centre Research Ethics Committee as a Research Tissue Bank approval. Consent was sought from all UK Biobank participants for participation. Participants were recruited from the National Health Service (NHS) patient registers and attended an initial assessment visit at one of 22 assessment centres. Here, they gave their consent to participate, detailed demographic information, physical measures such as blood pressure, biosamples, and consent for health record linkage. Repeat assessment visits took place in 2012–2013, as well as online follow-up questionnaires. The UK Biobank Imaging study (ongoing) aims to scan the brain, heart, tissue and bones of 100,000 UK Biobank participants using MRI (magnetic resonance imaging), ultrasound, and DXA (dual-energy X-ray absorptiometry). Participants living within reasonable travelling distance of four imaging assessment centres have been invited to participate (85,000 scanned so far). Imaging visits including brain MRI from 2014 to 2022, with repeat (second) imaging visits from 2019 onwards. The sample included in the present study (N = 42,802) are Biobank participants who took part in the first imaging visit and provided brain imaging data from 2014 onwards (thus providing data on potential mediators) as well as exposure, outcome, and covariate data (for timeline of participant assessment see Fig. 1). The following participant sociodemographic information was included in the present study, as self-reported at the initial assessment visit (2006–2010) or based on addresses provided at the initial assessment visit: age, sex, household income, ethnicity, education (highest qualification completed), smoking, and area-level deprivation (English, Welsh or Scottish Indices of Multiple Deprivation (IMD, WIMD or SIMD)).

2.2. Exposures

Individual-level environmental exposure prior to the brain imaging visit has previously been estimated for the UK Biobank cohort, assuming their residential locations (based on NHS records and self-report) are the same in 2009–2010 as at their initial assessment visit (2006–2010). Annual air pollution estimates for the year 2010 have been modelled based on residential addresses provided at the initial assessment visit using a Land Use Regression (LUR) model from the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (Beelen et al., 2013). Estimates were generated for nitrogen dioxide (NO_2), Nitrogen Oxides (nitrogen dioxide and nitric oxide, NOx), Particulate Matter less than 10 μm (PM_{10}), Particulate Matter less than 2.5 μm ($PM_{2.5}$), $PM_{2.5}$ absorbance ($PM_{2.5abs}$, a proxy for elemental carbon), and Particulate Matter between 2.5 and 10 μm (PM_{coarse}).

Annual exposure to traffic noise for the year 2009 was modelled based on residential addresses using the Common Noise Assessment Methods in Europe (CNOSSOS-EU) model (Morley et al., 2015). Estimates of annual average exposure to A-weighted noise in decibels (dB

(A)) were generated for daytime noise between 7 am and 7 pm (Lday), evening noise between 7 pm and 11 pm (Leve) and nighttime noise between 11 pm-7 am (Lnight). However, Pearson's correlations between these metrics exceeded 0.999, therefore only Lday was included in analyses. Finally, residential greenspace exposure was estimated based on addresses reported at the initial assessment visit, using the Generalised land use data base for England (GLUD) 2005 data and the Centre for Ecology and Hydrology (CEH) 2007 Land Cover Map for Scotland and Wales. The percentage of land cover classed as greenspace for each Census Output Area (COA) (England) or 25 m grid (Scotland and Wales) within a 300 m (GS300m) and a 1000 m (GS1000m) buffer of the home location was averaged, weighted according to the proportion of each COA or grid within the home location buffer (Wheeler, 2017).

2.3. Outcomes of interest

The UK Biobank receives and unifies hospital records from different data providers in England, Wales and Scotland in order to obtain linked inpatient hospital data for the whole cohort (more information about this process can be found at https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/inpatient_mapping.html and https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/HospitalEpisodeStatistics.pdf). The outcomes of interest were any first reported occurrences in hospital inpatient records of conditions falling within the ICD10 classification F00 Dementia in Alzheimer's disease (AD), F01 Vascular dementia (VD), F02 Dementia in other diseases classified elsewhere (OD), or F03 Unspecified dementia (UD) within Chapter V Mental and Behavioural disorders, coded as 0 (no diagnosis present) or 1 (diagnosis present). A binary composite variable was also created for all dementia, reflecting a diagnosis across any of the four categories. For those with a diagnosis (which occurred between 01/07/1944 and 08/12/2022), cases occurring before a participants' first imaging visit (visits ranging from May 2014 to February 2020) were excluded in the corresponding analysis, as brain volumes at the imaging visit were measured after these pre-existing conditions occurred and were therefore not sensible mediators to test.

