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Associations between residential environments and late-onset schizophrenia in UK Biobank: Interaction with genetic risk factor

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ABSTRACT

Background: Environment and genes both contribute to schizophrenia. However, the impact of different natural environments surrounding residential addresses on schizophrenia in urban settings remains unknown. This study aimed to investigate the association of urbanisation, measured by residential environments, with late-onset schizophrenia and explore whether genetic risk for schizophrenia modified the associations.

Methods: We examined the associations between residential environments and late-onset schizophrenia and its interaction with genetic risk factors in UK Biobank, followed from 2006 to 2010 (baseline) to Dec 2021. Residential environments, including greenspace, domestic garden, blue space, and total natural environment, were evaluated using land use coverage percentage. The polygenic risk score (PRS) of schizophrenia was derived using a Bayesian approach and adjusted it against ancestry. Cox proportional hazard regression model was used to assess the associations between per interquartile (IQR) increase of each type of residential environments and late-onset schizophrenia. Interactive effects of PRS and residential environments on late-onset schizophrenia were assessed on both additive and multiplicative scales.

Results: A total of 393,680 participants were included in the analysis, with 844 cases of late-onset schizophrenia being observed after 12.8 years of follow-up. Within 300 m buffer surrounding the residential addresses, per interquartile increase in greenspace (31.5 %) and total natural environment (34.4 %) were both associated with an 11 % (HR = 0.89, 95 % CI 0.80, 0.99) lower risk of late-onset schizophrenia. Domestic garden and blue space did not show significant protective effects on late-onset schizophrenia. A strong dose-response relationship between schizophrenia PRS and schizophrenia was found, while no additive or multiplicative interaction effects were present between residential environments and PRS on late-onset schizophrenia.

Conclusion: Residential greenspace and total natural environment may protect against late-onset schizophrenia in older people regardless of genetic risk. These findings shed light on the prevention of schizophrenia and urban planning to optimise ecosystem benefits linked to schizophrenia.

1. Introduction

Schizophrenia is a common type of psychotic disorder and affects approximately 24 million people worldwide or 1 in 300 people (World Health Organization, 2022). Schizophrenia is associated with significant distress and impairment in all areas of life, including personal, social, and occupational functioning (Charlson et al., 2018). Multifactorial risk factors may contribute to the onset and course of schizophrenia, including psychosocial, genetic, and environmental factors (Greenwood et al., 2019; Schizophrenia Working Group of the Psychiatric Genomics,

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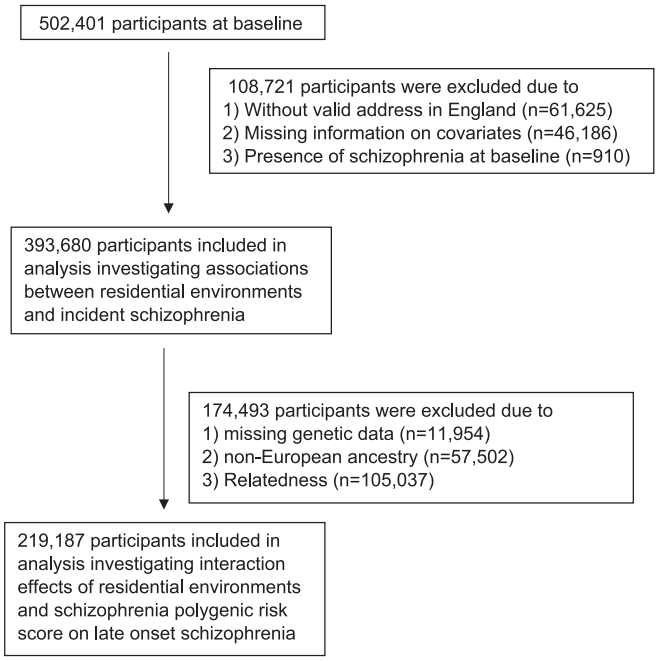

Fig. 1. Flow chart for inclusion of UK Biobank participants.

2014; van Os and Kapur, 2009; van Os et al., 2010). Although schizophrenia typically emerges in late adolescence and early adulthood, one in four schizophrenia cases have an onset of disorder after age 40 years (Cohen et al., 2015). Adults with schizophrenia have accelerated brain ageing that may contribute to age-related chronic diseases and are 2 to 3 times more likely to die prematurely than the general population (Constantinides et al., 2023; Laursen et al., 2014). However, studies on schizophrenia in middle-aged and older adults are scarce, representing only 1 % of schizophrenia literature (Cohen et al., 2015).

Human living environments are changing with a growing body of urban and shrinking areas of rural landscapes. It was estimated that 86.6 % of the population in developed regions would be resident in urban areas by the year 2050 (United Nations, 2018). Although urbanisation has brought various benefits, studies have found that urbanisation is associated with increased mental health problems such as schizophrenia and suicide (Gruebner et al., 2017; Solmi et al., 2017). Contrarily, exposure to natural environment near the residence, e.g., greenspace (vegetation-based), might be beneficial for mental health, predominantly on depression and anxiety (Geneshka et al., 2021). A few studies showed that childhood exposure to greenspace is associated with lower schizophrenia rates during adolescence (Engemann et al., 2020a; Engemann et al., 2020b), but large-scale longitudinal studies on greenspace exposure and schizophrenia in adults are scarce (Rotenberg et al., 2022). In addition, these studies considered general greenspace without taking into account different types of greenspace (e.g. public versus private), which may have specific health impacts. Domestic garden (a specific type of non-natural greenspace) constitute a significant proportion of urban areas, up to 90 % in the UK (Coisnon et al., 2019). However, there has been little empirical research investigating mental health in relation to domestic garden where human-nature interaction is limited. Blue space (water-based) is another essential natural environmental factor that is currently understudied. The health effects of blue space have recently attracted researchers' exploration, but how blue space affects mental health has yet to reach a consensus (Geneshka et al., 2021). To our knowledge, no longitudinal studies have investigated the associations between different types of natural environments surrounding residential addresses and schizophrenia in urban settings. However, such studies will shed important insights into clinical implications of schizophrenia and urban planning, especially in areas with a high prevalence of schizophrenia.

