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Green space, genetic susceptibility, and risk of osteoporosis:a cohort study from the UK Biobank

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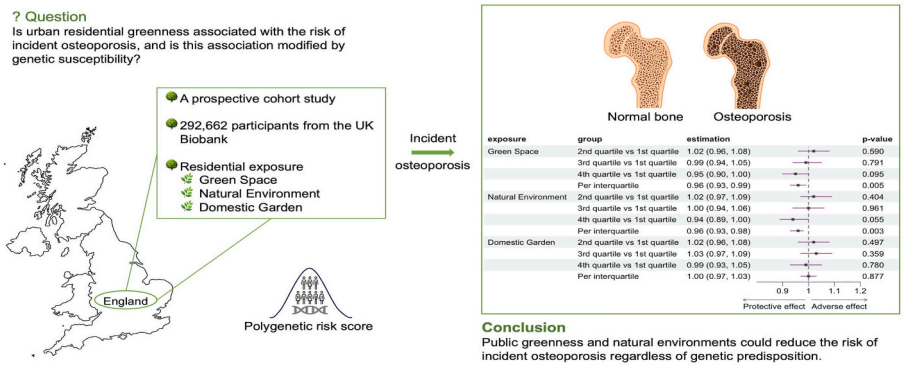
HIGHLIGHTS

- Residential greenness and natural space were related to lower incident osteoporosis.
- Such protective associations were not found for domestic gardens.
- Gene did not modify the associations of residential environments with osteoporosis.
- Our results show important implications for urban planning to prevent osteoporosis.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective: This study aimed to investigate the effect of residential exposure to green space on the incident osteoporosis and further explore the modification effect of genetic susceptibility.
Methods: Participants from the UK Biobank were followed from 2006 to 2010 (baseline) to December 31st, 2022. Using land use coverage, we evaluated exposure to residential surrounding green space, natural environment, and domestic gardens. We used the Cox regression to examine the association between the residential environment and incident osteoporosis. The interactive effects between polygenic risk score (PRS) of osteoporosis and residential environments on incident osteoporosis were investigated.

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Results: This study included 292,662 participants. Over a median follow-up period of 13.65 years, we documented 9177 incidents of osteoporosis. Per interquartile (IQR) increase in greenness and natural environment at a 300 m buffer was associated with a 4% lower risk of incident osteoporosis [HR = 0.96 (95% CI: 0.93, 0.99)] and [HR = 0.96 (95% CI: 0.93, 0.98)], respectively. We did not identify any interactive effects between genetic risk and residential environment on incident osteoporosis.
Conclusions: This study found that public greenness and natural environments could reduce the risk of incident osteoporosis regardless of genetic predisposition. Developing sustainable and publicly accessible natural environments might benefit populations' bone health.

1. Introduction

Osteoporosis is a common chronic disease characterised by systemic low skeletal mass, microarchitectural deterioration, and increased bone fragility, resulting in a high risk of fracture (Compston et al., 2019). As of 2021, the estimated prevalence of osteoporosis was 19.7% among the general population older than 50 globally (Xiao et al., 2022). High illness burdens were brought on by osteoporosis for individuals and society. The main adverse consequence of osteoporosis is fracture, which increases mortality and accounts for 1% of non-communicable disease-related impairment globally (Cummings and Melton, 2002; Johnell and Kanis, 2006). Therefore, managing osteoporosis has been elevated to a global public health priority (Compston et al., 2019; Khosla and Hofbauer, 2017; Chen et al., 2024).

Recent studies have shown that green space in the residential environment has health protection effects, including better physical functioning, lower body mass index, lower risk of cardiovascular disease, and lower risk of mortality (de et al., 2019; Ji et al., 2019; Klompmaker et al., 2018; Yuan et al., 2021). Residential natural environments may help reduce systematic inflammation or oxidative stress, which is thought to be beneficial in reducing the risk of osteoporosis (Markevych et al., 2017; McLean, 2009; Kimball et al., 2021). Expanding urbanisation has changed human living environments with a shrinking chance of exposure to natural areas (Dzhambov et al., 2020; Lin et al., 2021). Some cross-sectional studies with limited sample sizes showed that people living in rural areas expressed higher bone mineral density than those living in urban areas (Pongchaiyakul et al., 2005; Gu et al., 2007; Specker et al., 2004). Other studies that investigated women found no such association or found that living in rural areas could be a risk factor for osteoporosis (Wang et al., 2020; Rosengren et al., 2010). Domestic gardens, another composition compromised of residential environment, were identified as a specific type of non-natural green space belonging to one part of the building environment that resulted from urbanisation (Morton et al., 2023; Wheeler, 2023). Investigating the associations between different types of residential environments (e.g., greenness, natural environments, and domestic gardens) and osteoporosis in urban settings will shed important insights into osteoporosis prevention. Only three studies have investigated the association between green space and bone health, with inconsistent findings, and all focused on the Chinese population (Lin et al., 2021; Jiang et al., 2022; Zhu et al., 2023).