2.4. MRI assessed brain volumes (mediators)

This study focussed on structural brain MRI data from Imaging visit 1 (02.05.2014—13.7.2022) as only 3 cases of dementia and 0 cases of AD occurred after Imaging visit 2. Brain MRI data were acquired using a Siemens Skyra 3 T scanner, as described in the UK Biobank brain scan protocol (Resource 2367 https://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367&_gl=1*1gn6abl*_ga*MjAwNzI2MTU4Ni4xNzM0NDI4OTEw*_ga_NY8L5SJPMB*MTczNDQzMDk2NS4yLjEuMTczNDQzMTQwNC4wLjAuMA). Global and regional brain volume information had been estimated by the UK Biobank brain imaging team and was provided by the UK Biobank. Based on existing literature which suggested their plausibility as potential mediators (areas associated with dementia and environmental exposures), the following brain volumes were selected a priori to explore: total brain volume (Bigler & Tate, 2001; Li et al., 2023), peripheral cortical grey matter (Cho et al., 2020; Li et al., 2023; Mouton et al., 1998), total grey matter (Ikram et al., 2010; Li et al., 2023; Paul et al., 2019), total white matter (Li et al., 2023; Smith et al., 2000), thalamus (Cho et al., 2020; de Jong et al., 2008; Hedges et al., 2020; Power et al., 2018; Watson et al., 2016), caudate (Cho et al., 2020; Frings et al., 2014; Hilal et al., 2015; Power et al., 2018; Watson et al., 2016), putamen (de Jong et al., 2008; Hilal et al., 2015; Power et al., 2018; Watson et al., 2016), pallidum (Cho et al., 2020; Power et al., 2018), hippocampus (Cho et al., 2020; den Heijer et al., 2006; Hilal et al., 2015; Ikram et al., 2010), amygdala (Cho et al., 2020; den Heijer et al., 2006), nucleus accumbens (Cho et al., 2020; Hilal et al., 2015), frontal pole (Cho et al., 2020; Frings et al., 2014; Ikram et al., 2010), insular cortex (Cho et al., 2020; Fathy et al., 2020), temporal lobe (Cho et al., 2020; Frings et al., 2014; Ikram et al., 2010; Mak et al., 2017), frontal medial cortex (Cho et al., 2020; Ikram et al., 2010), and cingulate gyrus (Cho et al., 2020; Mak et al., 2017). Total brain, grey and white matter volumes were generated using the FSL FAST (Zhang et al., 2001), subcortical volumes using FSL FIRST (Patenaude et al., 2011), and individual grey matter cortical segmentations in accordance with the Harvard-Oxford Atlas (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). Usable data was acquired for 81.06 % of participants. More information about the brain imaging process and quality control can be found in Miller et al. (2016) and Alfaro-Almagro et al. (2018).

2.5. Covariates

To adjust for potential confounding by sociodemographic and health differences, the following individual-level covariates were selected a priori: age in years in 2023; index of multiple deprivation; sex as a binary variable; ethnicity, education, smoking and household income as categorical variables. The categories into which variables were coded can be found in Table 1. All were self-reported at the initial assessment visit, except for IMD, which was based on residential address from both self-report and health record linkage.

2.6. Statistical analysis

Associations between brain volumes and dementia outcomes, exposure to air pollution or noise and brain volumes, and exposure to air pollution or noise and dementia outcomes, were evaluated using complete cases linear (brain volume outcomes) or logistic regression (dementia outcomes) adjusted for age, sex, household income, ethnicity, education, smoking, and area-level deprivation (IMD, WIMD or SIMD).

