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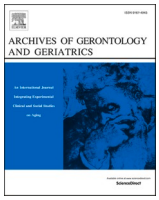

Association of greenspace and natural environment with brain volumes mediated by lifestyle and biomarkers among urban residents

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HIGHLIGHTS

- Greater proximity to greenspace was associated with larger brain volumes.
- Greater proximity to natural environment was associated with larger brain volumes.
- Smoking and physical activity mediated associations between greenspace and brain volumes.
- Vitamin D, red blood cell indices, and creatinine were important mediators for the association.

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ABSTRACT

Objectives: To examine the associaiton between environmental measures and brain volumes and its potential mediators.
Study design: This was a prospective study.
Methods: Our analysis included 34,454 participants (53.4% females) aged 40–73 years at baseline (between 2006 and 2010) from the UK Biobank. Brain volumes were measured using magnetic resonance imaging between 2014 and 2019.
Results: Greater proximity to greenspace buffered at 1000 m at baseline was associated with larger volumes of total brain measured 8.8 years after baseline assessment (standardized β (95% CI) for each 10% increment in coverage: 0.013(0.005,0.020)), grey matter (0.013(0.006,0.020)), and white matter (0.011(0.004,0.017)) after adjustment for covariates and air pollution. The corresponding numbers for natural environment buffered at 1000 m were 0.010 (0.004,0.017), 0.009 (0.004,0.015), and 0.010 (0.004,0.016), respectively. Similar results were observed for greenspace and natural environment buffered at 300 m. The strongest mediator for the association between greenspace buffered at 1000 m and total brain volume was smoking (percentage (95% CI) of total variance explained: 7.9% (5.5–11.4%)) followed by mean sphered cell volume (3.3% (1.8–5.8%)), vitamin D (2.9% (1.6–5.1%)), and creatinine in blood (2.7% (1.6–4.7%)). Significant mediators combined explained 18.5% (13.2–25.3%) of the association with total brain volume and 32.9% (95% CI: 22.3–45.7%) of the

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association with grey matter volume. The percentage (95% CI) of the association between natural environment and total brain volume explained by significant mediators combined was 20.6% (14.7–28.1%)).
Conclusions: Higher coverage percentage of greenspace and environment may benefit brain health by promoting healthy lifestyle and improving biomarkers including vitamin D and red blood cell indices.

1. Introduction

Dementia is amongst the leading causes of death globally, (Nichols, Szoeke & Vollset, 2019) and the number of people living with dementia is expected to rapidly rise in the future decades. (Ahmadi-Abhari, Guzman-Castillo & Bandosz, 2017; Livingston, Huntley & Sommerlad, 2020) Brain structure may influence the development of dementia, (Lombardi, Crescioli & Cavedo, 2020) and accelerated brain atrophy patterns may signal neurodegenerative changes. (Hou, Dan & Babbar, 2019) Although numerous chronic conditions and biomarkers have been linked to brain atrophy, these traditional factors appear to explain a small amount of variance in brain volumes. (Shang, Zhang & Huang, 2022; Cox, Lyall & Ritchie, 2019) Thus, it is important to identify other determinants for brain atrophy.

Evidence has highlighted the importance of environmental factors including greenspace and air pollution on physical and mental health. (Sarkar, Webster & Gallacher, 2018; Roscoe, Mackay & Gulliver, 2022) Data from the UK biobank demonstrated that more greenspace was associated with lower risk of major depressive disorders. (Sarkar et al., 2018) A cross-sectional analysis of 13,594 women from the Nurses' Health Study II showed that increasing greenspace was associated with better cognitive health. (Jimenez, Elliott & DeVille, 2022) Two studies with a relatively limited number of participants have investigated the association between greenspace and brain volume with inconsistent findings. (Besser, Lovasi & Michael, 2021; Min, Kim & Park, 2021) One study of 2542 adults aged 45–96 years found that increasing greenspace (each interquartile range increase in enhanced vegetation index) was associated with greater cortical thickness of the parietal (11 μm (95% CI: 3–20)) and occipital regions (9 μm (95% CI: 1–16)) amongst the urban population but not amongst the rural population, (Min et al., 2021) whereas the other study of 1125 non-demented participants aged 65 years or older did not find a significant association between greenspace and brain volume. (Besser et al., 2021) Previous studies have shown that physical activity, air pollution, and social interaction mediated associations between greenspace and mental health, (Dzhambov, Browning, Markevych, Hartig & Lercher, 2020) which may help explore underlying mechanisms of the greenspace effect. (Yang, Zhao & Hu, 2021) It is unknown whether lifestyle and biomarkers mediate the association between greenspace and brain health.

Investigating the association between greenspace/natural environment and brain health, and the potential mediators would provide evidence on urban planning and design for promoting brain health. Using the UK Biobank, we sought to examine associations of greenspace and natural environment with brain volumes and whether lifestyle and biomarkers mediated these associations.

2. Methods

2.1. Study population

Our analysis was based on the UK Biobank, which is a population-based cohort of more than 500,000 participants aged 40 years or older at baseline (2006–2010). (Sudlow, Gallacher & Allen, 2015) The study design has been detailed elsewhere. (Sudlow et al., 2015) Out of approximately 9.2 million people invited, baseline data was collected from 502,505 participants.

The UK Biobank Study's ethical approval has been granted by the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee (REC reference: 16/NW/0274). All participants provided informed consent through electronic signature at recruitment.

2.2. Brain magnetic resonance imaging

Brain magnetic resonance imaging (MRI) data were collected between August 2014 and October 2019. A standard Siemens Skyra 3T scanner with a standard 32-channel radio-frequency receiver head coil was used to produce images. (Alfaro-Almagro, Jenkinson & Bangerter, 2018) The T1- and T2-weighted scans were analysed with the Functional MRI of the Brain Software Library. Total brain volume was calculated by summing the grey matter and white matter volumes (excludes cerebrospinal fluid). Total brain and regional brain volumes (grey matter, white matter, and white matter hyperintensity [WMH]) were normalized for head size based on the external surface of the skull, using the ratio-corrected method. (Alfaro-Almagro et al., 2018) Given the positively skewed distribution, WMH was log-transformed in the analysis. Brain volumes were standardized to a mean of 0 and SD of 1. Larger volumes of total brain, white matter, and grey matter and smaller WMH load represent better brain health.