Table 1
UK Biobank participant characteristics at baseline assessment (2006–2010) (n = 393,680).

	N (%)
Age, years	
<44	40,569 (10.3)
45–54	111,997 (28.5)
55–64	167,580 (42.6)
65+	73,534 (18.7)
Sex	
Female	211,607 (53.8)
Male	182,073 (46.3)
Ethnicity	
White	374,038 (95.0)
Non-white	19,642 (5.0)
Education level	
University or college	130,651 (33.2)
A-levels or equivalent	45,041 (11.4)
GCSEs or equivalent	86,501 (22.0)
Other	131,487 (33.4)
Household income	
Less than £18,000	79,419 (20.2)
£18,000 to £30,999	91,002 (23.1)
£31,000 to £51,999	93,088 (23.7)
£52,000 or above	92,038 (23.4)
Prefer not to answer	38,133 (9.7)
Index of Deprivation	
Qn1 (least deprived)	73,262 (18.6)
Qn2	80,909 (20.6)
Qn3	82,709 (21.0)
Qn4	80,833 (20.5)
Qn5 (most deprived)	75,967 (19.3)
Body mass index	
Underweight (<18.5 kg/m^2)	1994 (0.5)
Normal (18.5 to <25 kg/m^2)	129,714 (33.0)
Overweight (25 to <30 kg/m^2)	167,984 (42.7)
Obese (30 kg/m^2 or higher)	93,988 (23.9)
Smoking status	
Never	215,561 (54.8)
Previous	138,707 (35.2)
Current	39,412 (10.0)
Alcohol drinking	
Never	15,529 (3.9)
Previous	13,214 (3.4)
Current	364,937 (92.7)
Frequency of family/friend visits	
Almost daily	44,881 (11.4)
2–4 times a week	120,967 (30.7)
About once a week	141,563 (36.0)
About once a month	53,828 (13.7)
Once every few months	26,202 (6.7)
Never or almost never	5413 (1.4)
No friends/family outside household	826 (0.2)
Stressful live events in the past 2 years	
No	217,915 (55.4)
Yes	175,765 (44.7)

Genetics is an important etiologic risk factor of schizophrenia due to its high heritability as indicated by previous genome-wide association studies (GWAS) (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Evidence has shown that genetic factor may influence the risk of psychotic syndrome by altering environmental sensitivity and gene-environment interaction studies are a more promising next step. However, previous gene-environment interaction studies on schizophrenia considered e.g., childhood adversity, cannabis use, and hearing impairment as the environmental risk factors (Guloksuz et al., 2019; van Os et al., 2022). Few large-scale psychiatric studies have collected both residential environments and genetic information (van Os et al., 2010). Investigation of the effect of the interaction between gene and residential environments on schizophrenia would contribute to our understanding of the causes of schizophrenia and provide new clues for its prevention.

Here we investigated the associations between urbanisation,

Table 2
Residential environment profile in the UK Biobank participants (n = 393,680).

Type of residential environments	Min	Max	Mean	SD	Median	IQR
Greenspace (%), buffer 300 m	0.23	99.20	35.56	23.34	29.84	17.36, 48.85
Domestic garden (%), buffer 300 m	0.02	77.37	31.39	14.68	32.16	21.06, 42.06
Blue space (%), buffer 300 m	0	97.88	0.88	2.91	0.13	0.01, 0.61
Total natural environment (%), buffer 300 m	0	100	26.85	25.49	19.64	6.25, 40.63
Greenspace (%), buffer 1000 m	4.42	99.19	45.40	21.65	42.04	27.76, 60.47
Domestic garden (%), buffer 1000 m	0.06	66.14	24.40	11.29	24.47	16.59, 32.18
Blue space (%), buffer 1000 m	0	59.44	1.25	2.49	0.51	0.19, 1.26
Total natural environment (%), buffer 1000 m	0	100	41.46	25.76	37.64	19.90, 59.79

IQR: interquartile range; SD: standard deviation.

measured by residential environments (greenspace, domestic garden, blue space, and total natural environment), and late-onset schizophrenia based on a national longitudinal cohort in England. In addition, we explored whether genetic risk for schizophrenia modified the associations between residential environments and late-onset schizophrenia.

2. Methods

2.1. Study population

We used data from UK Biobank, a national cohort which recruited ~500,000 volunteer participants between 2006 and 2010, aged 40–69 years, and followed until 31st December 2021. Details of the cohort profile have been reported elsewhere (Sudlow et al., 2015). In brief, participants completed questionnaires on lifestyle and gave biological samples (e.g., for genotyping) and physical measure assessments at baseline. They also gave consent to follow-up via record linkage. Participants with schizophrenia at baseline and missing data on exposure and covariates were excluded.

