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Greenspace and mortality in the U.K. Biobank: Longitudinal cohort analysis of socio-economic, environmental, and biomarker pathways

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A B S T R A C T

Exposure to natural greenspace benefits health through direct and indirect pathways: increasing physical activity, improving mental health, relieving social isolation, reducing exposure to extreme temperature, noise, and air pollution. Understanding the etiologic pathway of greenspace and health is needed. Here, we used a large cohort follow-up data from the U.K. Biobank to quantify the magnitude of behavioural factors, psychological factors, biomarkers/physiological measurements, co-morbid diseases, and environmental exposure as potential mediators in the relationship between greenspace and mortality. We estimated hazard ratios (HR) with Cox proportional hazards models, and undertook exploratory mediation analyses to quantify the relative contribution of five types of mediators. Our results indicate greenspace was strongly associated with lower mortality risks [per IQR of public greenspace (HR = 0.90 (95% CI 0.86-0.84)) and domestic gardens (HR = 0.91, (95% CI 0.88–0.94))]. The protective associations were especially pronounced among those with lower individual-level socioeconomic status or living in places with area-level deprivation. Exploratory mediation analysis detected benefits in pathways through reducing air pollution, relieving social isolation and depression, increased physical activity and time spent outdoor, better lung function (FEV1/FVC), and having higher serum vitamin D levels.

1. Introduction

Living in areas with higher proportions of greenspace is associated with better health outcomes(WHO, 2016). Observational cohort studies showed higher greenspace is associated with lower mortality in Europe (Orioli et al., 2019),(Vienneau et al., 2017),(Klompmaker et al., 2020), (Nieuwenhuijsen et al., 2018), North America (James et al., 2016), (Crouse et al., 2017),(Villeneuve et al., 2012), and China (Ji et al., 2019), for all-cause (Rojas-Rueda et al., 2019),(Orioli et al., 2019),(Ji et al., 2019), cardiovascular, cerebrovascular (Orioli et al., 2019), respiratory(Vienneau et al., 2017), and cancer mortalities (James et al., 2016). Greenspace has also been suggested to benefit the health by promoting mental well-being (Wang et al., 2021),(Pun et al., 2018), decreasing anxiety and depression (Taylor et al., 2015),(Hartley et al., 2021), increasing propensity for physical activity (Almanza et al., 2012), reducing obesity (Sarkar, 2017),(Luo et al., 2020), and decreasing noise (Dzhambov et al., 2018), extreme heat (Loughner et al., 2012),(Maimaitiyiming et al., 2014), and the concentration of air pollutants such as fine particulate matter and nitrogen dioxide (Nowak et al., 2006).

There is an unanswered question of whether these relationships are due to residual confounding, varying measurement methods of greenspace, and biological etiology and mechanisms. First, residual confounding is possible as socio-economic status (SES) is associated with both exposure to greenspace and adverse health outcomes, and thus prior studies often include an adjustment variable or stratified analysis by SES (Klompmaker et al., 2020),(Villeneuve et al., 2012). However, some studies generated contrasting findings (Crouse et al., 2017),(de Keijzer et al., 2017). A cohort study conducted in Canada reported that people with higher income benefited more from greenspace (Crouse et al., 2017), while another study conducted in Spain showed that the protective effect of greenspace on mortality was only found in areas with lower SES (de Keijzer et al., 2017). One study also showed that people in

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the U.K. with higher income were more likely to have higher levels of greenspace (Mitchell & Popham, 2008), which motivated us to explore the association between SES, greenspace, and health. Second, greenspace is measured in a variety of ways, such as using normalized difference vegetation index (NDVI) (Wang et al., 2021),(Pun et al., 2018),(Hartley et al., 2021),(Almanza et al., 2012),(Sarkar, 2017),(Luo et al., 2020),(Dzhambov et al., 2018), street view (Wang et al., 2021), tree density (Taylor et al., 2015),(Dzhambov et al., 2018), percentage of greenspace (Dzhambov et al., 2018), as well as percentage of landscape (Maimaitiyiming et al., 2014) from remote sensing methods. Third, for biological etiology, mediation analysis is an approach to disentangle the different pathways that could explain the effect of an exposure on an outcome and therefore helps to assess the extent to which the effect of an exposure is explained (Richiardi et al., 2013).

In the U.K., proximity to greenspace access may likely be a reflection of external determinants of health such as SES, and exposure to greenspace might benefit health through different pathways (Pretty et al., 2017),(Barton et al., 2016),(Wood et al., 2016). Here, we aimed to investigate the health effects of different types of greenspace (comprising both public greenspace and domestic gardens) and possible effect modification by socio-economic status, including both individual level and area-level SES. We also used a exploratory mediation analysis approach to quantify to what extent behavioral factors, psychological factors, biomarkers/physiological measurement, co-morbid diseases, and environmental factors might mediate the association of greenspace with mortality in the U.K..

2. Methods

2.1. Study design and participants

The U.K. Biobank is a prospective cohort study. Between 2007 and 2010, U.K. Biobank invited and recruited some 500,000 participants. Participants underwent baseline assessment visit, which included obtaining information on a participant's health and lifestyle, a range of physical measurements, and blood, urine, and saliva samples. Mortality events were ascertained through record linkage and could occur from baseline assessment to the date of censoring. The U.K. Biobank included only 440,860 participants with greenspace exposure data. We excluded 85,119 participants due to missing data. The final study population thus comprised 355,741 participants (Fig. 1). Our exploratory mediation analyses were conducted based on availability of mediators variables.

2.2. Greenspace exposure assessment

The percentage of the land classified as greenspace or domestic garden, as a proportion of all land use types, was modeled using 2005 data from the Generalized Land Use Database for England (GLUD) for the 2001 Census Output Areas in England. Data were extracted for the lowest geographical scale for UK administrative boundary data: lower layer super output areas (LSOAs). These geographical units were defined as areas with populations of between 1000 and 3000 persons, and between 400 and 1200 households. Each residential address collected in baseline survey was allocated a circular distance buffer of 1000 m, and the proportion of public greenspace (public greenspace %) and domestic garden (domestic garden%) were included in the analysis. Within the GLUD, the greenspace was classified as green land cover designated as public spaces (including parks, communal gardens, and cemeteries) and agricultural land, and domestic garden included parcels of land annexed by residential buildings (Dennis & James, 2017). The timeline of U.K. biobank data collection is shown in the supplementary file (Fig. S1).