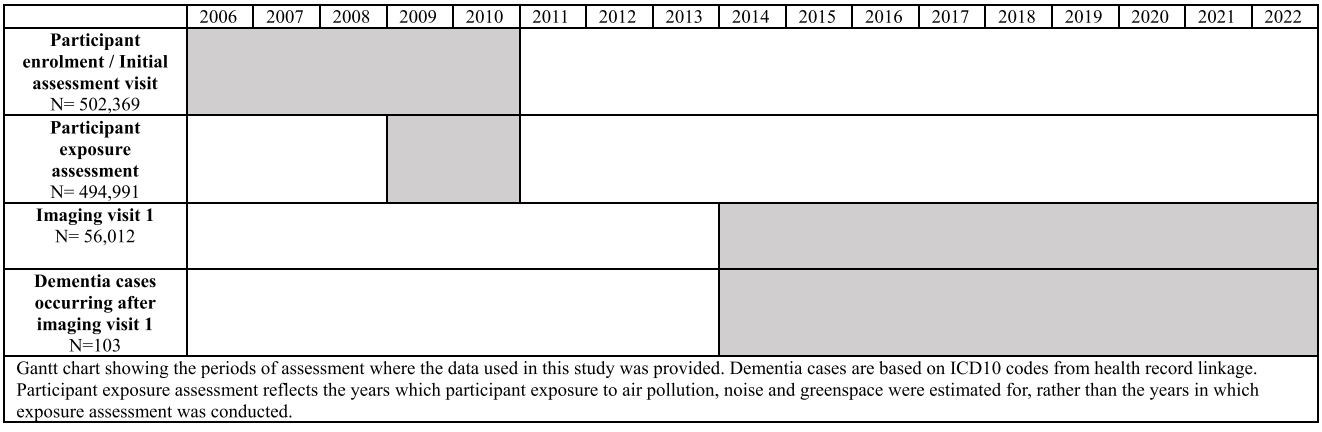

Fig. 1. Timeline of participant assessment.

Table 1
Sociodemographic and health descriptive statistics.

Characteristic	Total analytical sample [a] N = 42,802	Incident Dementia cases [b] N = 103	Data source/ timepoint
Mean age in years (range)	69.97 (53–87)	78.30 (57–85)	Calculated 2023, based on self-reported year of birth at initial assessment visit (2006–2010)
N missing	0	0	
Mean IMD (range)	15.12 (0.61–82.33)	16.89 (1.74–80.29)	Based on residential address LSOA in 2010 (2010 edition of English IMD), 2008 (2008 edition of Scottish IMD, SIMD), or 2009 (2009 edition of Welsh IMD, WIMD)
N missing	1029	1	
Sex N (%)			Self-reported at initial assessment visit (2006–2010), but may have been updated by participant or NHS record linkage
Female	22,585 (52.77 %)	44 (42.72 %)	
Male	20,217 (47.23 %)	59 (57.28 %)	
N missing	0	0	
Household income N (%)			Self-reported at initial assessment visit (2006–2010)
<£18,000	4553 (10.64 %)	21 (20.39 %)	
£18,000–30,999	8608 (20.11 %)	27 (26.21 %)	
£31,000–51,999	11,847 (27.68 %)	27 (26.21 %)	
£52,000–100,000	11,057 (25.83 %)	12 (11.65 %)	
£100,000+	3071 (7.17 %)	4 (3.88 %)	
Prefer not to answer	2821 (6.59 %)	5 (4.85 %)	
N missing	845 (1.97 %)	7 (6.80 %)	
Highest qualification completed N (%)			Self-reported at initial assessment visit (2006–2010)
Higher, vocational, or professional degree/ qualification	24,431 (57.08 %)	55 (53.40 %)	
A levels/AS levels or equivalent	5554 (12.98 %)	8 (7.77 %)	
O levels, GCSEs, CSEs or equivalent	9958 (23.27 %)	20 (19.42 %)	
None of the above	2722 (6.36 %)	20 (19.42 %)	
N missing	137 (0.32 %)	0 (0.00 %)	
Ethnic background			Self-reported at initial assessment visit (2006–2010)
White	41,428 (96.79 %)	102 (99.03 %)	
Mixed	205 (0.48 %)	0 (0.00 %)	
Asian or Asian British	450 (1.05 %)	0 (0.00 %)	
Black or Black British	281 (0.66 %)	1 (0.97 %)	
Chinese	124 (0.29 %)	0 (0.00 %)	
Other ethnic group	236 (0.55 %)	0 (0.00 %)	
N missing	78 (0.18 %)	0 (0.00 %)	
Current tobacco smoking			Self-reported at initial assessment visit (2006–2010)
Yes, on most or all days	1685 (3.94 %)	2 (1.94 %)	
Only occasionally	970 (2.27%)	2 (1.94%)	
No	40,126 (93.75%)	99 (96.12%)	
N missing	21 (0.05 %)	0 (0.00 %)	

IMD: Indices of Multiple Deprivation.
LSOA: Lower layer Super Output Areas.
WIMD: Welsh IMD.
SIMD: Scottish IMD.
[a] The analytical sample contains all persons who attended imaging visit 1 and provided brain imaging data, though the sample size of each analysis varies by the completeness of exposure, outcome, and mediator data.
[b] Incident cases of dementia within the analytical sample. Cases were only included that occurred after an individual's first imaging visit.