2.2. Measures

2.2.1. Residential environment profile

Residential greenspace (publicly accessible), domestic garden, and blue space were estimated for England residents based on the 2005 Generalised Land Use Database for England, linking to the 2001 Census Output Areas (COA) (Communities and Local Government The UK, 2007). The area percentages of greenspace, domestic garden, and water space were calculated for each COA, as a proportion of all 9 land use types including greenspace, domestic garden, blue space, domestic buildings, nondomestic buildings, roads, paths, railways, and others (largely hard standing). Participant residential addresses were buffered at 300 m and 1000 m polygon, allocated an area-weighed mean of each land use percentage coverage. Participants who lived outside of England were excluded from this linkage. Total natural environment was estimated based on 2007 Land Cover Map data of the Centre for Ecology and Hydrology including greenspace and blue space (Morton et al., 2011). Domestic garden was classified as built environment based on Land Cover Map data. The percentage coverage of "natural environment" at 300 m and 1000 m buffers surrounding participants' residential addresses was calculated.

2.2.2. Polygenic risk score (PRS)

Genotyping data were available for 488,000 participants and were imputed using the Haplotype Reference Consortium (HRC) and UK10K haplotype resource to identify ~96 million variants in total. Quality control (QC) of genotyping data was performed by Thompson et al. (2022). In brief, participants with >2 % variant missing, genetic sex mismatching self-reported sex, and heterozygosity outliers were excluded. For related participants with up to 3rd degree relatedness (kinship coefficients >0.044), only one member from each group of

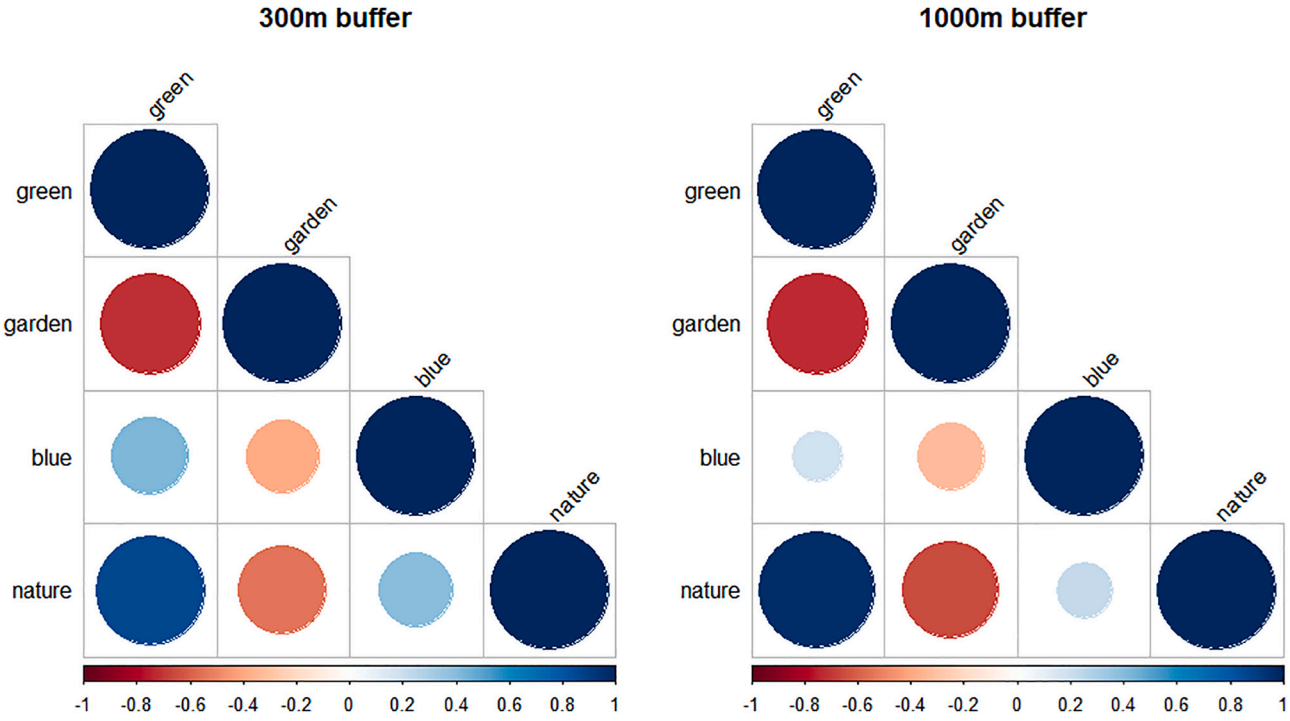

Fig. 2. Spearman correlation coefficients between residential environment estimates at 300 m and 1000 m buffers in the UK Biobank participants (n = 393,680).

Table 3
Associations of greenspace, domestic garden, blue space, and total natural environment within 300 m surrounding residential addresses with late-onset schizophrenia in the UK Biobank participants (n = 393,680).