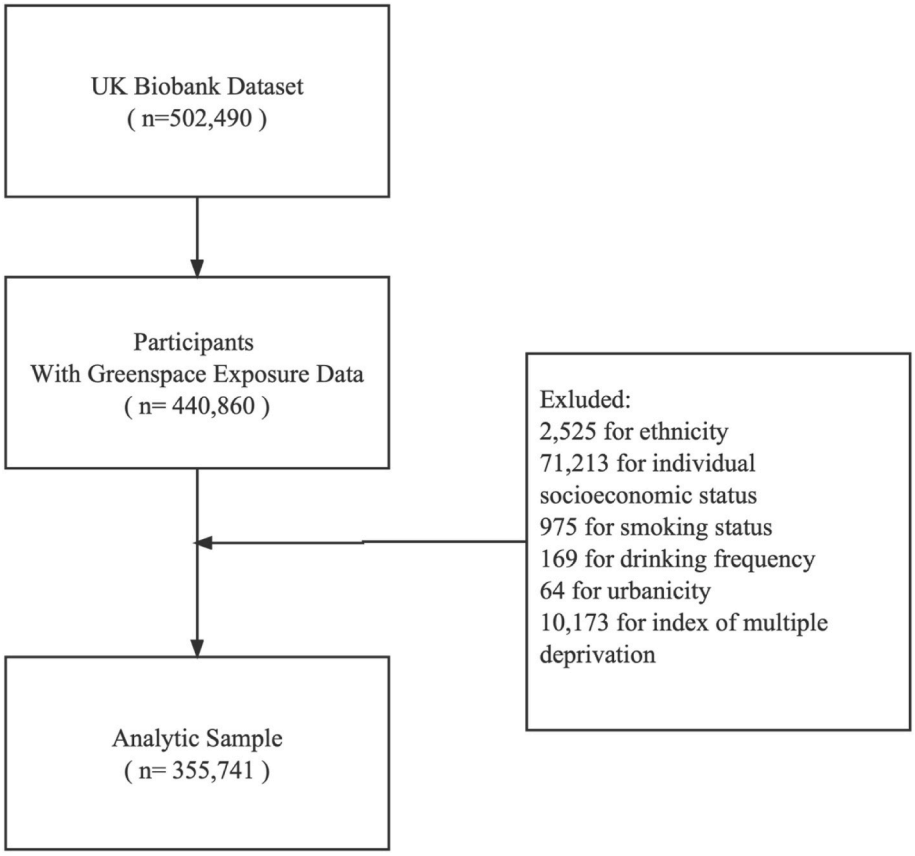

Fig. 1. Study population, showing the inclusion/exclusion criteria and the number of incident death cases.

2.3. Mortality assessment

Outcomes were ascertained through individual-level record linkage of the U.K. Biobank cohort to routine administrative databases. All-cause mortality and cardiovascular disease (CVD) mortality were used as the main health outcomes in this study. Date and cause of death were obtained from death certificates held by the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland). Follow-up was conducted from April 2007 to December 2020 for mortality.

2.4. Potential mediators

Physical activity [total metabolic equivalent of task (MET) minutes] was self-reported and weighted for intensity: self-reported minutes of walking (× 3.3), moderate exercise (× 4.0), and vigorous exercise (× 8.0). These were then summed to create an overall physical activity score (Lyall et al., 2019).

Time spent outdoors was self-reported at baseline assessment and was measured by using two questions from the touch screen questionnaire: "In a typical day in summer/winter, how many hours do you spend outdoors?". We recoded the response "less than an hour per day" as 0.5 h/day. We excluded participants who responded "Do not know" and 'Prefer not to answer," as well as extreme outliers defined as >12 h/day outdoors in summer or >8 h/day outdoors in winter from the analysis. Then, we calculated the average time spent outdoors per day for each participant.

Sedentary time was calculated by using the questions related to the leisure time spent watching T.V., the leisure time spent using a computer, and the total time spent driving, in which participants responded in the same way as in the time spent outdoors questions. We recoded the response "less than an hour per day" as 0.5 h/day. Extreme outliers in three sedentary activities (>9 h/day watching T.V., >6 h/day using computer, and >11 h/day driving) were coded as missing values. Sedentary time was computed by calculating the sum of the total number of hours per day that participants spent in three sedentary activities (Miguet et al., 2021).

A healthy sleep score was generated according to five sleep factors [chronotype, sleep duration, insomnia, snoring, and daytime dozing]. Low-risk sleep factors were defined as follows: early chronotype ('morning' or 'morning than evening'); sleep 7–8 h per day; reported never or rarely insomnia symptoms; no self-reported snoring; and no frequent daytime sleepiness ('never/rarely' or 'sometimes'). For each sleep factor, the participant received a score of 1 if classified as low risk for that factor or 0 if at high risk. All component scores were summed to obtain a healthy sleep score ranging from 0 to 5, with higher scores indicating a healthier sleep pattern (Fan et al., 2020).

A social isolation score was derived similarly to previous studies(de Lange et al., 2021) using the following questions: (1) "Including yourself, how many people are living together in your household?" (1 point for living alone); (2) "How often do you visit friends or family or have them visit you?" (1 point for friends and family visit less than once a month); and (3) "Which of the following [leisure/social activities] do you engage in once a week or more often?" (1 point for no participation in social activities at least weekly).

A healthy diet score was calculated based on the following diet factors: vegetable intake ≥ four table-spoons/day; fruit intake ≥ three pieces/day; fish intake ≥ twice/week; unprocessed red meat intake ≤ twice/week; and processed meat intake ≤ twice/week. Each 1 point was given for each favourable diet factor, and the healthy diet score ranged from 0 to 5 for each participant.

Depression was measured by a continuous score of current depressive symptoms based on the frequency of four items from the Patient Health Questionnaire: (1) depressed mood, (2) disinterest or absence of enthusiasm, (3) tenseness or restlessness, and (4) tiredness or lethargy in the previous 2 weeks (1 point for more than half of the days or nearly every day). The depression score ranged from 0 to 4 for each participant. People with depression score >1 were grouped into "with depression" group (de Lange et al., 2021).

A neuroticism score was derived from the Eysenck Personality Questionnaire-Revised Short Form. 12 items were used, comprising the following questions: (1) "Does your mood often go up and down?", (2) "Do you ever feel 'just miserable' for no reason?", (3) "Are you an irritable person?", (4) "Are your feelings easily hurt?", (5) "Do you often feel 'fed-up?" (6) "Would you call yourself a nervous person?" (7) "Are you a worrier?", (8) "Would you call yourself tense or 'highly strung'?", (9) "Do you worry too long after an embarrassing experience?", (10) "Do you suffer from 'nerves'?", (11) "Do you often feel lonely?", (12) "Are you often troubled by feelings of guilt?" (1 point for yes). The neuroticism score ranged from 0 to 12 for each participant (de Lange et al., 2021).