2.3. Environment measures

Residential greenspace surrounding participants' geocoded addresses at baseline was estimated using land data obtained from the 2005 Generalized Land Use Database, provided by the Department for Communities and Local Government of the Government of the UK (https://www.gov.uk/government/statistics). The coverage percentage for greenspace (a proportion of all land-use types) in circular distance buffers surrounding each home location polygon was allocated an area-weighted mean of the land use coverage percentage for each participant. We used 300 m and 1000 m buffers to capture near-residence greenspace.

The percentage of the home location buffer defined as 'Natural Environment' (including land, water, arable, and coastal) in the Land Cover Map 2007 was estimated using the Land Cover Map, 2007. The 23 land cover classes were reclassified as 'Natural Environment' (1–21) and 'Built environment' (22–23). The percentage of natural environment with home location data buffered at 300 m and 1000 m was calculated. (Sarkar, Webster & Gallacher, 2015; Sarkar & Webster, 2017)

Air pollution measured by the Small Area Health Statistics Unit (http://www.sahsu.org/) was linked centrally to UK Biobank data. Particulate matter air pollutants as annual average values in $\mu g/m^3$ were estimated. Particulate matter air pollution (PM2.5) measured at baseline (2006–2010) was adjusted for as a covariate in the analysis.

2.4. Genetic data

BiLEVE Axiom array, or the UK Biobank Axiom array was used for genotyping by Affymetrix. Apolipoprotein E Ɛ4 (APOE4) genotype was directly genotyped using two single-nucleotide polymorphisms (rs7412/rs429358). APOE4 was defined by APOE4+ dominant model of E2/E4, E3/E4 or E4/E4.

2.5. Demographic and lifestyle factors

Demographic information on age, sex, ethnicity, education, and income were self-reported. Neighbourhood-level socioeconomic status was assessed using Townsend index of material deprivation. (Townsend

& Phillimore, 1988) Data on diet, smoking, sleep duration, and frequency of alcohol consumption were obtained using a questionnaire. A healthy diet score was then computed based on seven commonly eaten food groups with a higher score representing a healthier diet. (Lourida, Hannon & Littlejohns, 2019) A short form of the International Physical Activity Questionnaire was used to estimate levels of physical activity during work and leisure time.

2.6. Blood tests

Plasma lipids including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides were measured by direct enzymatic methods (Konelab, Thermo Fisher Scientific, Waltham, Massachusetts). Glycated haemoglobin (HbA1c) was assessed using high-performance liquid chromatography on a Bio-Rad Variant II Turbo. Other plasma biomarkers such as vitamin D and creatinine were also measured (https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/serum_biochemistry.pdf).

2.7. Urinary biomarker data

Urinary biomarkers such as sodium, potassium, microalbumin, and creatinine were tested by an ion-selective electrode analysis on a Beckman Coulter AU5400 (https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/urine_assay.pdf).

2.8. Multimorbidity risk score

Chronic diseases including hypertension, depression, heart disease, and stroke at baseline were defined using self-reported data, interviews, or inpatient data. Body mass index (BMI) was calculated based on measured weight and height. A multimorbidity score for brain atrophy was calculated based on 33 major diseases that were significantly associated with brain volumes. (Shang, Zhu & Zhang, 2022) The multimorbidity risk score was calculated using the formula: $\sum_{i=1}^{n}\beta_i \times D_i$, where β_i is the beta coefficient for brain volumes associated with the i th disease, D_i refers to whether individuals had the i th disease, and n is the total number of diseases that were significantly associated with brain volumes.

2.9. Statistical analysis

Baseline characteristics were expressed as frequency (percentage) or means ± standard deviations (SDs). ANOVA for continuous variables and Chi-square test for categorical variables were used to test the difference of characteristics across quintiles of the percentage of greenspace/natural environment.

General linear regression models were used to evaluate the association between the coverage percentage of greenspace and natural environment and brain volumes. Four models were tested: 1) Model 1 was adjusted for age (continuous) and gender (women, men); 2) Model 2 was adjusted for Model 1 plus ethnicity (white, non-white), education (college/university degree, upper secondary, final stage of secondary education, lower secondary, first stage of secondary education, vocational qualifications, none of above), household income (<18,000 pounds, 18,000–30,999 pounds, 31,000–51,999 pounds, 52,000–100,000 pounds, >100,000 pounds), and Townsend index (continuous); 3) Model 3 was adjusted for Model 2 plus smoking (never, former, current), physical activity (continuous), diet score (continuous), alcohol consumption (Daily or almost daily, 3/4 times/week, 1/2 times/week, 1–3 times/month, special occasions only, never), sleep duration (continuous), BMI (continuous), vitamin D (continuous), APOE4, and multimorbidity risk score (continuous); 4) Model 4 was adjusted for Model 3 plus particulate matter air pollution (continuous). These covariates, including geographic factors, socioeconomic factors, lifestyle and biomarkers, and air pollution, were selected based on their associations with brain atrophy and neurodegenerative disorders. Percentages of greenspace and natural environment buffered at 300 m and 1000 m were analysed in quintiles and as continuous variables (each 10%).

Whether associations between greenspace and natural environment and brain volumes were mediated by lifestyle factors and biomarkers individually and altogether was tested using general linear regression models. We established mediation using the following criteria (Lin, Fleming & De Gruttola, 1997): 1) the mediator was significantly associated with the proximity to greenspace and natural environment, 2) the proximity to greenspace and natural environment was significantly associated with brain volumes, 3) the mediator was significantly associated with brain volumes, and 4) the association between the proximity to greenspace and natural environment and brain volumes was attenuated by the mediator. The potential mediation effect of all these lifestyle factors and biomarkers that were associated with environmental factors and brain volumes in previous research were tested. Potential mediators examined included lifestyle factors ($n = 15$), health related conditions ($n = 3$), blood biomarkers ($n = 49$), and urinary biomarkers ($n = 4$) (Table S1). Benjamin-Hochberg's procedure was used to control the false discovery rate (FDR) at a 5% level for multiple comparisons. (Benjamini & Hochberg, 1995)

Whether associations between greenspace and natural environment and brain volumes were modified by age, sex, education, or Townsend index was tested using general linear regression models.