		Model 1	Model 2	Model 3
		HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
Greenspace	1st quartile	1	1	1
	2nd quartile	1.01 (0.85, 1.21)	0.95 (0.79, 1.13)	0.95 (0.80, 1.14)
	3rd quartile	0.85 (0.70, 1.02)	0.83 (0.69, 1.00)	0.84 (0.70, 1.02)
	4th quartile	0.69 (0.56, 0.84)	0.79 (0.64, 0.97)	0.81 (0.66, 0.99)
	Per IQR increase	0.81 (0.73, 0.89)	0.88 (0.79, 0.98)	0.89 (0.80, 0.99)
Domestic garden	1st quartile	1	1	1
	2nd quartile	0.77 (0.64, 0.93)	0.76 (0.63, 0.92)	0.77 (0.64, 0.93)
	3rd quartile	0.81 (0.67, 0.97)	0.85 (0.70, 1.02)	0.86 (0.71, 1.03)
	4th quartile	0.74 (0.62, 0.90)	0.89 (0.73, 1.08)	0.90 (0.74, 1.09)
	Per IQR increase	0.88 (0.80, 0.97)	0.96 (0.86, 1.06)	0.96 (0.86, 1.06)
Blue space	1st quartile	1	1	1
	2nd quartile	0.90 (0.75, 1.09)	0.97 (0.81, 1.18)	0.98 (0.81, 1.19)
	3rd quartile	0.87 (0.72, 1.05)	0.97 (0.80, 1.17)	0.98 (0.81, 1.19)
	4th quartile	0.99 (0.82, 1.19)	1.09 (0.90, 1.31)	1.09 (0.91, 1.32)
	Per IQR increase	1.00 (0.99, 1.01)	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)
Total natural environment	1st quartile	1	1	1
	2nd quartile	0.86 (0.72, 1.03)	0.89 (0.74, 1.07)	0.90 (0.75, 1.08)
	3rd quartile	0.84 (0.70, 1.01)	0.91 (0.75, 1.09)	0.92 (0.77, 1.11)
	4th quartile	0.61 (0.50, 0.75)	0.74 (0.60, 0.91)	0.77 (0.62, 0.94)
	Per IQR increase	0.79 (0.71, 0.87)	0.88 (0.79, 0.98)	0.89 (0.80, 0.99)

HR: hazard ratio; IQR: interquartile range.
Late-onset schizophrenia: n = 844.
Model 1: adjusted for age, sex, and ethnicity.
Model 2: additionally adjusted for education level, household income, index of deprivation, and length of time at current address.
Model 3: additionally adjusted for body mass index, smoking, alcohol drinking, frequency of family/friend visits, and stressful life events.

related participants was included. SNPs with a call rate < 95 %, a minor allele frequency < 0.01, deviation from Hardy-Weinberg equilibrium ($P < 10^{-6}$), or an imputation accuracy score < 0.1 were also dropped. Principal components analysis was performed to measure population structure given the diversity in ancestral origins of UK Biobank participants (Bycroft et al., 2017). Polygenetic risk score of schizophrenia (UKB data-field ID 26275) was derived using a Bayesian approach based on the meta-analysis of three GWAS summary statistics (total N cases/controls 97,456/334,331) (Thompson et al., 2022). Then the score was standardised against ancestry, so the distribution of standardised PRS was approximately zero mean and unit variance across all ancestries (Khera et al., 2019). We only included genetically unrelated participants of European ancestry in our analyses using PRS. Relatedness was determined based on the information on genetic kinship to other participants (UKB data-field ID 22021). Genetically unrelated participants are those classified as "no kinship found".

2.2.3. Late-onset schizophrenia

We used the first recording of diagnosis of a schizophrenia spectrum disorder between ages 40 and 69 years (including schizophrenia, schizotypal and delusional disorders) coded by the International Classification of Disease-10 (ICD-10) F20-F29 as the outcome. The first recording of diagnosis was extracted from the death register, primary care (i.e., recorded by healthcare professionals working at general practices), hospital admissions, and self-report (i.e., the condition diagnosed and coded by a trained nurse). The first recording of diagnosis included the earliest date and source of the extraction (death register, primary care, hospital inpatient, and self-report). We excluded participants with a schizophrenia spectrum disorder identified from any of these sources prior to the time when they attended the baseline assessment (n = 910). The remaining participants were followed up via record linkage at 40–69 years old from the baseline assessment date up until the date of death, the date of diagnosis of a schizophrenia spectrum disorder by general practitioners, the date of the hospital inpatient admission, the earliest date of diagnosis of a schizophrenia spectrum disorder reported by the participants, or 31st Dec 2021, whichever happened first.

2.2.4. Covariates

Potential confounders included socio-demographic factors (age, sex, ethnicity, highest education level, annual household income before tax, and length of time at the current address), body mass index (BMI), smoking and alcohol drinking, frequency of family/friend visits, and stressful life events (defined as any event of illness, injury, bereavement, and stress in the past 2 years), collected at baseline assessment. The length of time at the current address indicated the years participants had lived at their address prior to baseline. We also included the Index of Multiple Deprivation (IMD) 2010 to represent area-level deprivation in small areas in England (Lower-layer Super Output Areas), derived from residential addresses at baseline. IMD is a weighted average score of seven domains of deprivation, including income, employment, education, health, crime, barriers to housing and services, and living environment.