Inclusion of assessment sites (initial assessment visit or imaging visit 1) in multi-level models were tested but this did not substantially impact associations (Akaike information criteria (AIC) did not improve > 2). Therefore, we did not use multi-level models to maintain model parsimony. In our models, we employed specific magnitudes to quantify the impact of different factors. The magnitudes included a 1 cm^3 increase in brain volumes, a 1 IQR increase in air pollution metrics (originally in $\mu g/m^3$ except for $PM_{2.5abs}$ (absorbance units x $10^{-5}/m^{-1}$)), a 10 dB increase in noise volume, and a 1 % change in greenspace. Incident dementia was treated as a binary categorical variable, indicating the presence or absence of dementia cases.

Where a given brain volume was significantly ($p < 0.05$) associated with both an environmental exposure and a dementia outcome, mediation of the exposure-outcome association by the brain volume was tested. Mediation of exposure-outcome associations by plausible brain volumes (those associated with the exposure and outcome) were modelled using the quasi-Bayesian Monte Carlo method (using the function mediate and the package mediation in R). A mediation effect was considered significant if the total effect and the average causal mediated effect (ACME) were both significant ($p < 0.05$). Although significant ACME effects may be statistically detectable without a significant total effect, these were not considered clinically relevant, meaningful or interpretable (Twisk, 2024).

2.7. Sensitivity analyses

Total brain volume is associated with constituent brain volumes so presents a potential confounder in associations between environmental exposures, brain volume and clinical outcomes. Therefore, we planned to adjust significantly mediated associations for total brain volume, except for associations mediated by total grey matter, total white matter, and total peripheral cortical grey matter, as these were considered too closely related to total brain volume. Additionally, given the potential for mutual confounding effects presented by exposure covariance, some multi-exposure models were tested by including two exposures in regression models, thus adjusting each exposure for the impact of the other. Based on high collinearities and multiple comparisons considerations, the following multi-exposure models were evaluated in relation to brain volumes and dementia outcomes: $NO_2 + PM_{coarse}$, NO_2 + Lday, PM_{coarse} and Lday, PM_{coarse} and GS1000m, Lday and GS1000m (between each pair of exposures, Pearson's $R < 0.5$). Exposure-outcome associations were also evaluated for the wider Biobank sample to see if these replicated those found in participants providing brain imaging data. To check for selection bias in the UK Biobank neuroimaging study as compared with the wider UK Biobank, the inverse probabilities of taking part in the Imaging study (calculated using the ipw package in R, based on age, education, ethnicity, retirement status, home ownership, smoking, BMI, high blood pressure and diabetes (Bradley & Nichols, 2022)) were used as weights to estimate the associations between exposure to air pollution or noise and dementia outcomes in the analytical sample.

Finally, a sensitivity analysis was performed on the significant mediation effects for violation of the sequential ignorability assumption. The sequential ignorability assumption states that unobserved covariates do not confound associations between the mediator, exposure, and outcome, meaning that they are statistically independent of each other given adjustment for the observed confounders (Imai, Keele, & Tingley, 2010). Using the 'medsens' function (mediation package in R), the average causal mediating effect (ACME) and direct effect were calculated for different degrees of the sensitivity parameter rho, which indexes the extent of the sequential ignorability violation (the correlation between the error terms of the mediator and outcome models) (Imai, Keele, Tingley, et al., 2010).

3. Results

3.1. Descriptive statistics

Brain imaging data from Imaging Visit 1 was available for 42,802 participants of UK Biobank, thus constituting the analytical sample. Descriptive statistics of the sample's sociodemographic, health outcome, and environmental information is summarised in tables 1 and 2. There were 103 cases of dementia occurring after brain imaging visit, further classified into Alzheimer's disease (AD) (n = 41), vascular dementia (VD) (n = 25), dementia in other diseases classified elsewhere (OD) (n = 11) and unspecified dementia (UD) (n = 50). Dementia cases may have received more than one of these diagnoses and therefore belong to more than one category.