Biomarkers were measured at a dedicated central laboratory between 2014 and 2017, and physiological measurements were collected at baseline. Our analyses included an immunological biomarker C-reactive protein (mg/L), vitamin D (nmol/L), an indicator of diabetes Hb1Ac (mmol/mol), a lipid biomarker ApoB/ApoA (ratio), an indicator of kidney function cystatin C (mg/L), an indicator of lung function FEV1/FVC, indicators of obesity BMI (Kg/m2), waist-hip ratio and blood pressure. Body mass index (BMI) was derived by dividing weight (kilograms) by square of standing height (square metres). Obesity was expressed using the World Health Organization's definition (cut-offs for BMI ≥30 kg/m2) (WHO, 2021). Hypertension status was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. In contrast, diabetes status was self-reported, according to the touchscreen question "Has a doctor ever told you that you have diabetes?". Participants were divided into two FEV1/FVC groups: ≤0.7 and > 0.7 when conducting mediation analysis.

The distinct diagnosis codes a participant had had recorded across all their hospital inpatient records in either the primary or secondary position. A diagnosed of COPD was based on ICD-10 code: J44; a diagnose of cancer was based on ICD-10: C00-D09; a diagnose of cardiovascular disease was based on ICD-10: I10–I25, I42.0, I42.6, I42.7, I42.9, I50.0, I50.1, I50.9, I60–I64; a diagnose of kidney disease was based on ICD-10: N18. If participants were diagnosed to suffer any specific disease, they would be categorized as with specific disease in Table 4.

Regarding noise pollution, noise estimates for the year 2009 were modeled using a version of the Common NOise aSSessment methOdS (CNOSSOS-EU) noise model (Centre et al., 2012); an average level of noise pollution in decibels (dB) was calculated as the average daytime/evening/night-time sound level of noise pollution, and further categorized as ≤55, >55 to ≤60, >60 to ≤65, and >65 dB[A] in Table 1.

The annual average concentrations of $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, NO_2, and NO_x for the year 2010 were estimated with a Land Use Regression (LUR) model developed from the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (Eeftens et al., 2012). The spatial variations of annual average air pollutant concentrations were calculated using the LUR model, including the geospatial predictor variables generated from the Geographic Information System, such as traffic, land use, and topography. Air pollution exposures of all participants were linked to the records through residential addresses given at the baseline visit.

Except for co-morbid diseases, all potential mediators were collected at baseline. Co-morbid diseases were measured between baseline survey and end event, based on health records.

2.5. Socio-demographic and other confounders

Individual socio-economic status (SES) was defined based on practical definitions from the previous research (Zhang et al., 2021). The definition criteria are shown in the supplementary file (Fig. S2). Area-level SES was assessed based on the index of multiple deprivation (IMD). The English Indices of Deprivation 2010 were measures of multiple deprivation at the small area level. The model of multiple

Table 1
Characteristics of the cohort, stratified by quartiles of public greenspace %.

	Overall (n = 355741)	Q1 (4.42%–27.38%) (n = 87490)	Q2 (27.38%–41.51%) (n = 88233)	Q3 (41.51%–60.00%) (n = 89312)	Q4 (60.00%–99.19%) (n = 90706)
Mean (SD) age (years)	56.25 (8.08)	55.46 (8.21)	56.07 (8.17)	56.6 (8.00)	56.83 (7.87)
Incidence Death Cases [n (%)]	21612 (6.08%)	5019 (5.74%)	5725 (6.49%)	5716 (6.40%)	5152 (5.68%)
Male [n (%)]	168709 (47.42%)	40706 (46.53%)	41810 (47.39%)	42793 (47.91%)	43400 (47.85%)
Ethnicity [n (%)]					
British	316729 (89.03%)	69650 (79.61%)	77993 (88.39%)	82786 (92.69%)	86300 (95.14%)
Others	39012 (10.97%)	17840 (20.39%)	10240 (11.61%)	6526 (7.31%)	4406 (4.86%)
Residential Area [n (%)]					
Urban	304039 (85.47%)	87444 (99.95%)	87984 (99.72%)	86147 (96.46%)	42464 (46.81%)
Others	51702 (14.53%)	46 (0.05%)	249 (0.28%)	3165 (3.54%)	48242 (53.19%)
Individual SES [n (%)]					
Low	96318 (27.08%)	23790 (27.19%)	27028 (30.63%)	25424 (28.47%)	20076 (22.13%)
Medium	191280 (53.77%)	43578 (49.81%)	46368 (52.55%)	49811 (55.77%)	51523 (56.8%)
High	68143 (19.16%)	20122 (23%)	14837 (16.82%)	14077 (15.76%)	19107 (21.06%)
Index of Multiple Deprivation [n (%)]					
Q1	121300 (34.1%)	19099 (21.83%)	25367 (28.75%)	36408 (40.76%)	40426 (44.57%)
Q2	119172 (33.5%)	26307 (30.07%)	27599 (31.28%)	28814 (32.26%)	36452 (40.19%)
Q3	115269 (32.4%)	42084 (48.1%)	35267 (39.97%)	24090 (26.97%)	13828 (15.24%)
Smoking [n (%)]					
Never	193571 (54.41%)	45277 (51.75%)	47176 (53.47%)	49516 (55.44%)	51602 (56.89%)
Previous	125587 (35.3%)	31202 (35.66%)	31234 (35.4%)	31207 (34.94%)	31944 (35.22%)
Current	36583 (10.28%)	11011 (12.59%)	9823 (11.13%)	8589 (9.62%)	7160 (7.89%)
Drinking [n (%)]					
Never	25767 (7.24%)	7778 (8.89%)	6940 (7.87%)	6084 (6.81%)	4965 (5.47%)
Rarely	38843 (10.92%)	10350 (11.83%)	10419 (11.81%)	9778 (10.95%)	8296 (9.15%)
1–3/month	39539 (11.11%)	9610 (10.98%)	10252 (11.62%)	10378 (11.62%)	9299 (10.25%)
1–2/week	90661 (25.49%)	20636 (23.59%)	22714 (25.74%)	24227 (27.13%)	23084 (25.45%)
3–4/week	84753 (23.82%)	19736 (22.56%)	20239 (22.94%)	21403 (23.96%)	23375 (25.77%)
Daily	76178 (21.41%)	19380 (22.15%)	17669 (20.03%)	17442 (19.53%)	21687 (23.91%)
Mean (SD) Public Greenspace %	45.3 (21.7)	20.2 (4.77)	34.1 (4.08)	50.32 (5.27)	75.46 (10.81)
Mean (SD) Domestic Garden %	24.35 (11.28)	32.94 (11.28)	29.57 (7.33)	23.65 (5.4)	11.68 (6.06)
$PM_{2.5}$					
Mean (SD)	9.97 (1.04)	10.71 (1)	10.32 (0.84)	9.86 (0.74)	9.03 (0.72)
NA	4005	1581	761	541	1122
NO_2					
Mean (SD)	26.55 (7.56)	33.42 (6.71)	29.17 (5.64)	24.88 (4.51)	19.05 (4.38)
NA	3805	1532	714	492	1067
Vitamin D					
Mean (SD)	49.36 (21.05)	46.62 (20.98)	48.6 (21.05)	50.23 (21.15)	51.87 (20.67)
NA	35390	8979	8673	8798	8940
BMI					
Mean (SD)	27.37 (4.74)	27.2 (4.88)	27.51 (4.85)	27.54 (4.72)	27.22 (4.49)
NA	6475	1631	1711	1634	1499
FEV1/FVC					
Mean (SD)	0.75 (0.07)	0.75 (0.07)	0.75 (0.07)	0.75 (0.07)	0.76 (0.06)
NA	98507	27888	25344	23271	22004
Physical Activity (MET-min)					
Mean (SD)	12535.34 (14178)	12220.17 (13887.26)	12537.15 (14386.59)	12487.68 (14214.53)	12885.37 (14212.44)
NA	57294	13274	14828	15045	14147
Sedentary Time					
Mean (SD)	4.75 (2.24)	4.53 (2.31)	4.8 (2.27)	4.91 (2.22)	4.77 (2.13)
NA	11318	3400	3068	2610	2240
Social Isolation					
Mean (SD)	0.71 (0.74)	0.79 (0.78)	0.73 (0.75)	0.68 (0.73)	0.66 (0.71)
NA	1983	682	544	429	328
Depression					
Mean (SD)	0.25 (0.69)	0.28 (0.74)	0.28 (0.74)	0.24 (0.68)	0.2 (0.6)
NA	31418	8324	8303	7920	6871