2.3. Statistical analysis

Cox proportional hazard models were used to assess the associations between per interquartile (IQR) increase of each type of residential environments (greenspace, domestic garden, blue space, total natural environment) and late-onset schizophrenia. Models were incrementally adjusted: Model 1 adjusted for demographic characteristics including age, sex (male/female), and ethnicity (white/non-white). Model 2 additionally adjusted for individual- and area-level socioeconomic status including education level (University or college, A-level, GSCE, other), household income (less than £18,000, £18,000 to £30,999, £31,000 to £51,999, £52,000 or above), IMD quintiles, and length of time in the current address in quintiles. Model 3 additionally adjusted for lifestyle and psychosocial factors including BMI [normal (18.5 to <25 kg/m^2), underweight (<18.5 kg/m^2), overweight (25 to <30 kg/m^2), and obese (30 kg/m^2 or higher)], smoking (never, previous, current), alcohol drinking (never, previous, current), frequency of family/friend visits, and stressful life events in the past 2 years (yes/no). We also examined the association between schizophrenia PRS (in decile categories) and the presence of schizophrenia at the end of follow-up (31st Dec 2021) using logistic regression, controlling for age, sex, and the top 10 genetic principal components (PC) to adjust for confounding by population structure.

We assessed the interactive effects of PRS and residential environments on late-onset schizophrenia on both additive and multiplicative scales. Residential environment variables with quartile categories and a binary PRS variable with a median split were used when assessing additive and multiplicative interactions. We calculated the relative excess risk due to interaction (RERI) to estimate the additive interaction (Knol et al., 2011). A RERI of <0 indicates negative additive interaction (i.e., combined excess risk < sum of individual excess risks). A RERI of 0 indicates no additive interaction (i.e., combined excess risk = sum of individual excess risks). A RERI of >0 indicates positive additive interaction (i.e., combined excess risk > sum of individual excess risks).

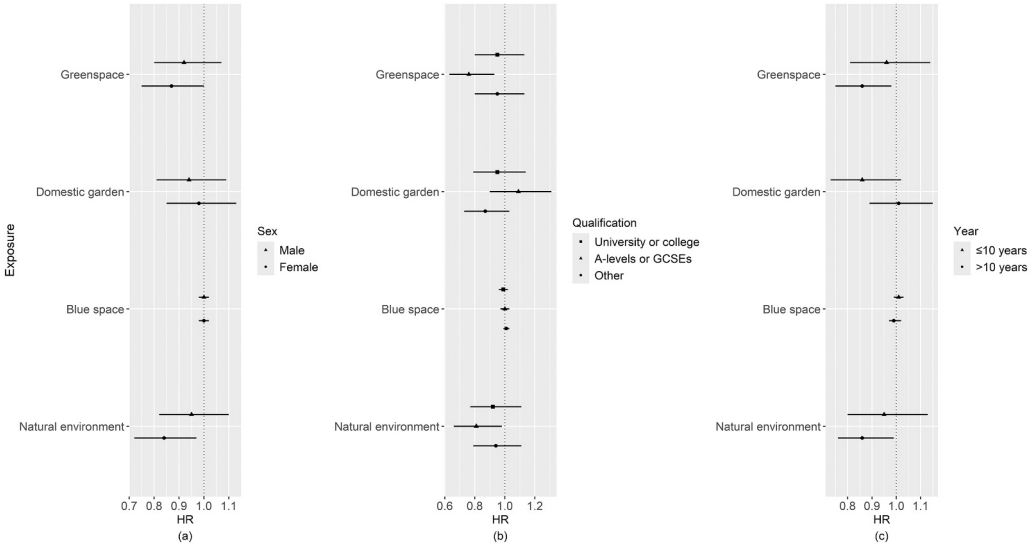

Fig. 3. Associations of an interquartile range increase in greenspace, domestic garden, blue space, and total natural environment within 300 m surrounding residential addresses with late-onset schizophrenia, stratified by sex (a), education level (b), and length of time in the current address (c) (n = 393,680). HR: hazard ratio.

In this context, positive additive interaction suggests that the benefits of residential natural environment are less evident in participants with a high genetic risk of schizophrenia. We also assessed the interaction effect on a multiplicative scale by the significance of the interaction term. Covariates included age, sex, ethnicity, education level, income, IMD quintiles, length of time in the current address in quintiles, BMI, and the top 10 genetic PCs. We also investigated whether the associations between residential environments and schizophrenia varied by sex, education level, and length of time in the current address by assessing the significance of interaction terms. Stratified analyses by these factors were also conducted.

We conducted several sensitivity analyses to assess the robustness of our findings. First, we conducted analyses using alternative distance buffer sizes (1000 m) for each type of residential environments. Second, we excluded participants who developed schizophrenia within the first year of follow-up to minimise potential reverse causation. Third, we adjusted for environmental pollutants, including air pollution [annual concentration of Particulate Matter with a diameter of <2.5 μm ($PM_{2.5}$)] and traffic noise (weighted road-traffic noise level over the 24 h period in 2009) in addition to the confounders adjusted in Model 3. Land-use regression (LUR) model was used to estimate the exposures of $PM_{2.5}$ based on participants' residential addresses at baseline (Eeftens et al., 2012). Noise sound pressure level on all roads within 500 m of participants' residential addresses was estimated using the CNOSSOS-EU noise model (Morley et al., 2015). We did not adjust for these environmental pollutants in our main models as we considered these to be on the causal pathways (i.e., mediators). All statistical analyses were conducted with STATA 16.0 and R version 4.2.2.

3. Results

A total of 393,680 participants were included in the present analysis. The detailed flow diagram for the inclusion of participants is shown in Fig. 1. Table 1 shows that more than half of the participants were female (53.8 %) and were primarily white (95.0 %). 33.2 % of participants had a university or college education, and 23.4 % had a household income higher than £52,000. Two-thirds of participants (66.6 %) were overweight or obese, and 10.1 % were current smokers. Most participants (78.1 %) visited their family and friends at least once per week. 44.7 % of participants had experienced stressful life events in the past 2 years.