3.2. Associations between exposure to air pollution, noise, greenspace, incident dementia and brain volumes

In those providing brain imaging data, NO_2, NOx, PM_{10}, PM_{coarse}, Lday, GS300m and GS1000m exposure were not associated ($p > 0.10$) with increased risk of overall dementia, AD, VD, OD, or UD. The association between $PM_{2.5abs}$ and increased risk of VD was approaching significance (OR = 1.45, $p = 0.05$, Table 3).

Although not significantly associated with incident dementia, air pollutants and noise were significantly associated with lower volumes across many brain-wide and regional measures, and greenspace with higher volumes. The beta coefficients and p values for exposure-mediator, and mediator-outcome associations can be found in Supplementary Information (SI) tables SI1 and SI2, respectively.

3.3. Mediation

The following brain volumes were significantly associated with at least one environmental exposure and at least one dementia outcome and were therefore tested as mediators: Total brain volume, peripheral cortical grey matter, total grey matter, right hippocampus, left amygdala, right amygdala, right nucleus accumbens, left frontal pole, right frontal pole, left temporal lobe, right temporal lobe, right frontal medial cortex, and left anterior cingulate gyrus. All tested mediation relationships can be found in table SI7.

Table 4 illustrates the mediation effects of brain volumes on the pathway of air pollution or noise and dementia where both the total and indirect effects were significant. These suggest significant mediating processes between exposure to $PM_{2.5abs}$ and increased dementia risk by reduced total brain volume, NOx and AD risk by reduced peripheral cortical grey matter, $PM_{2.5abs}$ and VD risk by reduced peripheral cortical grey matter, $PM_{2.5abs}$ and OD risk by reduced total grey matter, and PM_{10} and OD risk by reduced total grey matter.

3.4. Sensitivity analyses

Only total brain volume, total grey matter and peripheral cortical grey matter were found to significantly mediate associations between air pollution and dementia risks. Associations between total grey matter/peripheral cortical grey matter and dementia risk were not further adjusted for total brain volume due to high collinearity (Pearson's R = 0.85 and 0.83, respectively, both $p < 0.001$). Multi-exposure models were tested for the impact of co-exposure to NO_2 + PM_{coarse}, NO_2 + Lday, PM_{coarse} and Lday, PM_{coarse} and GS1000m, Lday and GS1000m, however associations between exposures and brain volumes (SI3) and between exposures and outcomes (SI4) did not substantially change with the inclusion of co-exposures (significance level or direction of effect) so confounding influences were unlikely. As presented in SI5, in the wider Biobank sample (N = 402,503–455,251), many associations between environmental exposures and dementia outcomes were observed that were not found in the imaging subsample (N = 37,726–40,278); NO_2, NOx and $PM_{2.5}$ were significantly ($p < 0.05$) associated with dementia and AD (higher exposure = higher risk), and greenspace measures were significantly associated with all outcomes but OD (higher exposure = lower risk). Exposure-outcome associations in the imaging study were not substantially impacted by inverse probability weighting (SI6), therefore it was not applied to the remaining analyses.

Sensitivity analysis showed generally reasonable robustness to violation of the sequential ignorability assumption. According to figures SI8 A-E, the rho (ρ) at which true mediation = 0 ranged from −0.15 to −0.25, and unobserved confounding variables would need to account for roughly 5–10 % of the mediator variance and 10–20 % of the outcome variance for the true mediation effects to be 0.

4. Discussion

Overall, this study found evidence for mediation of longitudinal associations between air pollution and increased risk of dementia by brain volumes. The results were consistent with existing evidence that air pollution and dementia outcomes are associated with lower brain volumes and provides the first epidemiological evidence known to the

Table 2
Descriptive statistics for exposure data in analytical sample (N = 42,802).