deprivation which underpins the Indices of Deprivation 2010 was based on the idea of distinct domains of deprivation which can be recognised and measured separately (Communities & Local, 2011). Participants were categorized into area deprivation tertiles from Q1 (lowest area deprivation tertile) to Q3 (highest area deprivation tertile). Urbanism is derived by combining each participants' home postcode with data generated from the 2001 census information on population density from the Office of National Statistics. Ethnicity, smoking status and drinking frequency were collected through touchscreen questions.

2.6. Statistical analyses

Cox proportional-hazard models were used to analyze the association between greenspace and mortality, with the results reported as hazard ratios (HR) and 95% confidence intervals (CI). Assumption of proportional harzard was tested by using Schoenfeld residuals. Effect modifications were considered by adding interaction terms, and stratified analyses based on age, gender, urbanism, individual socio-economic status and area-level deprivation were also conducted. P values of interaction were calculated by introducing interaction terms into the

regression models.

We studied five groups of potential mediators of the association between greenspace and all-cause mortality: behavioral factors [physical activity, sleep quality, sedentary time, time spent outdoor and healthy diet], psychological factors [social isolation, depression, and neuroticism], serum biomarkers and physiological measurement [C-reactive protein, vitamin D, ApoB/ApoA, Hb1Ac, FEV1/FVC, blood pressure, body mass index, waist-hip ratio and cystatin C], co-morbid disease [chronic obstructive pulmonary disease (COPD), cancer, cardiovascular diseases, kidney disease] and environmental factors [noise, NO_2 and $PM_{2.5}$]. We assumed age, sex, ethnic background, smoking status, alcohol intake frequency, urbanism, individual SES and IMD to be the common set of confounders for exposure-outcome, exposure-mediator, and mediator-outcome relationships. The groups of mediators were included in the Cox models to examine whether, and to what extent, the associations between greenspace and mortality were attenuated. We performed a regression-based mediation analysis to quantify the extent to which the associations between greenspace and mortality were mediated. First, death events were regressed by greenspace variables, potential mediators and confounders in a Cox model. The potential mediators were then regressed by greenspace variables in either logistic (for binary mediators) or multiple linear (for continuous mediators) models adjusting for confounders. The two models were then combined to compute the natural direct effect (NDE) and natural indirect effect (NIE) (Valeri & VanderWeele, 2015),(Valeri & Vanderweele, 2013). Mediation proportion was calculated as NIE/Total Effect. To consider exposure-mediator interaction, we further induced a three-way decomposition of a total effect into direct, indirect, and interactive effects(VanderWeele, 2013).

Missing data were handled using complete case analysis. We compared the baseline characteristics between the included and excluded participants. We also did sensitivity analyses by assigning the median value for the missing variables and then repeating our analyses procedure. We further conducted multiple imputation analyses, generating 10 imputed datasets to confirm that missing data did not drive the results. All analyses were conducted using R version 3.6.3 and 4.1.2 with packages survival, mice and regmedint.

3. Results

A total of 355,741 participants were included in the analysis, with a median follow-up of 11.7 years (Q1: 10.8; Q4: 12.8; total person-years: 4,088,024), and 21,612 (6.08%) mortality events. We excluded 146,749 based on the exclusion criteria presented in Fig. 1. Comparison of the baseline characteristics between the included and excluded participants are in Table S1. In general, higher public greenspace was associated with lower-level air pollution (Spearman's correlation: −0.78 with NO_2, -0.65 with $PM_{2.5}$), while higher of domestic garden was moderately associated with higher-level air pollution (spearman's correlation: 0.44 with NO_2, 0.33 with $PM_{2.5}$) (Fig. 2). Participants with more exposure to public greenspace were more likely to be older, have high individual SES, normal BMI, higher level of physical activity, lower levels of depression and social isolation, and less exposed to domestic garden, $PM_{2.5}$ and NO_2 (Table 1). Considering SES, we found that participants with higher individual level SES or living in less deprived areas were more likely to have higher exposure to domestic garden and public greenspace, and some participants with high individual level SES still lived in more deprived area. (Figure S3, S4 and S5).