Table 2 provides summary statistics for residential environment profile at baseline. Greenspace, blue space, and total natural environment were positively correlated, with a stronger correlation observed between greenspace and total natural environment than that between greenspace and blue space at both 300 m and 1000 m buffers. However, domestic garden was negatively correlated with greenspace, blue space, and total natural environment coverage at both 300 m and 1000 m buffers (Fig. 2).

After ~13 (mean: 12.8, SD: 1.0) years of follow-up, 844 participants developed schizophrenia. Table 3 shows that in the fully adjusted model (Model 3), compared to participants with greenspace coverage within 300 m surrounding residential addresses in the 1st quartile, those with greenspace coverage in the 4th quartile had ~20 % lower risks of late-onset schizophrenia (HR: 0.81, 95 % CI 0.66, 0.99). We also found that total natural environment within 300 m in the 4th quartile was associated with a lower risk of late-onset schizophrenia (HR = 0.77, 95 % CI 0.62, 0.94). An interquartile increase in greenspace at 300 m buffer (31.5 %) was associated with an 11 % lower risk of late-onset schizophrenia (HR = 0.89, 95 % CI 0.80, 0.99). An interquartile increase in total natural environment at 300 m buffer (34.4 %) was also associated with an 11 % lower risk of late-onset schizophrenia (HR = 0.89, 95 % CI 0.80, 0.99). The associations of domestic garden and blue space with late-onset schizophrenia were not marked. The associations between different types of residential environments and schizophrenia did not vary by sex, education level, or length of time in the current address (all *P* values for interaction >0.1), although stratified analyses (Fig. 3) showed that the associations of greenspace and total natural environment with late-onset schizophrenia were slightly stronger in females, participants with education level of A-levels/GCSEs, and non-movers (i.e., >10 years at current address prior to baseline).

Appendix Fig. A1 shows the distribution of the PRS for schizophrenia in participants with schizophrenia and controls. Appendix Fig. A2 shows a strong dose-response relationship between PRS decile and schizophrenia. Compared to those in the lowest decile, individuals in the highest PRS deciles had 583 % higher odds of schizophrenia after adjusting for age, sex, and the top 10 genetic PCs (odds ratio = 6.83, 95 % CI: 4.98, 9.39). The PRS explained a 2.9 % risk of schizophrenia (The increase in Nagelkerke's pseudo-R^2 when adding PRS to the model with covariates only was 0.029).

Tables 4 and 5 show the results of gene-environment interaction analysis between schizophrenia PRS and residential environments on late-onset schizophrenia. Given that neither the RERI nor *P* value for interaction was significant, no additive or multiplicative interaction effects were present between residential environments and PRS on late-

Table 4
Additive interaction effects of greenspace, domestic garden, blue space, and natural environment within 300 m surrounding residential addresses and polygenic risk score of schizophrenia on late-onset schizophrenia in unrelated participants of European ancestry (n = 219,187).

		Polygenic risk score		RERI
		Low	High	
		HR (95 % CI)	HR (95 % CI)	
Greenspace	4th quartile	1	2.98 (1.87, 4.73)	
(300 m buffer)	3rd quartile	1.31 (0.78, 2.21)	2.56 (1.61, 4.09)	−0.72 (−1.95, 0.51)
	2nd quartile	1.44 (0.86, 2.41)	2.93 (1.85, 4.64)	−0.48 (−1.69, 0.73)
	1st quartile	1.63 (0.97, 2.72)	3.15 (1.98, 5.00)	−0.45 (−1.72, 0.81)
Domestic garden	4th quartile	1	2.80 (1.79, 4.38)	
(300 m buffer)	3rd quartile	1.32 (0.80, 2.18)	2.08 (1.31, 3.30)	−1.04 (−2.25, 0.18)
	2nd quartile	1.04 (0.62, 1.76)	2.32 (1.48, 3.65)	−0.52 (−1.60, 0.57)
	1st quartile	1.28 (0.77, 2.11)	2.86 (1.84, 4.44)	−0.22 (−1.29, 0.86)
Blue space	4th quartile	1	2.08 (1.40, 3.10)	
(300 m buffer)	3rd quartile	0.71 (0.43, 1.19)	2.19 (1.47, 3.26)	0.40 (−0.36, 1.15)
	2nd quartile	1.10 (0.70, 1.74)	1.73 (1.14, 2.63)	−0.45 (−1.32, 0.42)
	1st quartile	0.94 (0.59, 1.52)	2.10 (1.41, 3.13)	0.07 (−0.71, 0.86)
Total natural environment	4th quartile	1	2.43 (1.54, 3.84)	
(300 m buffer)	3rd quartile	1.19 (0.71, 2.00)	2.63 (1.68, 4.12)	0.01 (−1.01, 1.02)
	2nd quartile	1.26 (0.76, 2.09)	2.79 (1.79, 4.34)	0.10 (−0.91, 1.10)
	1st quartile	1.45 (0.88, 2.39)	2.72 (1.74, 4.27)	−0.16 (−1.23, 0.91)

HR: hazard ratio; RERI: relative excess risk due to interaction.
Adjusted for age, sex, education level, household income, index of deprivation, length of time at current address, body mass index, smoking, alcohol drinking, frequency of family/friend visits, stressful life events, and the first 10 genetic principal components.
We used the 4th quartile of each residential environment variable as the reference group to calculate RERIs for the other three quartile groups.