For diseases affected by genetic and environmental factors, environmental risk factors may trigger the development of diseases in people with genes predisposing them to certain diseases (Yu et al., 2023; Cui et al., 2023). For example, gene-environment interactions have been discussed in type 2 diabetes, asthma, Alzheimer's disease, and Parkinson's disease (Franks et al., 2013; Gref et al., 2017; Dunn et al., 2019). Interaction effects have been shown between genes and air pollution on idiopathic pulmonary fibrosis and osteoporosis (Yu et al., 2023; Cui et al., 2023). It is hypothesised that interactions between genetic and environmental risk factors raise disease risk in a synergistic manner (Franks et al., 2013). Understanding the interactions between genetic and environmental risk factors may provide a better understanding of mechanisms for osteoporosis susceptibility and provide evidence for osteoporosis prevention strategies. However, to the best of our knowledge, the interaction effects between genetic predisposition and the residential environment on osteoporosis have not been investigated yet.

Here, we aimed to investigate the effects of residential exposure to green space, natural environment, and domestic gardens on the incident osteoporosis using the UK Biobank, a large-scale prospective population cohort. In addition, we aimed to explore whether the genetic risk of osteoporosis modified the associations between the residential environment and osteoporosis.

2. Method

2.1. Study participants and data source

The data we used for this study is from a national cohort, UK Biobank. Briefly, this cohort comprised over 500,000 participants in the UK who were 40–69 years old when first recruited in the cohort from 2006 to 2010. Comprehensive data regarding phenotypic information were provided through questionnaires, physical assessments, and biological sampling. UK Biobank also collected genotypic information and various longitudinal health outcomes with multi-sources data linkage. Participants with available information on the residential environment, covariates, and bone health status were included in the current study, and those with osteoporosis at baseline were excluded.

2.2. Exposure assessment

Environmental exposure assessed in this study includes percentage coverage of the natural environment, green spaces, and domestic gardens. Green space and domestic garden coverage were calculated using land use data from the 2005 Generalized Land Use Database (GLUD) for England at the 2001 Census Output Areas (COA) level. Natural environment coverage was estimated according to the 2007 Land Cover Map data of the Centre for Ecology and Hydrology (Morton et al., 2023). The percentage of each environmental type was calculated as a proportion of all land-use types buffered at 300 m surrounding the participants' residential addresses. 300 m was an accessible walking distance surrounding one's home in 5 min (Annerstedt van den Bosch et al., 2016; Yang et al., 2023). Additionally, environmental exposures at 1000 m buffers were investigated in the sensitivity analyses.

2.3. Outcomes and covariates

Participants were followed from the first date of attending the assessment centre until the first occurrence of osteoporosis, death, loss of follow-up, or data observation end (Dec 31, 2022), whichever is the earliest. Osteoporosis was identified by the International Classification of Disease-10 (ICD-10): M80-M82. The first occurrence of osteoporosis was obtained from the multi-sources linked health records, including death register, primary care, hospital admissions, and self-reports.

Potential covariates included socio-demographic factors (age, sex, ethnicity, the highest educational qualification, annual household income before tax, and the length of time living in current address) and lifestyle factors [body mass index (BMI), smoking status, alcohol status,