Exposure to residential greenspace was associated with lower mortality rates (Table 2). Participants with more greenspace had lower rates of all-cause death [domestic garden (per IQR): HR 0.91, 95% CI 0.88–0.94; public greenspace (per IQR): HR 0.90, 95% CI 0.86–0.94] (Table 2, Model 3). The associations were attenuated after adjustment for potential mediators, notably air pollution, social isolation score, depression score, and serum vitamin D levels. We found similar results for cardiovascular disease mortality (domestic garden: HR 0.91, 95% CI 0.84–0.98; public greenspace: HR 0.90, 95% CI 0.82–0.99). After adjusting for the concentration of NO2, the protective association of public greenspace and CVD mortality got weaker (HR 0.95, 95% CI 0.84–1.06), while the protective effect of the domestic garden remained (HR 0.92, 95% CI 0.85–1.00) (Table S2).

Both domestic garden and public greenspace were associated with lower mortality rates in low and medium individual SES participants, but not in people with high individual SES (for high SES, domestic garden: HR 0.95 95% CI: 0.85–1.07; public greenspace: HR 0.92 95% CI: 0.79–1.06; for low SES, domestic garden: HR 0.89 95% CI: 0.85–0.93; public greenspace: HR 0.90 95% CI: 0.85–0.95). Considering area-level

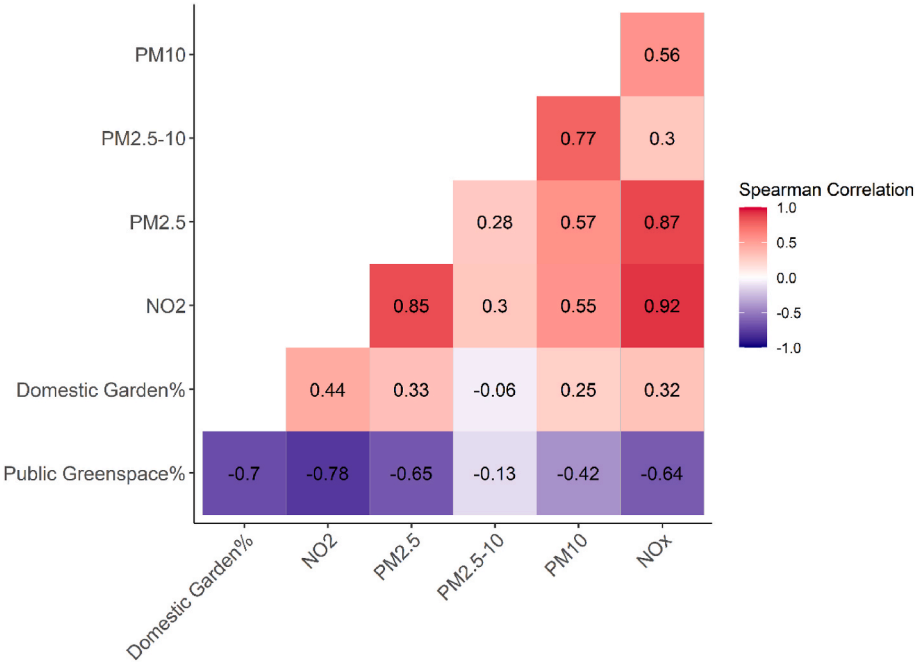

Fig. 2. Correlation matrix of different environmental variables.

Table 2
Associations between greenspace and all-cause mortality by adjustment models.

	All-Cause Mortality			
	Domestic Garden % (per IQR: 15.6%)		Public Greenspace % (per IQR: 32.6%)	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Model 0 (n = 355741)	0.87 (0.85–0.89)	<0.0001	0.85 (0.83–0.88)	<0.0001
Model 0: Crude Model, domestic garden% and greenspace% only				
Model 1 (n = 355741)	0.80 (0.78–0.83)	<0.0001	0.75 (0.73–0.77)	<0.0001
Model 1: age, sex, ethnic background, domestic garden% and greenspace% only				
Model 2(n = 355741)	0.89 (0.86–0.91)	<0.0001	0.88 (0.85–0.91)	<0.0001
Model 2: smoking status, alcohol intake frequency, urbanicity and individual SES additionally				
Model 3 (n = 355741)	0.91 (0.88–0.94)	<0.0001	0.90 (0.86–0.94)	<0.0001
Model 3: IMD and assessment centre additionally.				
+ Physical Activity (n = 298447)	0.92 (0.88–0.95)	<0.0001	0.91 (0.87–0.95)	<0.0001
+ Sleep Quality (n = 298070)	0.90 (0.87–0.94)	<0.0001	0.90 (0.86–0.95)	<0.0001
+ Sedentary Time (n = 344423)	0.91 (0.87–0.94)	<0.0001	0.89 (0.85–0.93)	<0.0001
+ Time Spent Outdoor (n = 332276)	0.91 (0.88–0.94)	<0.0001	0.91 (0.87–0.95)	<0.0001
+ Healthy Diet (n = 351018)	0.91 (0.88–0.94)	<0.0001	0.90 (0.86–0.94)	<0.0001
+ Social Isolation (n = 353758)	0.92 (0.89–0.95)	<0.0001	0.91 (0.87–0.95)	<0.0001
+ Depression (n = 324323)	0.91 (0.88–0.95)	<0.0001	0.90 (0.86–0.94)	<0.0001
+ Neuroticism (n = 292362)	0.90 (0.86–0.93)	<0.0001	0.89 (0.85–0.93)	<0.0001
+ C-Reactive Protein (n = 334090)	0.91 (0.88–0.95)	<0.0001	0.9 (0.86–0.94)	<0.0001
+ ApoB/ApoA (n = 303116)	0.92 (0.89–0.96)	<0.0001	0.9 (0.86–0.95)	<0.0001
+ Vitamin D (n = 320351)	0.92 (0.89–0.96)	<0.0001	0.91 (0.87–0.95)	<0.0001
+ Hb1Ac (n = 332963)	0.91 (0.87–0.94)	<0.0001	0.90 (0.86–0.94)	<0.0001
+ FEV1/FVC (n = 257234)	0.94 (0.9–0.98)	0.004	0.93 (0.89–0.99)	0.015
+ Hypertension (n = 339344)	0.91 (0.88–0.94)	<0.0001	0.91 (0.87–0.95)	<0.0001
+ Diabetes (n = 354928)	0.91 (0.88–0.94)	<0.0001	0.90 (0.86–0.94)	<0.0001
+ BMI (n = 349266)	0.91 (0.88–0.94)	<0.0001	0.90 (0.86–0.94)	<0.0001
+ Waist-Hip Ratio (n = 354574)	0.91 (0.88–0.94)	<0.0001	0.90 (0.86–0.94)	<0.0001
+ Cystatin C (n = 334807)	0.91 (0.88–0.94)	<0.0001	0.89 (0.86–0.94)	<0.0001
+ Noise (n = 351936)	0.91 (0.88–0.95)	<0.0001	0.91 (0.87–0.95)	<0.0001
+ NO_2 (n = 351936)	0.92 (0.89–0.96)	<0.0001	0.94 (0.89–0.99)	0.023
+ $PM_{2.5}$ (n = 338386)	0.92 (0.88–0.95)	<0.0001	0.92 (0.88–0.97)	0.003
+ COPD (n = 353989)	0.92 (0.89–0.95)	<0.0001	0.91 (0.87–0.95)	<0.0001
+ CVD (n = 320360)	0.92 (0.88–0.96)	<0.0001	0.92 (0.87–0.97)	0.0001
+ Cancer (n = 337852)	0.88 (0.85–0.91)	<0.0001	0.89 (0.85–0.93)	<0.0001
+ Kidney Disease (n = 355231)	0.91 (0.88–0.94)	<0.0001	0.9 (0.87–0.95)	<0.0001