Table 5
Multiplicative interaction effects of greenspace, domestic garden, blue space, and natural environment within 300 m surrounding residential addresses and polygenic risk score of schizophrenia on late-onset schizophrenia in unrelated participants of European ancestry (n = 219,187).

		Main effects	Interaction effects	P value for
		HR (95 % CI)	HR (95 % CI)	interaction
Greenspace	4th quartile	1	1	
	3rd quartile	1.31 (0.78, 2.21)	0.66 (0.35, 1.22)	
	2nd quartile	1.44 (0.86, 2.41)	0.68 (0.37, 1.25)	
	1st quartile	1.63 (0.97, 2.72)	0.65 (0.35, 1.19)	0.47
Domestic garden	4th quartile	1	1	
	3rd quartile	1.32 (0.80, 2.18)	0.56 (0.31, 1.03)	
	2nd quartile	1.04 (0.62, 1.76)	0.80 (0.43, 1.47)	
	1st quartile	1.28 (0.77, 2.11)	0.80 (0.45, 1.44)	0.31
Blue space	4th quartile	1	1	
	3rd quartile	0.71 (0.43, 1.19)	1.48 (0.81, 2.70)	
	2nd quartile	1.10 (0.70, 1.74)	0.76 (0.43, 1.34)	
	1st quartile	0.94 (0.59, 1.52)	1.07 (0.61, 1.88)	0.18
Total natural environment	4th quartile	1	1	
	3rd quartile	1.19 (0.71, 2.00)	0.91 (0.49, 1.68)	
	2nd quartile	1.26 (0.76, 2.09)	0.91 (0.50, 1.67)	
	1st quartile	1.45 (0.88, 2.39)	0.77 (0.42, 1.41)	0.86

Adjusted for age, sex, education level, household income, index of deprivation, length of time at current address, body mass index, smoking, alcohol drinking, frequency of family/friend visits, stressful life events, and the first 10 genetic principal components.

onset schizophrenia.

Sensitivity analyses showed that greenspace and total natural environment within 1000 m surrounding residential addresses were associated with lower late-onset schizophrenia (Appendix Table A1). We also found that greenspace and total natural environment within 1000 m were associated with a lower risk of late-onset schizophrenia. Genetic risk of schizophrenia did not additively or multiplicatively modify the associations (Appendix Tables A2 and A3). After excluding participants who developed schizophrenia within 1 year of follow-up (n = 42), the associations between residential environments and late-onset schizophrenia remained similar (Appendix Table A4). The associations between greenspace and total natural environment within 300 m and 1000 m and schizophrenia were not evident after adjusting for exposure to $PM_{2.5}$ but remained significant after adjusting for traffic noise (Appendix Table A5).

4. Discussion

Our study is the first to investigate different types of residential environments in relation to late-onset schizophrenia and its interaction with genetic risk factor. We found that more greenspace coverage surrounding the residence, rather than blue space and domestic garden, was associated with a lower risk of late-onset schizophrenia. Total natural environment coverage was also associated with a lower risk of schizophrenia. The associations between residential environments and schizophrenia did not vary by genetic risk factor.

Our findings are in line with previous longitudinal studies which also showed the association between more greenspace surrounding residence and a lower risk of schizophrenia (Chang et al., 2019; Engemann et al., 2020b; Rotenberg et al., 2022). Our study considered a wider range of covariates including air pollution, length of time in participants' residential addresses, and social deprivation status, which were seldomly discussed previously (Geneshka et al., 2021). To our best knowledge, this is the first study taking into account genetic risk using an adult population-based cohort study with over 10 years of follow-up. One similar study explored the relationship between childhood green space exposure and gene-environment interaction effect on adolescent schizophrenia (Engemann et al., 2020a). Consistent with this study, we observed PRS of schizophrenia significantly explained the risk of schizophrenia, however, neither our study nor the previous one found significant interactions between genetic propensity of schizophrenia and any type of natural environment, which indicated greenspace may be a protective factor on schizophrenia across populations with varied genetic risk. Health effects of blue space exposure have not been investigated as popular as green space. A few cross-sectional studies through questionnaires are emerging while limited longitudinal studies have investigated the relation between blue space exposure and mental health

(Wang et al., 2022). Some small-scale intervention studies provided preliminary clues of such protective effects (most n < 100) (Britton et al., 2020). We didn't find an obvious beneficial effect of exposure to blue space on the risk of schizophrenia, but total natural environment, which represents the combination of green and blue space, is beneficial for schizophrenia.

We found protective associations between greenspace and the total natural environment. There are several plausible explanations. Air pollution exposure is an important risk factor for schizophrenia as it could trigger oxidative and nitrosative stress as well as neuroinflammation (Attademo et al., 2017; Block and Calderon-Garciduenas, 2009), which play essential roles in the development of schizophrenia (Boll et al., 2017; Najjar and Pearlman, 2015). We found that the associations of greenspace and total natural environment with schizophrenia were not marked after adjusting for $PM_{2.5}$, indicating that greenspace and natural environment may protect against schizophrenia via reduced air pollution level. However, traffic noise pollution played a limited role in explaining the associations between residential environments and schizophrenia. In addition, it is also possible that exposure to greenspaces and natural environments might protect against schizophrenia via psychological restoration and more physical activity (Engemann et al., 2020b).