Given that a large proportion of the UK cohort without MRI data were excluded from the analysis, associations between environmental measures and brain volumes were tested using the inverse probability weighting method (IPWM) in the sensitivity analysis. Individuals with complete data are weighted by the inverse of their probability of being a complete case. (Hernán & Robins, 2006)

The proportion of variables with missing values for physical activity, income, education, BMI, and smoking was 15.1%, 9.8%, 1.8%, 1.3%, and 0.2%, respectively. Multiple imputations for missing data were conducted, and age, sex, and all covariates were included in the imputation models to create 5 imputed datasets.

Data analyses were conducted using SAS 9.4 for Windows (SAS Institute Inc.) and all P values were two-sided with statistical significance set at <0.05.

3. Results

3.1. Population selection

Individuals with missing values on MRI assessments ($n = 462,809$), with neurological disorders ($n = 1799$), or who lived in rural areas ($n = 3443$) at baseline were excluded from the analysis. We included 34,454 participants (53.4% females) in the final analysis (Figure S1). They were aged 40–73 (mean±SD: 54.7 ± 7.5) years at baseline when environmental measures, lifestyle, and biomarkers were conducted and aged 44–81 (63.5 ± 7.6) years when MRI assessments were conducted.

3.2. Baseline characteristics

Individuals living with higher greenspace coverage were more likely to be older, whites, physically active, and never smokers, and to have lower education and income. Greater greenspace was associated with lower levels of air pollution (Table 1). The greenspace coverage buffered at 1000 m was 43.0% (SD=17.2%) for individuals with a low education level (≤5 years) and 41.8% (SD=19.4%) for those with a high education level (≥13 years). The greenspace coverage was 43.9% (SD=18.8%) for individuals with a low income (≤100,000 pounds) and 38.9% (SD=19.5%) for those with a high income (>100,000 pounds).

Table 1
Baseline characteristics across quintiles of greenspace buffered at 1000 m.

	Greenspace buffered at 1000 m (%)					P-value*
	Quintile 1 (<25.6%)	Quintile 2 (25.6–35.8%)	Quintile 3 (35.9–47.6%)	Quintile 4 (47.7–61.5%)	Quintile 5 (>61.5%)	
Age (years)	54.03 ± 7.54	54.33 ± 7.49	54.86 ± 7.39	55.04 ± 7.43	55.11 ± 7.40	<0.0001
Ethnicity						<0.0001
White	6462 (93.8)	6590 (95.6)	6687 (97.1)	6738 (97.8)	6808 (98.8)	
Non-white	409 (5.9)	277 (4.0)	181 (2.6)	139 (2.0)	67 (1.0)	
Unknown	20 (0.3)	23 (0.3)	22 (0.3)	15 (0.2)	16 (0.2)	
Sex						1.00
Women	3677 (53.4)	3676 (53.4)	3677 (53.4)	3677 (53.4)	3677 (53.4)	
Men	3214 (46.6)	3214 (46.6)	3213 (46.6)	3215 (46.6)	3214 (46.6)	
Education						<0.0001
College/university degree	3872 (56.2)	3178 (46.1)	2856 (41.5)	2817 (40.9)	2949 (42.8)	
Upper secondary	825 (12.0)	879 (12.8)	861 (12.5)	961 (13.9)	928 (13.5)	
Final stage of secondary education	987 (14.3)	1195 (17.3)	1439 (20.9)	1504 (21.8)	1506 (21.9)	
Lower secondary	224 (3.3)	274 (4.0)	322 (4.7)	293 (4.3)	314 (4.6)	
First stage of secondary education	271 (3.9)	353 (5.1)	406 (5.9)	433 (6.3)	385 (5.6)	
Vocational qualifications	264 (3.8)	338 (4.9)	337 (4.9)	360 (5.2)	344 (5.0)	
None of above	448 (6.5)	673 (9.8)	669 (9.7)	524 (7.6)	465 (6.7)	
Household income (pounds)						<0.0001
<18,000	758 (11.0)	840 (12.2)	845 (12.3)	747 (10.8)	689 (10.0)	
18,000–30,999	1518 (22.0)	1591 (23.1)	1689 (24.5)	1683 (24.4)	1611 (23.4)	
31,000–51,999	2022 (29.3)	2130 (30.9)	2208 (32.0)	2273 (33.0)	2306 (33.5)	
52,000–100,000	1924 (27.9)	1841 (26.7)	1747 (25.4)	1832 (26.6)	1938 (28.1)	
>100,000	669 (9.7)	488 (7.1)	401 (5.8)	357 (5.2)	347 (5.0)	
Townsend index	−0.22 ± 3.13	−1.29 ± 2.75	−1.99 ± 2.60	−2.66 ± 2.26	−2.87 ± 2.05	<0.0001
Alcohol consumption						0.92
Daily or almost daily	1721 (25.0) (	1426 (20.7) (	1414 (20.5) (	1426 (20.7) (	1556 (22.6) (	
3/4 times/week	1893 (27.5) (	1902 (27.6) (	1896 (27.5) (	1931 (28.0) (	1979 (28.7) (	
1/2 times/week	1623 (23.6) (	1796 (26.1) (	1832 (26.6) (	1886 (27.4) (	1823 (26.5) (	
1–3 times/month	721 (10.5)	768 (11.1)	789 (11.5)	773 (11.2)	742 (10.8)	
Special occasions only	558 (8.1)	633 (9.2)	604 (8.8)	572 (8.3)	526 (7.6)	
Never	371 (5.4)	357 (5.2)	355 (5.2)	301 (4.4)	265 (3.8)	
Missing	4 (0.1)	8 (0.1)		3 (0.0)		
Smoking						<0.0001
Never	3923 (56.9)	4153 (60.3)	4238 (61.5)	4294 (62.3)	4392 (63.7)	
Former	2408 (34.9)	2235 (32.4)	2252 (32.7)	2241 (32.5)	2135 (31.0)	
Current	560 (8.1)	502 (7.3)	400 (5.8)	357 (5.2)	364 (5.3)	
Physical activity (MET-minutes/week)	2397 ± 2102	2453 ± 2178	2496 ± 2219	2487 ± 2266	2520 ± 2307	0.0009
Diet score†	4.16 ± 1.38	4.05 ± 1.41	3.98 ± 1.39	4.00 ± 1.36	4.02 ± 1.36	<0.0001
Sleep duration (hours)	7.15 ± 0.95	7.13 ± 0.95	7.17 ± 0.98	7.18 ± 0.95	7.19 ± 0.96	<0.0001
BMI (kg/m^2)	26.27 ± 4.18	26.67 ± 4.32	26.72 ± 4.28	26.68 ± 4.24	26.63 ± 4.09	<0.0001
Multimorbidity risk score‡	117.6 ± 16.0	118.5 ± 16.3	118.9 ± 16.4	119.0 ± 16.52	118.7 ± 15.9	<0.0001
Particulate matter air pollution (micro-g/m^3)	10.79 ± 0.97	10.48 ± 0.87	10.15 ± 0.79	9.77 ± 0.73	9.24 ± 0.70	<0.0001