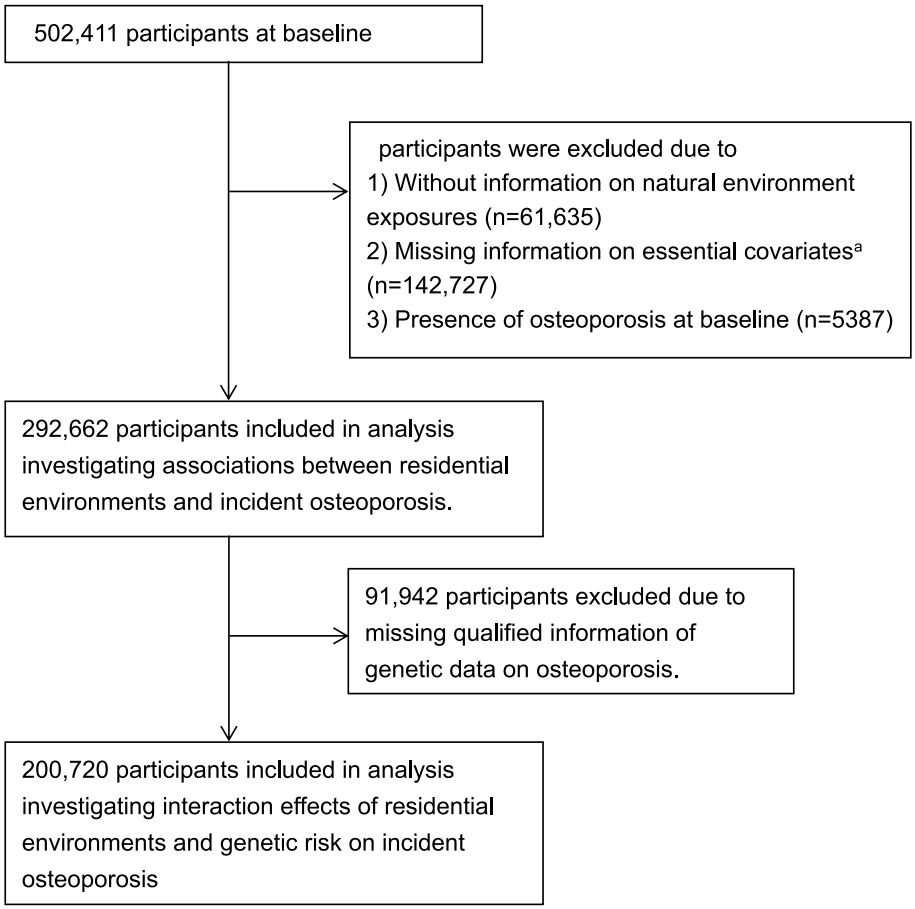

Fig. 1. Flowchart of participants selection
Note: [a] essential covariates in this study included age, sex, ethnicity, length of living in current address, annual household income before tax, employment status, the highest education qualifications, small area deprivation index, body mass index, smoke, alcohol status and physical activity group.

and level of physical activity]. The Index of Multiple Deprivation (IMD) was used as the small area-level socioeconomic indicator, a weighted score covering seven domains (income, employment, education, health, crime, barriers to housing and services, and living environment).

2.4. Polygenic risk score (PRS)

UK Biobank provided imputed genotyping data for 488,000 participants, and a genotyping quality control (QC) process was also conducted (Thompson et al., 2022; Bycroft et al., 2017). We included participants with available information on genetic ethnicity and whose genotyping data met QC criteria (participants with less than 98% variant missing, genetic sex matching to self-report, and without heterozygosity outliers). The polygenetic risk score of osteoporosis was derived from the UK Biobank data field 26258. It was standardised against participants' genotype ethnicity, resulting in a distribution with approximately zero mean and unit variance across all ancestries (Khera et al., 2019).

2.5. Statistical analysis

We used the Cox proportional hazard regression model to assess the associations between green space, natural environment, and domestic gardens and the incidence of osteoporosis. We classified participants into four groups based on quartiles of the exposures, and the 1st quartile (i.e., the lowest exposure group) was set as the reference group. We also treated the exposures as continuous variables, and the corresponding hazard ratio (HR) was calculated for each increase of one interquartile range (IQR) in the exposures.

Potential covariates were adjusted incrementally. Model 1 adjusted for demographic characteristics including age and sex only. Model 2 additionally adjusted for individual- and area-level socioeconomic status including ethnicity, annual household income before tax, the highest educational qualification, employment status, length of living in the current address (in quintiles), and IMD (in quintiles). Model 3 (main model) further adjusted for lifestyle factors including BMI [underweight ($<$18.5 kg/m^2), normal (18.5 to $<$25 kg/m^2), overweight (25 to $<$30 kg/m^2), and obese (30 kg/m^2 or higher)], smoking status, alcohol drinking status, and physical activity level. We tested whether the associations would be modified by sex, length of time in the current address, and level of physical activity by interaction analyses and stratification analyses.

A logistic regression model was used to assess the association between PRS of osteoporosis and the presence of osteoporosis, controlling for age, sex, and the top 10 genetic principal components (PCs). The PRS of osteoporosis was cut into deciles and analysed as a categorical variable, with PRS in the 1st decile as the reference group. Interactive effects of residential environments and PRS on incident osteoporosis were examined in additive and multiplicative scales. We grouped the osteoporosis PRS into low and high levels according to the medium value of PRS. We set the environmental exposures in the 4th quartile as the reference group to investigate the interaction between PRS and exposures. Then, we used relative excess risk due to interaction (RERI) to assess the additive interaction (Richardson and Kaufman, 2009). The calculations of RERI were presented in the supplementary file. A RERI of zero represents no additive interaction. A RERI greater than zero indicates positive additive interaction, i.e., the combined excess risk is

Table 1
Participant characteristics at baseline (2006–2010).

