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Associations of residential walkability and greenness with arterial stiffness in the UK Biobank

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ABSTRACT

Background: Arterial stiffness is a key non-invasive marker of early vascular ageing, however, little is known of its associations with urban built environment. We examined the associations of objectively-measured residential walkability and greenness with arterial stiffness in a large UK-wide population cohort.

Methods: We employed data from the baseline UK Biobank cohort comprising adult participants recruited over the period of 2006 to 2010. Residential walkability index, defined as a function of density (residential, retail and public transit), street-level design, and destination accessibility was measured using a 1-Km dwelling catchment, while greenness was modelled as the mean Normalized Difference Vegetation Index (NDVI) of 0.5-metre resolution assessed within a 0.5-Km catchment. Arterial stiffness index (ASI) was measured non-invasively from the pulse waveform. Linear regression models were developed to examine associations of walkability and greenness with arterial stiffness. Restricted cubic spline (RCS) models were developed to examine dose–response relationships. We also examined effect modifications by sex and age, as well as the interaction effect of greenness and walkability.

Results: This cross-sectional study used a target sample of 169,704 UK Biobank participants aged $\geq$ 39 years. After full adjustments, in reference to the lowest walkability exposure quartile, those in the highest were associated with lower ASI ($\beta = -0.083$ m/s, 95% CI: −0.14 to −0.03, $p = 0.005$). Participants in the third and fourth NDVI greenness exposure quartiles were also associated with lower ASI ($\beta = -0.074$ m/s, −0.14 to −0.01, $p < 0.020$ for the third and $\beta = -0.293$ m/s, −0.36 to −0.23, $p < 0.001$ for the fourth quartiles in reference to the first). The inverse association between NDVI greenness and ASI was more pronounced among women ($p < 0.001$), older adults ($p = 0.011$) and among participants in the highest walkability quartile ($p < 0.001$).

Conclusion: Designing more walkable and greener residential environments can be a preventive intervention aimed at lowering the population distribution of vascular ageing and associated cardiovascular risks.

1. Introduction

Cardiovascular diseases (CVDs) constitute the leading cause of global mortality, while high systolic blood pressure is the leading risk factor of global attributable deaths and the second leading risk factor of DALYs (Murray et al., 2020; Roth et al., 2018). Early vascular ageing is an important non-invasive predictor of cardiovascular risks and mortality, with better predictive potential than existing circulating biomarkers such as blood pressure, glycemia and lipids which are unstable in nature and provide only a snapshot of CVD risks (Lakatta, 2003; Nilsson et al., 2008). It can thus be a key criteria for early CVD screening and intervention (Nilsson et al., 2009). Arterial stiffness is a primary marker of early vascular ageing and a cumulative predictor of CVD events (Laurent et al., 2006). Arterial stiffness refers to the capacity of the arteries to expand and contracts in response to cardiac flow; stiffer arteries being an indicator of long-lasting arterial wall damage resulting in luminal dilation due to increased collagen deposition, wall thickening and combined fragmentation and degeneration of elastin (Said et al., 2018). Arterial stiffness has been directly associated with coronary atherosclerosis (Duprez and Cohn, 2007; Weber et al., 2004), CVD events (Blacher and Safar, 2005; Mattace-Raso et al., 2006), inflammatory disorders (Dregan, 2018; Zanoli et al., 2016), cognitive decline

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(Scuteri et al., 2007) and dementia (Hughes et al., 2018).

With increasing urbanization and approximately 70% of the global population projected to reside in urban zones by 2050, the role of built environmental exposures and associated non-pharmacological interventions in the prevention of vascular stiffening and cardiovascular diseases have become more relevant. A few previous studies have established the role of lifestyle-level factors, such as physical activity (Gando et al., 2010) and healthy diet (Pase et al., 2010), in slowing the progression of arterial stiffening. The role of built environment as a modifiable factor is also becoming acknowledged. An ecological-scale study showed an increased level of mean pulse wave velocity among individuals residing in urbanized areas in comparison to rural residents (urban–rural measured by satellite-derived land cover), and among those living in close proximity to the city centre (Corlin et al., 2018). Another study reported that higher satellite-derived measures of impervious surface area and night-time light was associated with elevated blood and central pulse pressure (Lane et al., 2017). Urban environmental exposures such as proximity to major roadway (Ljungman et al., 2018) and noise pollution (Foraster et al., 2017) have also been found to be associated with higher arterial stiffness. Air pollution exposure has also been related to arterial stiffness but the evidence is mixed. One study found changes in pulse wave velocity with higher levels of exposures to NO_2 and SO_2 (Lenters et al., 2010), while two other studies reported null associations between exposure to ambient air pollution such as fine particulates $PM_{2.5}$ and arterial stiffness (Ljungman et al., 2018; O'Neill et al., 2011).