SES, domestic garden and public greenspace were found to be associated with lower mortality rates only in participants living in the lowest and highest tertiles of deprivation. We also found that people living in most deprived area and with low SES benefit more from greenspace. The protective associations between greenspace and health was only found in participants living in urban areas (Table 3).

We summarized our exploratory mediation analyses findings in Table 4 and Table S3. Behavioral factors [physical activity and time spent outdoor], psychological factors [social isolation and depression], serum biomarkers and physiological measurement [vitamin D, FEV1/FVC, and ApoB/ApoA], co-morbid diseases [kidney disease and COPD] and environmental factors [$PM_{2.5}$ and NO_2] were chosen for the mediation analysis because of their associations with both greenspace and mortality outcomes. Detailed associations among greenspace, potential mediators and mortality were showed in Tables S4 and S5. The main mediators identified were: NO_2, $PM_{2.5}$, social isolation, FEV1/FVC, vitamin D, kidney disease, depression and time spent outdoor. Physical activity only significantly mediated the association between public greenspace and mortality rate, but not domestic garden. However, more public greenspace and domestic garden were significantly associated with longer sedentary time, obesity and higher waist-hip ratio, indicating negative mediation effects (Table 4, Table S4 and Table S5). The results for CVD mortality were generally similar except for air pollution, because air pollution mediated the association between public greenspace and CVD mortality strongly (Table S3). Inducing the three-way decomposition demonstrated similar results to traditional mediation analysis, except for the NO_2-public greenspace interaction. Public greenspace was found to interact with NO_2, and the uncertainties of estimations were large (Tables S6 and S7). Our sensitivity analyses by assigning the median value for the missing variables or by multiple imputation showed similar results (Tables S8–S13).

4. Discussion

This study showed that UK adults living in areas with more greenspace had lower mortality rates, even after accounting for socio-demographic and potential mediators. Greenspace was shown to be protective mainly among the low and medium individual SES groups. Greenspace was only protectively associated with population health in the least or most deprived areas. Our exploratory mediation analyses suggested that a large proportion of the association between greenspace and mortality might be explained through reducing air pollutant pathways, and amended psychological pathways of depression and social isolation. Compared with domestic gardens, public greenspace was associated with reduced mortality risk mainly due to reduced levels of air pollution. We also found that several biomarkers/physiological measurements, including vitamin D and FEV1/FVC, were involved in the association between greenspace and mortality.

As expected, our study found a relationship between greenspace and mortality, consistent with the existing evidence. A meta-analysis conducted in 2020 reported associations between greenspace exposure and all-cause and stroke mortality with pooled HR of 0.99 and 0.77 (Yu et al., 2021). Another meta-analysis conducted in 2019, identified an inverse association between greenspace and all-cause mortality with pooled HR of 0.96 (Rojas-Rueda et al., 2019). Our study confirmed that in the U.K. Biobank study, people with low individual SES or living in highly deprived area had less availability of greenspace. Furthermore, low SES people experiences higher marginal benefit from relatively limited exposure to greenspace.

Our study took on step further to explore the potential mechanistic framework linking greenspace and mortality. The five proposed pathways were tested explicitly in this study. Environmental and psychological pathways were found to mediate the association between greenspace and mortality most, which was consistent with previous studies (James et al., 2016),(Crouse et al., 2019). There were suggestions that greenspaces appeared to buffer exposure to air pollution (Dadvand et al., 2012) and minimize detrimental health effects of air pollution (Sun et al., 2020),(Ji et al., 2020), although greenspace and air pollution effects appeared to be independent in most studies. Previous studies also found that public greenspaces could offer escape, activities, events, and sociality (Neal et al., 2015), and therefore greenspaces could

Table 3
Association between greenspace and all-cause mortality by subgroup.

	All-cause Mortality					
	Domestic Garden			Public Greenspace		
	HR (95%CI)	P	$P_{interaction}$	HR (95%CI)	P	$P_{interaction}$
Age			0.071			0.371
≤50	0.97 (0.86–1.09)	0.595		0.89 (0.77–1.03)	0.09	
>50	0.90 (0.87–0.93)	<0.0001		0.90 (0.86–0.94)	<0.0001	
Sex			0.041			0.081
Female	0.94 (0.89–1.00)	0.036		0.90 (0.84–0.97)	0.006	
Male	0.89 (0.85–0.93)	<0.0001		0.90 (0.85–0.95)	<0.0001	
Urbanism			0.845			0.923
Urban	0.9 (0.87–0.94)	<0.0001		0.9 (0.86–0.94)	<0.0001	
Others	1.04 (0.84–1.29)	0.715		1.04 (0.8–1.34)	0.793	
SES			<0.0001			<0.0001
Low	0.89 (0.85–0.93)	**< 0.0001**		0.90 (0.85–0.95)	**0.0001**	
Medium	0.93 (0.88–0.98)	**0.01**		0.91 (0.85–0.98)	**0.008**	
High	0.95 (0.85–1.07)	0.391		0.92 (0.79–1.06)	0.255	
IMD[A]			0.12			0.53
Q1	0.90 (0.82–0.97)	**0.011**		0.88 (0.79–0.98)	**0.016**	
Q2	0.98 (0.91–1.06)	0.645		0.97 (0.89–1.06)	0.48	
Q3	0.90 (0.85–0.94)	**< 0.0001**		0.91 (0.86–0.97)	**0.003**	
SES + IMD[B]			/			/
Low + Q1	0.85 (0.72–1.01)	0.058		0.86 (0.7–1.05)	0.14	
Low + Q2	0.95 (0.84–1.07)	0.369		0.92 (0.8–1.06)	0.27	
Low + Q3	0.87 (0.82–0.93)	**< 0.0001**		0.92 (0.85–0.99)	**0.02**	
Medium + Q1	0.88 (0.79–0.99)	**0.036**		0.86 (0.74–0.99)	**0.036**	
Medium + Q2	1.02 (0.91–1.14)	0.709		1.02 (0.89–1.16)	0.782	
Medium + Q3	0.94 (0.86–1.03)	0.178		0.92 (0.83–1.03)	0.163	
High + Q1	1.01 (0.84–1.23)	0.900		0.98 (0.76–1.25)	0.869	
High + Q2	0.90 (0.73–1.12)	0.357		0.90 (0.69–1.17)	0.417	
High + Q3	0.94 (0.75–1.18)	0.601		0.89 (0.65–1.21)	0.45	