Characteristics	N (%)
	292662
Age, Mean (SD), years	56 (8.1)
≤ 45	40,914 (14.0)
45-55	90,031 (30.8)
55-65	123,692 (42.3)
> 65	38,025 (13.0)
Sex	
Female	147,625 (50.4)
Male	145,037 (49.6)
Ethnicity	
White	266,787 (91.2)
Non-white	25,875 (8.8)
Length of living in current address, Mean (SD), years	17.01 (11.66)
Education qualification	
University or college	106,910 (36.5)
A-levels or equivalent	35,168 (12.0)
GCSEs or equivalent	78,777 (26.9)
Other	71,807 (24.5)
Household income	
Less than £18,000	61,050 (20.9)
£18,000 to £30,999	72,931 (24.9)
£31,000 to £51,999	77,836 (26.6)
£52,000 to 100,000	63,372 (21.7)
Greater than 100,000	17,473 (6.0)
Employment status	
Employed	189,552 (64.8)
Retired	87,695 (30.0)
Unemployed	15,415 (5.3)
Index of Deprivation	
Qn1 (least deprived)	60,256 (20.6)
Qn2	59,526 (20.3)
Qn3	59,039 (20.2)
Qn4	57,839 (19.8)
Qn5 (most deprived)	56,002 (19.1)
Body mass index	
Underweight (<18.5 kg/m^2)	1342 (0.5)
Normal (18.5 to <25 kg/m^2)	96,947 (33.1)
Overweight (25 to <30 kg/m^2)	126,212 (43.1)
Obese (30 kg/m^2 or higher)	68,161 (23.3)
Smoking status	
Never	159,450 (54.5)
Previous	103,824 (35.5)
Current	29,388 (10.0)
Alcohol drinking	
Never	10,390 (3.6)
Previous	9509 (3.2)
Current	272,763 (93.2)
Physical activity	
Low	54,921 (18.8)
Medium	119,463 (40.8)
High	118,278 (40.4)

SD: standard deviation; Qn: Quantile.

greater than the sum of individual risks. A RERI less than zero represents negative additive interaction, i.e., the combined excess risk is smaller than the sum of individual risks. The multiplicative scale of interactive effects was evaluated by the significance of the interaction term in the regression model. Covariates adjusted in the analyses were age, sex, ethnicity, highest educational qualification, length of time at current living addresses, annual household income before tax, employment status, IMD, BMI, smoking and alcohol drinking status, physical activity level, and top 10 genetic PCs.

2.6. Sensitivity analysis

We conducted several sensitivity analyses to examine the robustness of the main findings. Firstly, we examined the association between green space, natural environment, and domestic gardens and incident osteoporosis within an alternative buffer (1000 m) to test if the distances to the exposures would influence the effects. Secondly, we excluded participants who developed osteoporosis in the first year of follow-up to minimise the reverse causation. Thirdly, we examined the association between green space, natural environment, and domestic gardens and incident osteoporosis among participants with genotyping data. Finally, we assessed the interactive effects of genetic and environmental exposure on incident osteoporosis among participants with no kinship in the cohort and of European ancestry only, to diminish bias of genetics from relatives and different ancestries. All statistical analyses were done by R software version 4.1.2. Package "interactionR" was used to calculate the interaction effects RERI.

3. Results

A total of 292,662 participants were included in the current study. During a median of 13.65 years follow-up (interquartile range: 12.91–14.31), we observed 9175 incident osteoporosis. The flowchart of the analytic sample is shown in Fig. 1. Baseline characteristics of the analytical sample are listed in Table 1. The average age of participants at baseline was 56 [standard deviation (SD): 8.10] years old. Half of the participants were female (50.4%), and the majority were White ethnicity (91.2%). Recruited participants had lived in the current addresses for an average of 17.01 (SD: 11.66) years.

The average coverage of green space, natural environment, and domestic gardens at 300 m buffer of residential surrounding were 35.57% (SD 23.51), 26.88% (SD 25.66), and 31.29% (SD 14.73), respectively (eTable 1). The average levels of green space and natural environment were higher at 1000 m buffer, while the coverage of domestic gardens was reduced. Green space and natural environment showed moderate to high positive correlations (Spearman coefficient >0.7) (Fig. 2). Domestic garden coverage was negatively related to green space and the natural environment.