Exposure	Mean	Min	5th perc	Median	95th Perc	Max	IQR
NO_x (μg/m^3) N missing = 507	42.38	19.74	22.61	41.38	68.83	263.94	16.83
PM_{10} (μg/m^3) N missing = 2959	16.03	11.78	12.9	15.90	19.91	26.33	1.77
$PM_{2.5abs}$ (absorbance units x10^{-5}/m^{-1}) N missing = 2959	1.16	0.83	0.87	1.10	1.66	3.54	0.28
Lday (dB(A)) N missing = 507	55.39	50.91	51.08	54.26	65.67	81.36	3.55
Greenspace (% landcover within 1000 m) N missing = 3111	47.49	4.96	16.37	44.82	88.74	99.18	33.79

Air pollution estimates were modelled based on residential address for the year 2010 using the ESCAPE LUR model, noise pollution estimates were modelled based on residential address for the year 2009 modelled using a version of the CNOSSOS-EU noise model, and greenspace exposure estimates were modelled based on home location at initial assessment visit (2006–2010) using the 2005 Generalised Land Use Database for England.
Perc = percentile.
ESCAPE: European Study of Cohorts for Air Pollution Effects.
LUR: Land Use Regression
CNOSSOS-EU: Common Noise Assessment Methods in Europe.
NO_2: nitrogen dioxide.
$PM_{2.5abs}$: Particulate Matter less than 2.5 μm absorbance (absorbance units per metre).
Lday: A-weighted average noise level between 7am-7 pm at residential address.

Table 3
Associations between environmental exposures and odds of dementia in analytical sample (participants providing brain imaging and covariate data).

Exposure	Outcome:	Dementia		AD		VD		OD		UD	
	N	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
NO_2	40,278	0.99	0.75; 1.31	0.80	0.49; 1.29	0.96	0.55; 1.69	1.41	0.71; 2.80	0.99	0.66; 1.47
NOx	40,278	0.98	0.78; 1.22	0.72	0.46; 1.13	0.92	0.58; 1.48	1.41	0.83; 1.94	0.96	0.69;1.32
PM_{10}	37,878	1.05	0.87; 1.27	0.85	0.61; 1.18	1.22	0.86; 1.74	1.38	0.85; 2.25	1.10	0.84;1.43
$PM_{2.5}$	37,878	0.98	0.75; 1.26	0.77	0.49; 1.21	0.95	0.56; 1.61	1.49	0.80; 2.77	0.91	0.62; 1.32
$PM_{2.5abs}$	37,878	1.12	0.90; 1.41	0.72	0.44; 1.19	*1.45*	*1.00; 2.10*	1.48	0.86; 2.56	1.12	0.81; 1.54
PM_{coarse}	37,878	1.03	0.86; 1.23	0.86	0.61; 1.23	1.19	0.88; 1.62	1.07	0.65; 1.76	1.03	0.80; 1.33
Lday	40,278	1.19	0.76; 1.84	0.74	0.31; 1.80	1.45	0.65; 3.21	1.91	0.67; 5.49	1.04	0.54; 2.00
GS1000m	37,726	1.00	0.99; 1.01	0.99	0.97; 1.00	1.00	0.98; 1.02	0.98	0.96; 1.02	1.00	0.98; 1.01
GS300m	37,726	1.00	0.99; 1.01	1.00	0.99; 1.01	1.00	0.98; 1.02	0.99	0.97; 1.02	1.00	0.99; 1.01

Logistic regression models adjusted for age, sex, household income, ethnicity, education, smoking, and area-level deprivation.
Air pollutants are per IQR increase, noise exposure assessed per 10 dB increase, and greenspace per 1 % increase.
AD: Alzheimer's disease.
VD: Vascular dementia.
OD: Dementia in other diseases classified elsewhere.
UD: Unspecified dementia.
NO_2: nitrogen dioxide.
NOx: nitrogen oxides, nitrogen dioxide and nitric oxide.
PM_{10}: Particulate Matter less than 10 μm.
$PM_{2.5}$: Particulate Matter less than 2.5 μm.
$PM_{2.5abs}$: PM2.5 absorbance.
PM_{coarse}: Particulate Matter between 2.5 and 10 μm.
Lday: A-weighted average noise level between 7am-7 pm at residential address.
GS1000m: % of landcover classified as Greenspace within 1000 m of home.
GS300m: % of landcover classified as Greenspace within 300 m of home.
Bold = $p < 0.05$, *Italics* = $p < 0.10$.

authors that differences in brain volumes may mediate the relationships between prior exposure to air pollutants and later dementia. This adds to the strength of causal inference underlying air pollution and dementia's association and adds to the wider and growing evidence base that air pollution may have harmful effects on the human brain with observable functional impacts.