Data are means ± standard deviations, or N (%). BMI, body mass index; MET, metabolic equivalent.

* T-test for continuous variables and Chi-square for categorical variables were used to test the difference of baseline characteristics across quintiles of greenspace.

† Diet score was computed based on seven commonly eaten food groups following recommendations on dietary priorities for cardiometabolic health with a higher score representing a healthier diet.

‡ A multimorbidity score for brain atrophy was calculated based on major diseases.

3.3. Greenspace/natural environment and biomarkers

Individuals in quintile 5 of greenspace buffered at 1000 m had higher levels of vitamin D, and urea, and lower levels of mean corpuscular volume (MCV), mean sphered cell volume (MSCV), and mean reticulocyte volume (MRV), immature reticulocyte fraction (IRF), and creatinine in urine compared with those in quintile 1 (Table S2). Similar results were seen for greenspace buffered at 300 m (Table S3) and natural environment buffered at 1000 m (Table S4) and 300 m (Table S5).

3.4. Lifestyle, biomarkers, and brain volumes

Former and current smokers had smaller total brain and grey matter volumes measured 8.8 years after baseline assessment compared with never smokers. Higher physical activity at baseline was associated with larger total brain volume. Higher levels of vitamin D were associated with larger volumes of total brain, grey matter, and white matter (Table S6).

3.5. Greenspace and brain volumes

A higher percentage of greenspace buffered at 1000 m at baseline was associated with larger volumes of total brain, grey matter, and white matter measured 8.8 years after baseline assessment. Individuals in quintile 5 had larger volumes of total brain (β (95% CI): 0.07 (0.03, 0.11)) and grey matter (0.07 (0.03, 0.11)), and white matter (0.06 (0.03, 0.10)) compared with those in quintile 1 after adjustment for geographic factors, socioeconomic status, lifestyle, BMI, multimorbidity risk score, and air pollution. Multivariable-adjusted βs (95% CIs) for total brain, grey matter, and white matter associated with each 10% increment of greenspace buffered at 1000 m were 0.013 (0.005, 0.020), 0.013 (0.006, 0.020), and 0.011 (0.004, 0.017), respectively (Table 2). The corresponding numbers for greenspace buffered at 300 m were 0.013 (0.006, 0.019), 0.010 (0.004, 0.016), and 0.011 (0.005, 0.017), respectively (Table S7).

3.6. Natural environment and brain volumes

Greater natural environment at baseline was associated with larger

Table 2
The association between greenspace buffered at 1000 m and brain volumes.

Brain volume	Greenspace buffered at 1000 m (%)						Each 10% increment
	Quintile 1 (<25.6%)	Quintile 2 (25.6–35.8%)	Quintile 3 (35.9–47.6%)	Quintile 4 (47.7–61.5%)	Quintile 5 (>61.5%)	P-value for trend*	
Participants (n)	6891	6890	6890	6892	6891		
Total brain							
β (95% CI), Model 1†	Reference	0.06 (0.03, 0.08)	0.07 (0.04, 0.10)	0.09 (0.06, 0.11)	0.10 (0.07, 0.12)	<0.0001	0.017 (0.012, 0.021)†
β (95% CI), Model 2	Reference	0.04 (0.02, 0.07)	0.05 (0.02, 0.08)	0.06 (0.03, 0.09)	0.07 (0.04, 0.10)	<0.0001	0.012 (0.008, 0.017) †
β (95% CI), Model 3	Reference	0.04 (0.01, 0.07)	0.05 (0.02, 0.08)	0.06 (0.03, 0.09)	0.07 (0.04, 0.10)	<0.0001	0.012 (0.008, 0.017) †
β (95% CI), Model 4	Reference	0.05 (0.01, 0.08)	0.06 (0.02, 0.10)	0.07 (0.03, 0.10)	0.07 (0.03, 0.11)	0.0065	0.013 (0.005, 0.020) †
Grey matter							
β (95% CI), Model 1	Reference	0.05 (0.02, 0.07)	0.06 (0.04, 0.09)	0.07 (0.05, 0.10)	0.07 (0.04, 0.09)	<0.0001	0.012 (0.008, 0.016) †
β (95% CI), Model 2	Reference	0.04 (0.01, 0.06)	0.05 (0.02, 0.07)	0.05 (0.02, 0.07)	0.04 (0.02, 0.07)	0.0014	0.008 (0.003, 0.012) †
β (95% CI), Model 3	Reference	0.04 (0.01, 0.06)	0.04 (0.02, 0.07)	0.05 (0.02, 0.07)	0.05 (0.02, 0.07)	0.0012	0.008 (0.004, 0.012) †
β (95% CI), Model 4	Reference	0.05 (0.02, 0.08)	0.07 (0.04, 0.10)	0.07 (0.04, 0.11)	0.07 (0.03, 0.11)	0.0004	0.013 (0.006, 0.020) †
White matter							
β (95% CI), Model 1	Reference	0.04 (0.01, 0.08)	0.05 (0.02, 0.08)	0.07 (0.04, 0.10)	0.09 (0.06, 0.12)	<0.0001	0.016 (0.010, 0.021) †
β (95% CI), Model 2	Reference	0.04 (0.00, 0.07)	0.04 (0.01, 0.07)	0.06 (0.02, 0.09)	0.08 (0.04, 0.11)	<0.0001	0.013 (0.008, 0.019) †
β (95% CI), Model 3	Reference	0.03 (0.00, 0.06)	0.04 (0.00, 0.07)	0.05 (0.02, 0.09)	0.07 (0.04, 0.11)	<0.0001	0.013 (0.007, 0.018) †
β (95% CI), Model 4	Reference	0.03 (0.00, 0.06)	0.03 (0.00, 0.07)	0.05 (0.01, 0.08)	0.06 (0.03, 0.10)	0.0014	0.011 (0.004, 0.017) †
White matter hyperintensity							
β (95% CI), Model 1	Reference	0.01 (−0.03, 0.05)	0.02 (−0.02, 0.05)	−0.00 (−0.04, 0.03)	0.02 (−0.02, 0.06)	0.50	0.001 (−0.005, 0.008)
β (95% CI), Model 2	Reference	0.01 (−0.03, 0.04)	0.01 (−0.03, 0.05)	−0.00 (−0.04, 0.03)	0.02 (−0.02, 0.06)	0.44	0.002 (−0.005, 0.008)
β (95% CI), Model 3	Reference	−0.01 (−0.04, 0.03)	0.00 (−0.04, 0.04)	−0.01 (−0.05, 0.02)	0.01 (−0.03, 0.05)	0.70	0.001 (−0.006, 0.007)
β (95% CI), Model 4	Reference	0.00 (−0.04, 0.04)	0.01 (−0.03, 0.05)	0.00 (−0.04, 0.05)	0.05 (−0.00, 0.09)	0.15	0.006 (−0.002, 0.013)