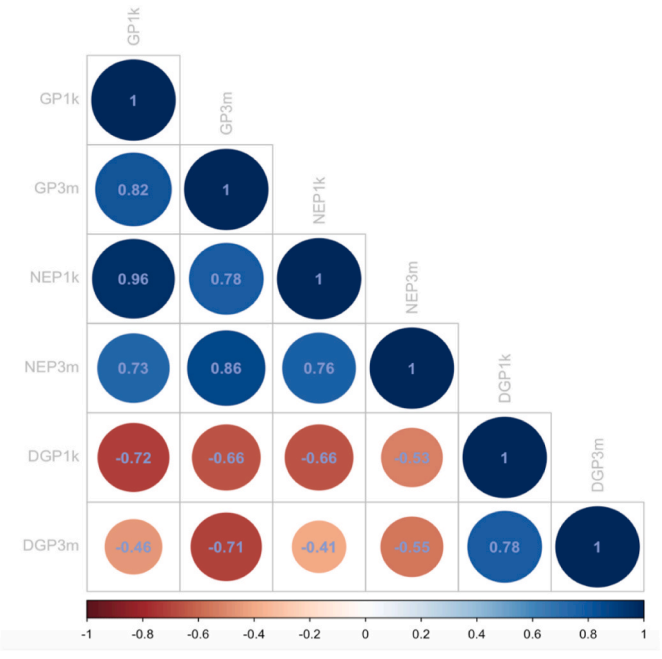

Fig. 2. Correlation plot of environmental exposures
GP1k: percentage of green space at 1000 m buffer of residential address, GP3m: percentage of green space at 300 m buffer of residential address, NEP1k: percentage of natural environment at 1000 m buffer of residential address, NEP3m: percentage of natural environment at 300 m buffer of residential address, DGP1k: percentage of domestic gardens at 1000 m buffer of residential address, DGP3m: percentage of domestic gardens at 300 m buffer of residential address. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Associations of greenness, natural environment, and domestic gardens with incident osteoporosis in a 300 m buffer (n = 292,662).

		Model 1	p-value	Model 2	p-value	Model 3	p-value
		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Green space	1st quartile	Ref		Ref		Ref	
	2nd quartile	1.01 (0.96, 1.07)	0.647	1.00 (0.94, 1.05)	0.878	1.02 (0.96, 1.08)	0.590
	3rd quartile	0.97 (0.92, 1.03)	0.387	0.97 (0.92, 1.03)	0.354	0.99 (0.94, 1.05)	0.791
	4th quartile	0.89 (0.84, 0.94)	<0.001	0.93 (0.88, 0.99)	0.016	0.95 (0.90, 1.00)	0.095
	P for trend		<0.001		0.008		0.041
	Per IQR increase	0.92 (0.90, 0.95)	<0.001	0.95 (0.92, 0.98)	0.001	0.96 (0.93, 0.99)	0.005
Natural environment	1st quartile	Ref		Ref		Ref	
	2nd quartile	0.99 (0.94, 1.05)	0.821	1.01 (0.95, 1.07)	0.825	1.02 (0.97, 1.09)	0.404
	3rd quartile	0.95 (0.90, 1.01)	0.085	0.98 (0.92, 1.04)	0.509	1.00 (0.94, 1.06)	0.961
	4th quartile	0.86 (0.81, 0.91)	<0.001	0.92 (0.87, 0.98)	0.009	0.94 (0.89, 1.00)	0.055
	P for trend		<0.001		0.003		0.014
	Per IQR increase	0.92 (0.89, 0.94)	<0.001	0.95 (0.92, 0.98)	0.001	0.96 (0.93, 0.98)	0.003
Domestic garden	1st quartile	Ref		Ref		Ref	
	2nd quartile	1.03 (0.97, 1.09)	0.325	1.02 (0.96, 1.08)	0.581	1.02 (0.96, 1.08)	0.497
	3rd quartile	1.02 (0.96, 1.08)	0.544	1.03 (0.97, 1.09)	0.395	1.03 (0.97, 1.09)	0.359
	4th quartile	0.94 (0.89, 1.00)	0.047	0.99 (0.93, 1.05)	0.738	0.99 (0.93, 1.05)	0.780
	P for trend		0.044		0.870		0.905
	Per IQR increase	0.98 (0.95, 1.01)	0.128	1.00 (0.97, 1.03)	0.911	1.00 (0.97, 1.03)	0.877

HR: hazard ratio; IQR: interquartile range.
Incidence of osteoporosis: n = 9175.
Model 1: adjusted for age and sex.
Model 2: additionally adjusted for ethnicity, highest educational qualification, length of time at current address, annual household income before tax, employment status, and index of deprivation.
Model 3: additionally adjusted for body mass index, smoking, alcohol drinking and physical activity group.