$PM_{2.5abs}$ is highly correlated with elemental carbon (EC) and therefore has been applied as a proxy for EC or motorised traffic-related air pollution (TRAP) in other research (Cyrys et al., 2003). Traffic is also an important source of ambient particulate matter and NOx emissions in urban setting (Beddows & Harrison, 2021; Hamra et al., 2015). TRAP has been shown to be associated with changes in brain volumes via multiple pathways including inflammation, oxidative stress, and neurovascular unit dysfunction (de Prado Bert et al., 2018). All these pathways could lead to loss of neurons and cellular damages in the central nervous system, which might explain the changes in brain volumes. EC has also been previously applied as a proxy for black carbon (BC), which has been associated with incident dementia (Briggs & Long, 2016; Li et al., 2022). Reduced volumes of total brain, peripheral cortical grey matter, and total grey matter are associated with dementia (Cho et al., 2020; Li et al., 2023; Mouton et al., 1998). Reduced total brain and grey matter volume is an indicator of accelerated brain aging and predicts incident dementia (Fotenos et al., 2005; Wang et al., 2019). Widespread reduction of cortical thickness occurs before the onset of dementia and accelerates as the dementia progresses (Im et al., 2008). However, the observed mediating effects were very small (<10 % of relationships explained) so other pathways must be co-occurring between environmental exposures and dementia, if the observed relationships are indeed causal. Therefore, this pathway is plausible, but more research is required to verify these findings further.

An association was not observed between $PM_{2.5abs}$ and vascular dementia in the wider UK Biobank cohort, whereas this was the strongest association in the imaging study subsample. This is perhaps due to selection bias or collider bias (participation in imaging study in our case). Conditioning on a collider (defined as the common effect of exposure and outcome) may create a spurious association between the exposure and outcome (Holmberg & Andersen, 2022). We took this into account by adopting the inverse probability weighting for selection from the wider UK Biobank cohort which still showed a significant association in the analytical sample. This suggests that unmeasured factors that are common effects of $PM_{2.5abs}$ and vascular dementia might drive the participation of imaging study and explain the lack of association in the wider UK Biobank cohort. In the larger Biobank sample, NO_2, NOx, $PM_{2.5}$, and greenspace were associated with dementia, and associations were observed for a wider range of outcomes (all-cause dementia, Alzheimer's disease, vascular dementia, and unspecified dementia), so there may be relationships we were unable to detect in the analytical (imaging) sample due to insufficient cases and therefore statistical power. Daytime noise and dementia risk were not significantly associated in either sample. This was contrary to hypotheses, based on prior research and *meta*-analysis (Manuella Lech et al., 2021; Meng et al., 2022), that traffic noise would be associated with greater risk of dementia, although the current evidence still has limitations (Paul et al., 2019), and detrimental associations have not been observed in all studies (Andersson et al., 2018; Iain et al., 2018).

The strengths of this study include its novelty, being the first study known to the authors to address whether changes in brain volume mediate associations between environmental exposures and incident dementia outcomes. The longitudinal design indicating a clear temporal relationship, where brain volumes were measured post-exposure and prior to diagnosis of dementia, is also a strength. Another strength is the inclusion of a range of exposures, including exploration of potential confounding or co-exposure effects using multi-exposure models, and a wide range of potential mediating brain volumes. Participants came from a wide range of sociodemographic backgrounds (in terms of IMD, educational level, and household income) and a wide range of exposure levels (to air pollution, noise and greenspace), and both genders were represented roughly equally.

However, although the brain volumes were measured after exposure levels, only absolute volumes were available, so these differences in volume could have preceded exposure. It is also important to note that a dementia diagnosis follows a gradual decline in functioning, so the presence of disease could have preceded the imaging visit even if diagnoses occurred afterwards. Future research would benefit from

Table 4
Mediating relationships between air pollution exposure and dementia risk by brain volumes in UK Biobank.