CI, confidence interval.
*General linear regression models were used to examine the association between greenspace buffered at 1000 m and brain volumes. The coefficients were standardized. Model 1 was adjusted for age and gender; Model 2 was adjusted for Model 1 plus ethnicity, education, household income, and Townsend index; Model 3 was adjusted for Model 2 plus smoking, physical activity, diet score, alcohol consumption, sleep duration, BMI, APOE4, vitamin D, and multimorbidity risk score; Model 4 was adjusted for Model 3 plus particulate matter air pollution.
† refers to a significant association after adjustment for FDR.

brain volumes measured 8.8 years after baseline assessment independent of covariates and air pollution. Multivariable-adjusted βs (95% CIs) for total brain, grey matter, and white matter volumes associated with coverage percentage of natural environment buffered at 1000 m (quintile 5 versus quintile 1) were 0.06 (0.02, 0.11), 0.07 (0.03, 0.10), and 0.05 (0.01, 0.09), respectively (Table 3). The corresponding numbers for natural environment buffered at 300 m were 0.05 (0.01, 0.08), 0.06 (0.02, 0.10), and 0.06 (0.02, 0.10), respectively (Table S8).

Table 3
The association between natural environment buffered at 1000 m and brain volumes.

Brain volume	Natural environment buffered at 1000 m (%)						Each 10%
	Quintile 1 (<17.8%)	Quintile 2 (17.8–30.3%)	Quintile 3 (30.4–44.3%)	Quintile 4 (44.4–60.5%)	Quintile 5 (>60.5%)	P-value for trend*	increment
Participants (n)	6897	6880	6895	6890	6892		
Total brain							
β (95% CI), Model 1	Reference	0.04 (0.01, 0.07)	0.06 (0.03, 0.09)	0.08 (0.05, 0.10)	0.09 (0.06, 0.11)	<0.0001	0.014 (0.010, 0.018) †
β (95% CI), Model 2	Reference	0.02 (−0.00, 0.05)	0.04 (0.01, 0.07)	0.05 (0.02, 0.08)	0.06 (0.03, 0.09)	<0.0001	0.010 (0.006, 0.015) †
β (95% CI), Model 3	Reference	0.03 (−0.00, 0.05)	0.04 (0.01, 0.07)	0.05 (0.02, 0.08)	0.06 (0.03, 0.09)	0.0005	0.010 (0.006, 0.014) †
β (95% CI), Model 4	Reference	0.02 (−0.01, 0.06)	0.04 (0.00, 0.08)	0.04 (0.00, 0.08)	0.06 (0.02, 0.011)	0.0758	0.010 (0.004, 0.017) †
Grey matter							
β (95% CI), Model 1	Reference	0.03 (0.01, 0.06)	0.06 (0.03, 0.08)	0.06 (0.04, 0.09)	0.07 (0.04, 0.09)	<0.0001	0.010 (0.006, 0.014) †
β (95% CI), Model 2	Reference	0.02 (−0.01, 0.05)	0.04 (0.01, 0.07)	0.03 (0.01, 0.06)	0.04 (0.01, 0.07)	0.0047	0.006 (0.002, 0.010) †
β (95% CI), Model 3	Reference	0.02 (−0.00, 0.05)	0.04 (0.01, 0.07)	0.03 (0.01, 0.06)	0.04 (0.01, 0.07)	0.0166	0.006 (0.002, 0.010) †
β (95% CI), Model 4	Reference	0.04 (0.01, 0.08)	0.06 (0.02, 0.09)	0.05 (0.01, 0.09)	0.07 (0.03, 0.10)	0.0084	0.009 (0.004, 0.015) †
White matter							
β (95% CI), Model 1	Reference	0.03 (−0.00, 0.06)	0.04 (0.01, 0.07)	0.06 (0.03, 0.10)	0.08 (0.05, 0.11)	<0.0001	0.013 (0.009, 0.018) †
β (95% CI), Model 2	Reference	0.02 (−0.01, 0.05)	0.03 (−0.01, 0.06)	0.05 (0.02, 0.09)	0.07 (0.03, 0.10)	<0.0001	0.012 (0.007, 0.016) †
β (95% CI), Model 3	Reference	0.02 (−0.02, 0.05)	0.02 (−0.01, 0.05)	0.05 (0.01, 0.08)	0.06 (0.03, 0.10)	0.0001	0.011 (0.006, 0.016) †
β (95% CI), Model 4	Reference	0.02 (−0.02, 0.05)	0.02 (−0.01, 0.05)	0.04 (0.01, 0.08)	0.05 (0.01, 0.09)	0.0040	0.010 (0.004, 0.016) †
White matter hyperintensity							
β (95% CI), Model 1	Reference	0.05 (0.02, 0.09)	0.00 (−0.03, 0.04)	0.01 (−0.03, 0.05)	0.02 (−0.01, 0.06)	0.95	0.001 (−0.005, 0.006)
β (95% CI), Model 2	Reference	0.05 (0.02, 0.09)	0.00 (−0.03, 0.04)	0.01 (−0.03, 0.05)	0.03 (−0.01, 0.07)	0.77	0.001 (−0.004, 0.007)
β (95% CI), Model 3	Reference	0.05 (0.01, 0.09)	−0.00 (−0.04, 0.04)	0.01 (−0.03, 0.05)	0.02 (−0.02, 0.06)	0.93	0.001 (−0.005, 0.006)
β (95% CI), Model 4	Reference	0.05 (0.02, 0.09)	0.01 (−0.03, 0.05)	0.03 (−0.01, 0.07)	0.05 (0.01, 0.10)	0.15	0.005 (−0.001, 0.012)