Table 2 showed associations of green space, natural environment, and domestic gardens with incident osteoporosis at 300 m buffer of residential addresses. In the fully adjusted model (Model 3), per IQR increase in green space (31.78%) was associated with a 4% lower risk of incident osteoporosis [Hazard Ratio (HR) = 0.96 (95% confidence interval (CI): 0.93, 0.99)]. One IQR increase in the natural environment (34.60%) was also associated with a 4% lower risk of incident osteoporosis [HR = 0.96 (95% CI: 0.93, 0.98)]. In the fully adjusted model 3, compared to the 1st quartile, exposure to the 4th quartile of green space and natural environment were associated with 5% and 6% lower risk of incident osteoporosis with marginal significance, respectively [HR = 0.95 (95% CI: 0.90, 1.00)] and [HR = 0.94 (95% CI: 0.89, 1.00)]. No association was observed between domestic gardens and incident osteoporosis.

Stratified analyses showed that the associations of green space and natural environment with incident osteoporosis were slightly stronger among females, participants living in the current addresses for longer than 10 years, and those with medium-level physical activity (Fig. 3). However, no interaction effects were found (Fig. 3).

The distribution of the PRS for osteoporosis in participants with and without osteoporosis is shown in eFigure 1. Compared to those in the lowest decile, individuals in the highest PRS deciles had 231% higher odds of incident osteoporosis [odds ratio = 3.31 (95% CI: 2.92, 3.75)] (eFigure 2). The osteoporosis PRS explained an 11.6% risk of osteoporosis (Nagelkerke's pseudo-R^2 = 0.116). Neither additive nor multiplicative interactive effects existed for gene-environment interactions (Table 3).

Results from several sensitivity analyses were consistent with our main findings. eTable 2 showed that green space and natural environments within 1000 m buffers were associated with a lower risk of incident osteoporosis. The associations remained unchanged after excluding participants who developed osteoporosis within the first year of their follow-up (eTable 3). The associations remained unchanged in participants with complete genotyping data (eTable 4). The gene-environment interaction effects remained insignificant after restricting participants to those with no kinship in the cohort (eTable 5).

4. Discussion

To our knowledge, this is the first study to examine the relationship between multi-type residential environments, including green space, natural environments, and domestic gardens, in connection to incident osteoporosis and its interaction with genetic risk. In this large-scale cohort study with over 13-year follow-up, our findings indicated that residential greenness and natural environment, but not domestic gardens, might be protective against osteoporosis. The associations were slightly stronger among females and participants living in the current addresses for longer than ten years. The associations did not vary by genetic risk factor.

Up to now, only three studies on the relationship between greenness and bone health have been identified. A community-based cross-sectional study covering 66,053 participants in southwest China showed that greenness might be associated with higher bone strength (Jiang et al., 2022). Our findings also align with a cohort study conducted among 23,940 residents (≥40 years old) in a Chinese eastern coastal city, which found long-term exposure to residential greenness could decrease the risk of incident fracture (Zhu et al., 2023). Another cohort study in Hong Kong, with around 4000 older people (≥65 years old), did not observe a protective association between green space and fracture (Lin et al., 2021). As an ultra-high-density city, people in Hong Kong living with higher green space tended to be less educated and have lower socio-economic status(Lin et al., 2021), which may differ from our study. Our study took into account a broader variety of confounders, such as length of time in individuals' residential addresses and social deprivation status, which had previously received less attention. To the best of our knowledge, this is the first study to consider genetic risk and utilise a population-based cohort study with over ten years of follow-up.

There are some potential explanations for the findings. Firstly, higher coverage of natural environments and green spaces helps reduce hazards caused by exposure to environmental stressors (e.g., air pollutants) and is therefore associated with a lower risk of osteoporosis. Previous studies have indicated that air pollutants may hinder bone metabolism, and several epidemiological studies have highlighted a positive association between exposure to air pollution and the risk of osteoporosis (Liu et al., 2021; Prada et al., 2017). There is consensus that areas around green space/natural environment generally have lower concentrations of air