Notably, we did not find a dose-response relationship between domestic garden and risk for late-onset schizophrenia, possibly because domestic garden is highly prevalent in the UK with 88 % of households having a garden. As domestic garden is a type of non-natural space as built environment, areas with high domestic garden cover in England normally have high coverage of built environment so publicly accessible greenspace or natural environment is limited. This is also confirmed by the strong negative correlations between domestic garden and other types of natural environments observed in our study. Additionally, domestic gardens have private attributes and are unlikely to have health effects on others. We did not find an association between schizophrenia and blue space within either 300 m or 1000 m surrounding residence, suggesting that access to blue space may have limited benefits on schizophrenia. It is also possible that the skewed distribution in blue space estimates and tiny variation in the vast majority of participants (i.e., >82.5 % of participants had <1 % blue space cover at 300 buffer) limit the power to detect associations.

We found that schizophrenia PRS was associated with schizophrenia in a monotonic manner after controlling for age, sex, and population structure, although it only captured a small proportion of schizophrenia risk. It has been indicated that genetic factor may influence schizophrenia risk by affecting individuals' susceptibility to environmental exposures, but gene-environment interaction research built on available genetic and environmental data and phenotypic assessment in the same sample is currently scarce and strongly recommended (van Os et al., 2010). However, we found no evidence of an additive or multiplicative gene-environment interaction, suggesting that genes and natural environment may affect schizophrenia via different biological mechanisms.

The large-scale UK Biobank dataset with detailed genotyping, environmental exposures, and phenotyping data provides a unique opportunity to disentangle the associations between different types of natural environments surrounding residence and schizophrenia risk as well as their interaction with genetic risk. However, this study has some limitations. First, UK Biobank participants are highly selected individuals with relatively high socioeconomic status, residential addresses near assessment centres (so individuals living in rural areas are underrepresented), and are predominantly white. Such selection bias might introduce spurious associations and limit the generalisability of the findings. Second, information on participants' residential addresses is available at baseline only. Although we adjusted for the length of time at their current address prior to baseline, we could not account for the change in residential addresses post baseline, which may influence cumulative exposure. However, the proportion of participants who relocated was found to be low (~2 %) in follow-up surveys, suggesting that relocation had little influence on our findings. In addition, land use characteristics in urban areas of England is relatively stable over time, so residential environments at baseline could be a good proxy of long-term exposure. Third, information on actual usage of natural environments is not available, which might generate more health benefits beyond immediate accessibility. We believe our findings may inform future studies to measure environmental utilisation comprehensively. Fourth, we were unable to distinguish different types of greenspace, which may have different biological effects on health (Li, 2010; Maes et al., 2021). Fifth, we could not rule out residual confounding (e.g., trauma, cumulative cannabis use). Sixth, the diagnosis of schizophrenia was based on ICD codes without rigorous clinical interviews, which might lead to misdiagnosis. However, rigorous clinical interviews are not always feasible in large-scale epidemiological studies, and the ICD-10 diagnosis of schizophrenia has demonstrated validation by showing very high agreement with the DSM-IV diagnosis (Jakobsen et al., 2005). One of the sources to identify schizophrenia was the death register, where the first occurrence date might not be valid. However, the proportion of cases identified from the death register was very small (3/844, 0.4 %). Thus, the potential overestimation of the protective effect of natural environments on schizophrenia due to incorrect first occurrence date is minimal. Seventh, this study is subject to potential reverse causation although we excluded participants who developed schizophrenia within the first year of follow-up. It is possible that an earlier diagnosis of schizophrenia is not identified. People with schizophrenia or prodromal symptoms more often move towards urban areas (Pedersen, 2015). High schizophrenia PRS also predispose individuals to live in urban environments (Maxwell et al., 2021).

Our study has important implications for disease prevention and urban planning. The associations of greenspace and total natural environment with lower late-onset schizophrenia indicate that accessing these areas may protect against late-onset schizophrenia, regardless of genetic predisposition of schizophrenia. The differential associations between different types of residential environments with schizophrenia could inform urban planning decisions to balance natural and built environments as well as different types of natural environments, to optimise ecosystem benefits linked to schizophrenia. Future research should collect information on green and blue space surrounding workplaces to enable a more comprehensive measure of individual exposure to natural environments. In addition, more nuanced estimates of greenspaces (e.g., woodland and grassland) and time spent in greenspace should be investigated in the future to understand better the biological mechanisms linking nature and health.

5. Conclusions

Our study found that exposure to greenspace and total natural environment surrounding the residence was associated with a lower risk of late-onset schizophrenia. No associations were observed between blue space or domestic garden and schizophrenia. Green and nature spaces potentially protect against late-onset schizophrenia regardless of genetic risk in this population. These findings contribute to our understanding of natural environment as an important protective factor for schizophrenia and suggest that not every type of natural environments may contribute equally, which has important implications for schizophrenia prevention and policy implications for urban planning.

Ethics

The study was approved by the North-West Multi-Centre Research Ethics Committee (Reference 16/NW/0274).

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CRediT authorship contribution statement

Chen Shen: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Xinning Tong:** Writing – original draft, Visualization, Project administration. **Jinjun Ran:** Writing – review & editing, Validation. **Shengzhi Sun:** Writing – review & editing, Validation. **Qian Yang:** Methodology, Investigation. **Huiyong Shen:** Project administration, Funding acquisition. **Xiaoxin I. Yao:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2024.06.008.

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