CI, confidence interval.
* General linear regression models were used to examine the association between natural environment buffered at 1000 m and brain volumes. The coefficients were standardized. Model 1 was adjusted for age and gender; Model 2 was adjusted for Model 1 plus ethnicity, education, household income, and Townsend index; Model 3 was adjusted for Model 2 plus smoking, physical activity, diet score, alcohol consumption, sleep duration, BMI, APOE4, vitamin D, and multimorbidity risk score; Model 4 was adjusted for Model 3 plus particulate matter air pollution.
† refers to a significant association after adjustment for FDR.

3.7. Mediation analysis for greenspace and brain volumes

After adjustment for FDR, 12 out of 71 factors examined significantly mediated the association between greenspace buffered at 1000 m and total brain volume. The strongest mediator was smoking (percentage (95% CI) of total variance explained: 7.9% (5.5–11.4%)) followed by MSCV (3.3% (1.8–5.8%)), vitamin D (2.9% (1.6–5.1%)), and creatinine in blood (2.7% (1.6–4.7%)). The total percentage (95% CI) explained by significant mediators combined was 18.5% (13.2–25.3%)).

Leading mediators for the association between greenspace buffered at 1000 m and grey matter volume included smoking (percentage (95% CI) of total variance explained: 15.8% (5.8–22.9%)), MSCV (6.6% (4.0–10.5%)), vitamin D (4.6% (2.7–7.8%)), creatinine in blood (4.3% (2.5–7.2%)), MCV (3.0% (1.6–5.5%)), and IRF (2.9% (1.5–5.7%)). The significant mediators combined explained 32.9% (95% CI: 22.3–45.7%) of the total variance (Fig. 1).

Similar results were seen for the association between greenspace buffered at 300 m and brain volumes (Figure S2).

3.8. Mediation analysis for natural environment and brain volumes

Twelve significant mediators were found for the association between natural environment buffered at 1000 m and total brain volume. The five leading mediators included smoking (percentage (95% CI) of total variance explained: 9.0% (6.2–12.8%)), vitamin D (3.7% (2.1–6.6%)), MSCV (3.1% (1.7–5.5%)), creatinine in blood (2.6% (1.5–4.5%)), and urea (2.3% (1.3–4.1%)). The total percentage (95% CI) explained by significant mediators combined was 20.6% (14.7–28.1%)). The corresponding number for the association between natural environment and grey matter volume was 38.4% (95% CI: 25.6–53.1%) (Fig. 2).

Similar results were seen for the association between natural environment buffered at 300 m and brain volumes (Figure S3).

3.9. Moderation analysis

The association between greenspace/natural environment and total brain and white matter volumes was stronger amongst older than younger individuals. No significant interaction was seen for other factors (Figure S4).

3.10. Sensitivity analysis

The IPWM analysis showed that both greater proximity to greenspace buffered at 1000 m (Table S9) and at 300 m (Table S10) were associated with larger volumes of total brain, grey matter, and white matter. Both greater proximity to natural environment buffered at 1000 m (Table S11) and at 300 m (Table S12) were associated with larger brain volumes.

4. Discussion

In this large cohort study, we found greater proximity to greenspace and natural environment were associated with larger volumes of total brain, grey matter, and white matter. These associations were significant