Pathway	Effect	Estimate	95 % CI Lower limit	95 % CI Upper limit	*p*
$PM_{2.5abs}$ −> Total brain volume −> Dementia risk N: 34,817 % mediated = 8 %	Indirect effect	2.48e-05	8.11e-06	5.28e-05	**<0.001**
	Direct effect	2.18e-04	1.67e-05	3.49e-04	**0.04**
	Total effect	2.43e-04	4.74e-05	3.72e-04	**0.04**
NOx −> Peripheral cortical grey matter −> AD risk N: 39,772 % mediated = 7 %	Indirect effect	7.37e-05	3.10e-05	1.60e-04	**<0.001**
	Direct effect	−1.18e-03	−3.48e-03	−4.66e-05	**0.02**
	Total effect	−1.11e-04	−3.35e-03	−8.96e-06	**0.04**
$PM_{2.5abs}$ −> Peripheral cortical grey matter −> VD risk N: 34,817 % mediated = 2 %	Indirect effect	4.31e-06	2.24–07	2.61e-05	**0.02**
	Direct effect	1.13e-04	3.18e-05	7.15e-04	**0.02**
	Total effect	1.18e-04	3.25e-05	7.51e-04	**0.02**
$PM_{2.5abs}$ −> Total grey matter −> OD risk N: 34,817 % mediated = 4 %	Indirect effect	3.13e-06	1.27e-07	1.55e-05	**<0.001**
	Direct effect	3.74e-05	4.08e-06	8.83e-05	**0.02**
	Total effect	4.06e-05	4.19e-06	9.52e-05	**0.02**
PM_{10} −> Total grey matter −> OD risk N: 34,817 % mediated = 4 %	Indirect effect	2.14e-06	1.40e-09	1.09e-05	**<0.001**
	Direct effect	5.23e-05	−2.12e-06	8.24e-05	*0.06*
	Total effect	5.44e-05	3.79e-08	8.52e-05	**0.04**

Effects are adjusted for age, sex, household income, ethnicity, education, smoking, and area-level deprivation
$PM_{2.5abs}$: Particulate Matter less than 2.5 μm absorbance.
NOx: nitrogen oxides, nitrogen dioxide and nitric oxide.
AD: Alzheimer's disease.
VD: Vascular dementia.
OD: Other dementia.
Bold = $p < 0.05$, *Italics* = $p < 0.10$.

longitudinal measures of brain volume (changes) and cognitive functioning to see if these responded to exposure, with a consequent follow-up of dementia cases (this may be possible in future use of Biobank data as more time elapses from the second imaging visit). The small number of all-cause and specific dementia cases with brain imaging data might limit detectability. More cases are likely to occur in future Biobank follow-up when participants are getting older, so more highly powered analyses may be possible in future. Exposure assessment was based on the residential address at baseline, so residential mobility during the follow-up might impact our results. However, only ~ 2 % of participants relocated based on follow-up surveys, suggesting that residential mobility is unlikely a major concern in our study. We only used air pollution estimates in 2010 when participants were aged between 40 and 74 years. Air pollution levels in 2005–2007 were estimated by a different model (EU-wide air pollution maps), so we could not combine or average these with air pollution estimates in 2010. The annual emissions of particulate matter (PM_{10} and $PM_{2.5}$) in the UK have been relatively consistent across time since 2010, whilst emissions of nitrogen oxides have been declining (https://www.gov.uk/government/statistics/emissions-of-air-pollutants/emissions-of-air-pollutants-in-the-uk-summary). Thus, particulate matter levels estimated in 2010 could be a proxy of long-term exposure, but the associations between NO_2/NOx and incidence of dementia might be underestimated. Sensitivity analyses pointed to the possible role of unobserved confounding, and it can't be ruled out that key unaccounted for risk factors associated with both mediator and outcome (such as genetic influences or substance use) could have confounded associations. Finally, the sample was overwhelmingly from a white ethnic background, which limits generalisability.

5. Conclusions

Overall, this study has added to the existing evidence that urban environmental exposures are associated with risk of dementia and differences in brain volumes, and that dementia is associated with differences in brain volumes which differ across disease subtypes. It has also contributed new evidence that differences in brain volumes may help partially explain the longitudinal associations between exposure to air pollution and dementia, although only a relatively small proportion (2%-8%). Substantial future research is required to investigate further whether differences in brain volumes resulting from environmental exposures are contributing to the aetiology of dementia and to unpack the other explanatory variables (such as markers of inflammation, oxidative stress, brain function and connectivity).

CRediT authorship contribution statement

Rhiannon Thompson: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Xinning Tong:** Writing – review & editing, Validation, Methodology. **Xueyi Shen:** Writing – review & editing, Validation, Methodology. **Jinjun Ran:** Writing – review & editing, Methodology. **Shengzhi Sun:** Writing – review & editing, Methodology. **Xiaoxin Iris Yao:** Writing – review & editing, Validation, Project administration, Methodology, Funding acquisition. **Chen Shen:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.109219.

Data availability

The authors do not have permission to share data.

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