HR's adjusted for age, sex, ethnic background, smoking status, alcohol intake frequency, urban and individual SES, IMD, and assessment centre.
A: IMD: index of multiple deprivation, Q1: lowest deprivation, Q3: highest deprivation.
B: Only conducted subgroup analysis are shown, p-interaction values were not interpreted.

restore feelings of social connection and lower cumulative incidence of loneliness (Astell-Burt et al., 2022). Also, air pollution, social isolation, and depression have already been linked to increased mortality risk (Ji et al., 2020),(Lennartsson et al., 2021),(Meng et al., 2020). Our study verified these associations in U.K. Biobank cohort, and through exploratory mediation analyses, we found that greenspace were likely to benefit health by reducing air pollution and improving mental health, which suggested that greenspace had the potential to promote health in different ways. We conducted a three-way decomposition analysis and found that public greenspace could interact with air pollution, suggesting that there were complex interactions and mediations between public greenspace and air pollution. Moreover, we found that air pollution mediated most greenspace effects on CVD mortality, some mediate percentages even exceeded 100%, but the uncertainties of estimations were also large. Previous studies did suggest that improving air quality might be a critical pathway linking the mortality benefits of public greenspaces (Riggs et al., 2021). This suggested a complex relationship among greenspace, air pollution and cardiovascular health, and deserved further verification.

Biomarkers/physiological measurements are often thought of as intermediate outcomes. Here, we showed that vitamin D levels is a statistically significant and key mediator of the association between greenspace and mortality. Previous studies had shown that higher greenspace was associated with having non-deficient vitamin D levels (Zhu et al., 2020), along with observations that higher vitamin D concentration is a marker of better health (Fan, Wang, et al., 2020),(Wan et al., 2021). The precise pathway might be that people with more public and private greenspace were more likely to have more opportunities or behaviorial incentives for exposure to sunlight, and therefore increasing biosynthesis of vitamin D (Zhu et al., 2020), or simply the green view could affect vitamin D concentration through biological processes. Higher greenspace has also been associated with better lung function (Yu et al., 2021),(Fuertes et al., 2020), and we showed that this protective effect might be an important way to reduce mortality risk. Recent studies showed that people with higher greenspace exposure had a lower level of C-reactive protein (Roberts et al., 2021), and lower serum cystatin C level (Xu et al., 2021). However, our analyses indicated that these associations were significantly weakened when adjusting for area-level deprivation (Table S3). The three-way decomposition analyses showed that no interactions among vitamin D, lung function, and greenspace were found in the U.K. Biobank participants. In general, biomarkers or physiological measurements could explain parts of the association between greenspace and mortality, suggesting that greenspace might benefit health through regulating biomarkers.

Inadvertently, we found that higher greenspace was associated with residents having unhealthy risk factors including higher BMI, higher waist-hip ratio and longer sedentary time, which would result in negative mediation effects. Previous studies often suggested that participants with more neighborhood greenspace were at lower or equal risk of higher waist-hip ratio and obesity (Luo et al., 2020),(Nichani et al., 2020),(O'Callaghan-Gordo et al., 2020). Moreover, the existing evidence for association between greenspace and sedentary time was inconsistent: a study in Brazil showed that no association between screen time and greenspace was found (Parajára et al., 2021); a study in Mexico found that greater time in greenspace was associated with decreased sedentary time (Benjamin-Neelon et al., 2019); and another study in Canada found that middle-aged and older adults with more greenspace reported more leisure sedentary time (Klicnik et al., 2022). Here we found that in the U.K., although greenspace could benefit overall health, more greenspace was associated with longer sedentary time and higher risk of obesity. This suggested that sedentary time and obesity could not have mediated the protective association. Therefore, the healthful mechanism of greenspace, when considering population behavior or selection factors, is complicated and needed further research.

We also found public greenspaces and domestic gardens are not

Table 4
Mediation analysis on the relationship between domestic garden & public greenspace on all-cause mortality.

	All-Cause Mortality				
	Association with Outcome[A]	Domestic garden %		Public Greenspace %	
		Association with Greenspace[B]	% Mediated (95% CI)[C]	Association with Greenspace	% Mediated (95% CI)
NO_2 (Increase)	+	–	15.18 (−3.5, 33.9)	–	52.33 (−19,123.6)
Social Isolation (Increase)	+	–	18.46 (9.3–27.6)	–	32.11 (9.8–54.4)
$PM_{2.5}$ (Increase)	+	–	16.94 (−4.0, 37.9)	–	46.13 (−17.2,109.5)
FEV1/FVC <0.7	+	–	12.25 (11.8–12.7)	–	14.85 (14.3–15.4)
Vitamin D (Increase)	–	+	6.97 (2.9–11.1)	+	19.81 (6.8–32.8)
COPD (Incidence)	+	–	3.47 (3.1–3.8)	/	0.32 (−0.1, 0.8)
Kidney Disease (Incidence)	+	–	3.08 (2.7–3.5)	–	3.03 (2.6–3.5)
Depression (Increase)	+	–	2.64 (0.6–4.7)	–	4.02 (0.4–7.6)
ApoB/ApoA (Increase)	–	+	1.79 (0.5–3.1)	+	4.7 (1.1–8.3)
Time Spent Outdoor (Increase)	–	/	0.61 (0.1–1.1)	+	1.19 (0.4–2.0)
Physical Activity (Increase)	–	–	−1.74 (−3.4,-0.1)	+	3.7 (0.1–7.3)
CVD (Incidence)	+	/		+	
Noise (Increase)	/	–		–	
Sleep Quality (Increase)	–	/		/	
Diabetes (With)	+	/		/	
C-Reactive Protein (Increase)	+	/		+	
Neuroticism (Increase)	+	/		–	
Cancer (Incidence)	+	/		/	
Hypertension (With)	/	+		+	
Cystatin C (Increase)	+	/		/	
Hb1Ac (Increase)	+	/		+	
BMI $\geq$ 30	+	+		+	
Healthy diet (Increase)	–	–		–	
Sedentary Time (Increase)	+	+		+	
Waist-Hip Ratio (Increase)	+	+		+	