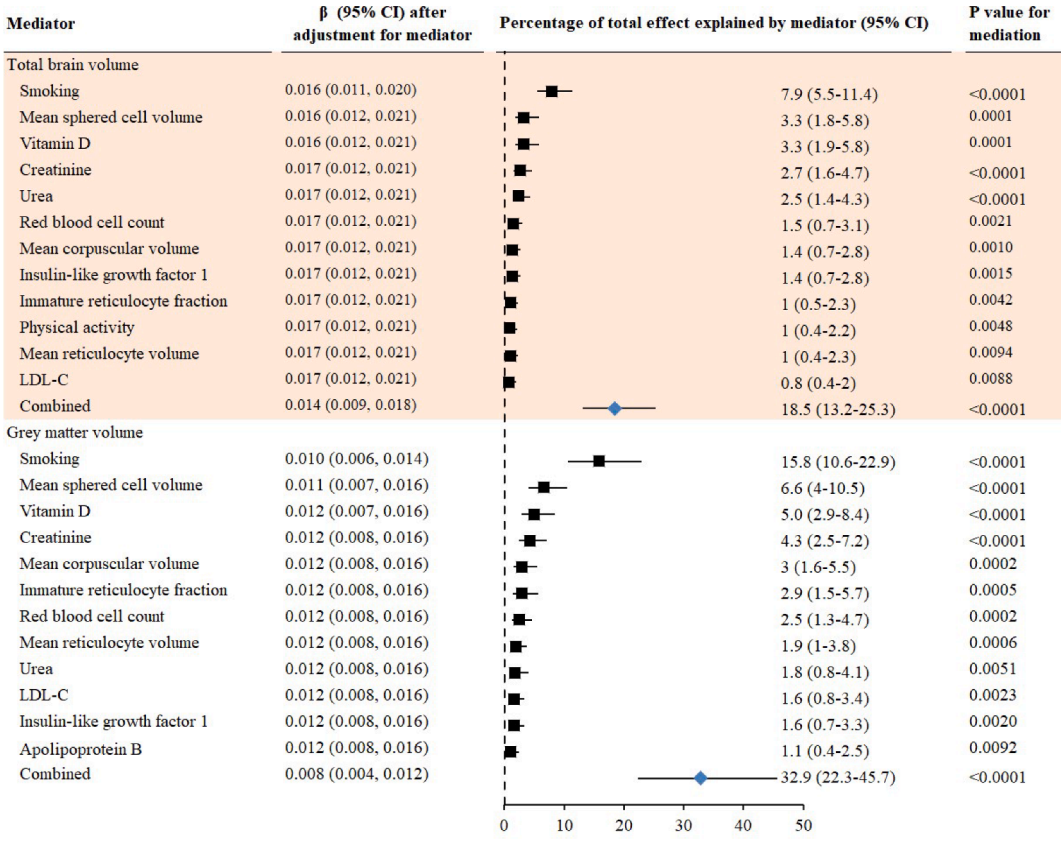

Fig. 1. Mediators for the association between greenspace buffered at 1000 m **and brain volumes** General linear regression models were used to estimate the potential mediation effects of lifestyle factors and biomarkers on the association between greenspace buffered at 1000 m and brain volumes. Mediation was established using the following criteria: (1) the mediator was significantly associated with greenspace coverage; (2) greenspace coverage was significantly associated with brain volumes; (3) the mediator was significantly associated with brain volumes; and (4) the association between greenspace coverage and brain volumes was attenuated by the mediator. The mediation effects of all significant mediators combined were also tested. Benjamin-Hochberg's procedure was used to control the false discovery rate at a 5% level for multiple comparisons. The cut-off for the raw P-value with a significant association was 0.0092. The figure only shows the results with significant mediation effects.

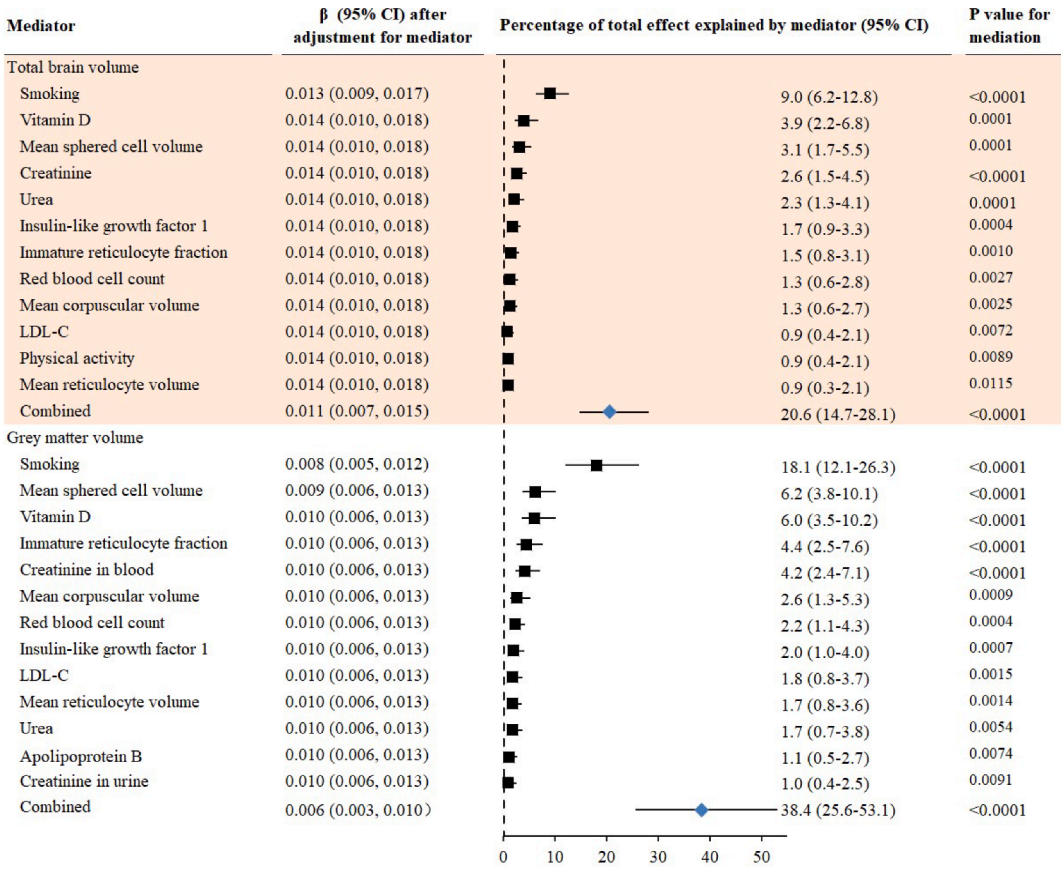

Fig. 2. Mediators for the association between natural environment buffered at 1000 m **and brain volumes** General linear regression models were used to estimate the potential mediation effects of lifestyle factors and biomarkers on the association between natural environment buffered at 1000 m and brain volumes. Mediation was established using the following criteria: (1) the mediator was significantly associated with natural environment coverage; (2) natural environment coverage was significantly associated with brain volumes; (3) the mediator was significantly associated with brain volumes; and (4) the association between natural environment coverage and brain volumes was attenuated by the mediator. The mediation effects of all significant mediators combined were also tested. Benjamin-Hochberg's procedure was used to control the false discovery rate at a 5% level for multiple comparisons. The cut-off for the raw P-value with a significant association was 0.0092. The figure only shows the results with significant mediation effects.

across different buffer sizes. The strongest mediators including smoking, MSCV, vitamin D, and creatinine in the blood combined largely mediated the association of greenspace/natural environment with grey matter, and moderately mediated the association with total brain. The association of greenspace and natural with total brain volume was stronger in older individuals (≥65 years) than in younger individuals (<65 years).