exposure	group	estimation	p–value	p–value for interaction term
Green Space	All subjects	0.96 (0.93, 0.99)	0.005	
	Sex			0.611
	Female	0.96 (0.93, 0.99)	0.011	
	Male	0.97 (0.91, 1.04)	0.432	
	Living length			0.805
	<= 10 years	0.96 (0.91, 1.01)	0.158	
	> 10 years	0.96 (0.93, 0.99)	0.025	
	Physical activity			0.794
	low–level activity	0.97 (0.91, 1.04)	0.383	
	medium–level activity	0.95 (0.91, 1)	0.041	
	high–level activity	0.96 (0.92, 1.01)	0.087	
Natural Environment	All subjects	0.96 (0.93, 0.98)	0.003	
	Sex			0.378
	Female	0.96 (0.93, 0.99)	0.008	
	Male	0.96 (0.9, 1.03)	0.282	
	Living length			0.792
	<= 10 years	0.96 (0.91, 1.01)	0.121	
	> 10 years	0.96 (0.92, 0.99)	0.014	
	Physical activity			0.281
	low–level activity	0.95 (0.89, 1.02)	0.161	
	medium–level activity	0.94 (0.9, 0.99)	0.015	
	high–level activity	0.97 (0.93, 1.02)	0.189	
Domestic Garden	All subjects	1.00 (0.97, 1.03)	0.877	
	Sex			0.036
	Female	1.01 (0.98, 1.05)	0.462	
	Male	0.95 (0.89, 1.02)	0.146	
	Living length			0.763
	<= 10 years	1 (0.95, 1.06)	0.967	
	> 10 years	1 (0.97, 1.04)	0.938	
	Physical activity			0.803
	low–level activity	1 (0.94, 1.07)	0.970	
	medium–level activity	1 (0.96, 1.05)	0.869	
	high–level activity	1 (0.95, 1.05)	0.973	

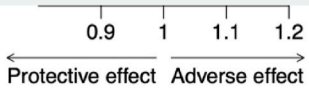

Fig. 3. Stratified analyses for the associations of greenness, natural environment, and domestic gardens with incident osteoporosis
N = 292,662; Greenness, natural environment, and domestic gardens were measured in a 300 m buffer.

pollutants, (Markevych et al., 2017; Diener and Mudu, 2021; Nowak et al., 2014; Sun et al., 2020) which indicates that higher natural environment and green space coverage could help reduce harm from air pollution and decrease the risk of osteoporosis. Secondly, exposure to green space and natural environments may promote psychological recovery (Hartig et al., 2014; de et al., 2013; Schmid et al., 2021). Previous findings showed chronic psychological stress was detrimental to bone health, and underlying mechanisms included endocrine changes, systemic inflammation, and behavioural changes that impede osteoclast genesis and induce bone loss (Ng and Chin, 2021). Thirdly, the natural environment and green space surrounding residential addresses may provide more opportunities for outdoor physical activity(Stewart et al., 2016; Tsai et al., 2016), which helps delay the loss of bone mineral density and is one of the effective measures to prevent osteoporosis (Bolam et al., 2013; Pinheiro et al., 2020; Manferdelli et al., 2019).

We found no association between domestic gardens and incident osteoporosis. Domestic garden is a common type of built environment in the UK, with 88% of families having a garden (Davies et al., 2009). Areas with a high household garden cover are typically residentially concentrated, with limited green space or natural environment. This explanation could be supported by the considerable negative associations discovered in our study between domestic gardens and green space or natural environment (Fig. 2).

PRS of osteoporosis was significantly associated with the risk of osteoporosis during our follow-up period (eFigure 2). Osteoporosis is a complex heritable polygenic disease. Environmental and genetic risk factors and gene-environment interactions contribute to the risk of developing osteoporosis (Karasik et al., 2016; Ackert et al., 2013; van MeursJBJ et al., 2008). Previous studies have shown that some health-protective behaviours, such as calcium intake, a low-fat diet, and increased physical activity, are positively associated with bone mass, and the associations interact with bone mass-related gene polymorphisms (Stathopoulou et al., 2010; Ackert et al., 2008; Sonoda et al., 2012; Li et al., 2008). Our study found that the protective association between residential environments and incident osteoporosis did not differ by genetic risk, suggesting that genes and residential

Table 3
Interaction of greenness, natural environment, and domestic gardens and polygenic risk score of osteoporosis on incident osteoporosis (n = 200,720)[b].