+ positive association; - negative association;/no significant association (with higher mortality risk).
A. Cox regression models with potential mediators as independent variables. Adjusted for age, sex, ethnic background, smoking status, alcohol intake frequency, urbanism, individual SES, and IMD.
B. Multiple linear or logistic-regression models with the potential mediator as the dependent variable and greenspace as the independent variable. Adjusted for age, sex, ethnic background, smoking status, alcohol intake frequency, urbanism, individual SES, and IMD.
C. Using baseline data of potential mediators to do mediation analyses. Because we pursued one different single mediator model each time, the relative sizes of mediate % were more meaningful than the sum. Potential mediators with insignificant associations with greenspace or with outcome were not chosen to conduct exploratory mediation analysis. Potential mediators with negative mediation effects indicated that such mediators are not parts of the association between greenspace and mortality, and were not presented in this table.

equivalent in promoting health. Although higher exposures to public greenspaces and domestic gardens were both statistically associated with a lower risk of mortality, people living in areas with more public greenspaces often had less access to domestic gardens. A previous study showed that private domestic gardens afforded outside, freedom, gardening, and privacy predominantly, and public greenspaces mainly provided nature, livability, and well-being (Coolen & Meesters, 2012). We found that public greenspace was associated with reduced mortality risk mainly due to reduced levels of air pollution. Moreover, previous studies already found that increased physical activity mediated the beneficial association between greenspace and health (Almanza et al., 2012),(Hu et al., 2022). However, most studies were based on NDVI and did not consider different types of greenspace. Here we found that higher public greenspace was associated with increased physical activity and significantly mediated the protective association between public greenspace and mortality, while higher domestic garden was associated with decreased physical activity. Therefore, public greenspaces and domestic gardens are not just simple substitutes for each other, and they might have relatively different mechanisms to improve health.

Our study also found that green space benefits lower-SES individuals than affluent people, consistent with a previous meta-analysis (Rigolon et al., 2021). Even if people with higher level SES were more likely have better accessibility to public greenspace and domestic garden, we found that more availability to greenspace was associated with better health in participants with low SES or living in most deprived area. This phenomenon can be explained because high-income populations have several health preventive strategies that depend not only on exposure to greenspace, but also on other factors such as access to medical services and preventive health (Asri et al., 2020). People with low SES might also benefit from greenspace by reducing harmful impacts of air pollutants (Son et al., 2021). Previous researches found that participants with a lower level of education might benefit more from residential greenspace, partly because they tended to spend more time near home and thus were more influenced by neighborhood environment (Huang et al., 2019). Moreover, we found that greenspace showed more beneficial associations only in the most and least deprived areas. This could be explained by the multiple ways greenspace could promote health. A previous study suggested that exposure of SO_2 could mediate the association between area level SES and health (Chaparro et al., 2018). Another study showed that higher levels of deprivation were associated with lower levels of walking and lower access to greenspace, and therefore could modify the association between greenspace and health (Pearson et al., 2014). In general, people with low socio-economic status had lower availability to, but benefited more from greenspace in the U.K.. Therefore, future research should focus on the associations among individual SES, area-level deprivation and activity-influencing residential environment.

This study design has some limitations due to the observational study nature. First, we excluded a relatively sizable proportion of the participants in our analysis, and the baseline characteristics between the included and excluded participants were relatively different. The excluded participants were more likely to have more death cases, and less public greenspace and domestic garden. Therefore, we might underestimate the association between greenspace and mortality. Our sensitivity analyses could not fully address this imbalance. Second, mediation analyses needed assumptions of the causal relationship between variables. In addition, as for temporal relationships in causal

mediation analysis, most of our findings were based on baseline-measured data, and longitudinal analysis along with replication in other cohorts were needed to establish causal and long-term relationships. Third, since we evaluated each single mediator model one at a time, we did not consider mediator-mediator interaction in this exploratory analysis. Further researches using advanced mediation analysis approaches were needed to establish causal pathways. Fourth, although GLUD 2005 provided different types of 'greenspace', they offered the only national coverage of detailed small area data based on a limited number of data sources and a streamlined methodology, and was much less detailed. We expected to use satellite-derived metrics with a higher spatial resolution to confirm our findings in future studies. Fifth, although we used two measures of greenspace, they were assessed using proportion of vegetation area cover. Therefore, they could not differ the construction and type of green space, as open grass and tree canopy could have different health effects (Astell-Burt et al., 2021). Therefore, studies utilizing street view greenness should be conducted in the future. Finally, other environmental variables not included in the analysis were exposures to extremes of temperature and amounts of damaging ultraviolet radiation, which might be mediators on the associations between greenspace and adverse health outcomes (He et al., 2020),(Wolf et al., 2020).

5. Conclusion

In the U.K. Biobank, we found public greenspace and domestic garden exposures are associated with higher health benefits. The association is modified by SES; we saw increasing marginal utility on health benefits for those with lower SES who also had lower level exposure to greenspace. Our exploratory mediation analyses found reduction in air pollution, lessening social isolation, regulating vitamin D levels, and relieving depression to be the likely pathways in which greenspace conferred health benefits. We also found that public greenspaces and domestic gardens had similar albeit not exactly the same mechanisms to improve health, and thus are not substitutes of each other. Using a large cohort, our findings elucidated the potential pathways of greenspace on health, and provided evidence of inequities of greenspaces access in conjunction with socioeconomic factors on population health. Urban greenspace may become a tool to prevent mortality for urban development and city planning, our research findings indicate the highest marginal effect of greenspace are among people with the least resources.

Contributors

SW and JSJ conceived and designed the study design. SW and JSJ did the statistical analysis. SW and JSJ drafted the manuscript. DRR, JP, CR, and PJ revised the manuscript and helped interpret data. All authors contributed to the interpretation of findings, provided revisions to the manuscript, and approved the final manuscript.

Ethics approval

UK Biobank received ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written informed consent before enrolment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki. Direct dissemination of the results to participants is not possible/applicable.

Declaration of competing interest

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2022.101194.

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