Although inconsistent findings are seen between several studies examining the association between greenspace and brain volume, (Besser et al., 2021; Min et al., 2021) our study is in line with previous research demonstrating that greater proximity to greenspace and less proximity to air pollution was associated with better physical and mental health. (Sarkar et al., 2018; Roscoe et al., 2022) Greater greenspace was associated with an increased likelihood of engaging in physical activities, (Richardson, Pearce, Mitchell & Kingham, 2013) and promotion of social interactions, (de Vries, van Dillen, Groenewegen & Spreeuwenberg, 2013) which might help improve brain health. It is possible that greenspace and natural environment reduce air pollution loads via absorption and deposition in urban areas. (APR, PS & RJ, 2016) This also explained why greater proximity to greenspace and natural environment were associated with greater brain volumes. Our findings are independent of demographic factors, socioeconomic status, and even air pollution suggesting that other underlying mechanisms need to be explored. Greater proximity to greenspace and natural environments was more beneficial for brain health amongst older individuals in our study. This might be partly attributed to the decelerated rate of brain loss in older people.

Lifestyle factors including smoking, (Cox et al., 2019) physical activity, (Palta, Sharrett & Gabriel, 2021) diet, (Ballarini, D, Brunner & Diet, 2021) alcohol consumption, (Williamson, Lewandowski & Forkert, 2018) and sleep duration (Zitser, Anatürk, & Zsoldos, 2020) have been linked to brain volumes. We found that smoking moderately mediated the association of greenspace/natural environment with total brain and grey matter volumes. Our study is consistent with a nationally representative study in England showing that individuals in the highest greenspace quartile had a 20% lower prevalence of former and current smoking, compared to those in the lowest quartile. (Martin, White, Pahl, May & Wheeler, 2020) We also found the adverse effects of current smoking on grey matter and total volumes were moderate or small. This suggests that smoking may play a role in the relationship between greenspace/natural environment and brain volumes. In our study, physical activity was another lifestyle factor that slightly mediated the association between greenspace/natural environment and total brain volume. Greater proximity to greenspace was associated with higher levels of physical activity, and physical activity might promote brain health, which indicates the potential mediation effect of physical activity. Our findings suggest increasing access to greenspace/natural environment may maximise brain health via reducing smoking prevalence and promoting physical activity.

Recent evidence has highlighted the importance of red blood cell indices, (Winchester, Powell, Lovestone & Nevado-Holgado, 2018; Beydoun, Hossain & MacIver, 2021) vitamin D, and creatinine in the

development of neurodegenerative disorders and brain atrophy. (Lee, Yoon, Kim & Youn, 2021) Although limited data are available regarding the effect of greenspace/natural environment on vitamin D status, most vitamin D in the human body is produced via skin proximity to sunlight. (Chen, Chimeh & Lu, 2007) Meanwhile, vitamin D has been shown to play a critical role in brain health. (Anjum, Jaffery, Fayyaz, Samoo & Anjum, 2018) We found individuals with greater greenspace/natural environment had higher levels of vitamin D probably because they were more likely to participate in physical activity and had greater proximity to sunlight. This explains why vitamin D is an important mediator for the association between greenspace/natural environment and brain volumes. A cross-sectional analysis of 213 participants showed that anaemia and red cell distribution width were associated with smaller brain volumes. (Beydoun et al., 2021) A Mendelian Randomization analysis demonstrated that anaemia may have a causal impact on cognition. (Winchester et al., 2018) We found that higher levels of red cell indices including MCV, MSCV, MRV, and IRF were associated with smaller total brain and grey matter volumes. Although the association between proximity to greenspace and natural environment and red cell indices has not been reported, higher levels of oxygens in greater greenspace and natural environment might increase the capability to deliver oxygen by red blood cells thus benefiting red cell function. We found that greater proximity to greenspace was associated with lower levels of MCV, MSCV, MRV, and IRF. This indicates that greater proximity to greenspace and natural environment may benefit brain health via improving red blood cell indices.

To our knowledge, this is the first large cohort study to investigate the association between greenspace and natural environment and brain volumes and the potential effects of lifestyle and biomarkers. There are several potential limitations in the study. Firstly, causal relationships cannot be established based on our findings because of the cross-sectional design. Secondly, a large proportion of the UK cohort without MRI data was excluded from the analysis. However, similar results between sensitivity analysis using IPWM and the main analyses were seen, which suggests the reliability of our findings. Thirdly, length of time at the address recorded or past addresses (used to derive greenspace and natural environment measurements) was not available in the study, which might have resulted in biases. Fourthly, MRI data at baseline were not collected in the study, so the changes in brain volumes associated with proximity to greenspace and the natural environment could not be analysed. Changes in lifestyle and environment during this period might also impact brain volumes, but these associations could not be tested in our study. Finally, the majority of participants included in the analysis had European ancestry, potentially limiting the applicability of our findings to other ethnic groups.

In conclusion, greater proximity to greenspace and natural environment are associated with better brain health especially amongst older individuals. Leading mediators including smoking, vitamin D, sphered cell volume, creatinine, and physical activity largely mediate the association between greenspace/natural environment and brain volumes. Our findings suggest urban planning and design may help promote brain health via the improvement of lifestyle and biomarkers.

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Availability of data and materials

Data are available in a public, open access repository (https://www.ukbiobank.ac.uk/). The data used in this study is available in the UK Biobank database under the application number of 88365.

CRediT authorship contribution statement

Xianwen Shang: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Conceptualization. **Wei Wang:** Writing – review & editing, Project administration, Investigation, Funding acquisition, Data curation. **Le Tian:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Danli Shi:** Writing – review & editing, Writing – original draft, Visualization, Data curation. **Yu Huang:** Writing – review & editing, Writing – original draft, Conceptualization. **Xueli Zhang:** Writing – review & editing, Writing – original draft, Visualization. **Zhuoting Zhu:** Writing – review & editing, Project administration, Data curation. **Xiayin Zhang:** Writing – review & editing, Writing – original draft. **Jiahao Liu:** Writing – review & editing, Writing – original draft, Formal analysis. **Shulin Tang:** Writing – review & editing, Writing – original draft. **Yijun Hu:** Writing – review & editing, Writing – original draft. **Zongyuan Ge:** Writing – review & editing, Writing – original draft, Formal analysis. **Honghua Yu:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition. **Mingguang He:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition.

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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2024.105546.

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