		Polygenic risk score		RERI	P value for interaction[c]
		Low	High		
		HR (95% CI)	HR (95% CI)		
Green space[a]	4th quartile	Ref	1.65 (1.49, 1.83)		
	3rd quartile	0.99 (0.88, 1.11)	1.76 (1.59, 1.95)	0.12 (−0.06, 0.30)	
	2nd quartile	1.06 (0.94, 1.19)	1.74 (1.57, 1.93)	0.03 (−0.16, 0.22)	
	1st quartile	1.00 (0.89, 1.13)	1.73 (1.56, 1.92)	0.07 (−0.12, 0.26)	0.649
Natural environment	4th quartile	Ref	1.70 (1.53, 1.88)		
	3rd quartile	1.06 (0.95, 1.19)	1.76 (1.59, 1.95)	0.00 (−0.19, 0.19)	
	2nd quartile	1.06 (0.94, 1.18)	1.85 (1.67, 2.05)	0.10 (−0.10, 0.29)	
	1st quartile	1.05 (0.93, 1.18)	1.78 (1.61, 1.98)	0.04 (−0.16, 0.23)	0.974
Domestic garden	4th quartile	Ref	1.68 (1.52, 1.86)		
	3rd quartile	1.00 (0.89, 1.13)	1.76 (1.59, 1.95)	0.08 (−0.11, 0.27)	
	2nd quartile	1.00 (0.89, 1.12)	1.67 (1.50, 1.85)	−0.01 (−0.20, 0.18)	
	1st quartile	1.00 (0.89, 1.12)	1.70 (1.53, 1.88)	0.02 (−0.17, 0.21)	0.838

HR: hazard ratio; RERI: relative excess risk due to interaction.
[a]Greenness, natural environment, and domestic gardens were measured in a 300 m buffer.
[b]Adjusted for age, sex, ethnicity, qualification, household income, index of deprivation, length of time at current address, body mass index, smoking, alcohol drinking, and the first 10 genetic principal components.
[c]P value for interaction: polygenic risk score * per IQR increase.

environments may have distinct biological pathways in the development of osteoporosis.

Our study has the following strengths. This large-scale cohort study, with more than 292 thousand participants, had a long follow-up period with a median of over 13 years, which allowed the observations of incident chronic diseases with sufficient statistical power. So far, few studies investigated the associations between residential environments and bone health, and we found our study is the first piece of evidence on several types of residential environments and incident osteoporosis. In addition, we investigated whether the genetic risk of osteoporosis modified the associations between the residential environment and osteoporosis. Our gene-environment interaction study, based on sound data, provides valuable evidence for the research of osteoporosis. Nevertheless, there are some limitations in this study. Firstly, prospective cohort studies are susceptible to selection bias. Participants in UK Biobank were recruited voluntarily, and their residential addresses are relatively near the assessment centre, which might affect the representativeness and generalisability. Secondly, we could not consider the residential environmental coverage as a time-varying exposure because the follow-up exposure measures were limited. However, the relocation rate of participants in the UK Biobank was low at around 2% according to the follow-up surveys, and the land use characteristic of England should be relatively stable over time. Therefore, the baseline residential environmental exposures should be an appropriate proxy for long-term exposure. Thirdly, we have conducted a sensitivity analysis to exclude participants who developed osteoporosis within the first year of follow-up to avoid potential reverse causation, but it is possible that some patients with early-stage osteoporosis are not diagnosed. Finally, we could not rule out the possibility of residual confounding. However, we have adjusted for a wide range of essential confounding factors, including demographic characteristics, individual- and area-level socioeconomic status, length of time in the current address, and health-related behaviours.

5. Conclusions

This large-scale, long-term cohort study demonstrated that exposure to green space and the natural environment surrounding residences was associated with a lower risk of incident osteoporosis. No association was observed between exposure to domestic gardens and incident osteoporosis. Our findings indicated that public greenness and natural environments could reduce the risk of incident osteoporosis regardless of genetic predisposition to osteoporosis. Our research provided some insights into osteoporosis prevention and urban residential environment planning. Our findings would support policymakers on urban planning in better-organising urbanisation processes to build sustainable and publicly accessible natural neighbourhoods that yield larger benefits to population bone health. Future studies could further investigate the pathways between natural environments and osteoporosis and the specific characteristics of green space that have the largest impact on bone health.

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Ethics

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

CRediT authorship contribution statement

Xiaoxin I. Yao: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Writing – original draft. **Xinning Tong:** Formal analysis, Methodology, Software, Writing – review & editing. **Chen Shen:** Conceptualization, Data curation, Investigation, Resources, Validation, Writing – original draft. **Yichang Song:** Writing – review & editing. **Shengzhi Sun:** Supervision, Writing – review & editing. **Keng Chen:** Supervision, Writing – review & editing. **Huiyong Shen:** Supervision, Writing – review & editing.

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2024.141632.

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