Improving neighbourhood walkability and greenspace has become a widely adopted instrument in pursuit of the UN Sustainable Development Goal of achieving population health and wellbeing by 2030 via creating cities that are inclusive, safe, and sustainable. It has been suggested that well-designed built environment (with attributes such as walkability and green exposure) act as modifiable factors inducing positive lifestyle behaviours, such as higher levels of physical activity (enhanced cardio-respiratory fitness), social interaction and sense of community, thereby being beneficial upon cardiovascular health (Koohsari et al., 2020; Sallis et al., 2012; WHO, 2016, 2018; Xie et al., 2021; Zang et al., 2019). However, evidence establishing associations between beneficial built environment attributes and reduced arterial stiffening is still scant and inconsistent. Previous studies have reported on the inverse associations of neighbourhood level walkability with blood pressure and hypertension (Sarkar et al., 2018a) and active commuting and cardiovascular mortality (Celis-Morales et al., 2017) but there have, to our knowledge, been no studies examining associations with arterial stiffness. Furthermore, there has been no prior study examining simultaneously the association of neighbourhood walkability and greenness with arterial stiffness and potential interactions. Owing to pressure fluctuations, traditional measures of brachial blood pressure may not detect cardiovascular risks precisely (Franklin, 2008). One study examining associations between satellite-derived residential greenness and pulse wave velocity, reported null findings (de Keijzer et al., 2020). Another study found that lower exposure to neighbourhood greenness was associated with elevated central pulse pressure (Lane et al., 2017). These previous studies on links between built environment and arterial stiffness have been small scale in homogeneous settings and used built environment measures of coarse resolution, limiting robustness and statistical power. In the present study, we leverage a large-scale UK-wide cohort to examine associations between arterial stiffness and neighbourhood walkability and greenness measured at high resolution. We also conducted sub-group level analyses to examine effect modification by age and sex. We further tested for interaction effect of walkability and greenness upon arterial stiffness.

2. Methods

2.1. Study participants

We used data from the UK Biobank, a prospective cohort aiming to study and understand prevention, diagnosis and treatment of chronic diseases including cardiovascular diseases among adults. Around 9.2 million potential participants from the UK National Health Service Register were contacted and approximately half-a-million Britons across 22 UK cities (with a response rate of 5.5%) were recruited over the period between March 2006 and December 2010. The cohort was extensively phenotyped and genotyped, via participants responding to a touch-screen questionnaire; a brief computer-assisted interview; examination for physical and functional measures; and blood, urine, and saliva samples (Sudlow et al., 2015). Detailed data including sociodemographics, lifestyle, mental health battery, clinical diagnosis and treatment, genetics, imaging and physiological biomarkers from blood and urine samples were also collected. The cohort protocol can be found elsewhere (UK Biobank, 2007). All participants provided electronic informed consent and UK Biobank received ethical approval from the - North West Multi-centre Research Ethics Committee (MREC) covering the whole of UK.

2.2. Outcome

Our primary outcome was pulse wave arterial stiffness index (ASI), measured non-invasively during a participant's visit to a UK Biobank Assessment Centre. The detailed assessment protocol is available elsewhere (UK Biobank, 2011). Briefly, pulse waveform was taken by clipping a photoplethysmograph transducer (PulseTrace PCA 2^{TM}, CareFusion, USA) to the rested participant's finger (any finger or thumb, preferably the index finger). Participants were asked to breathe in and out slowly five times in a relaxed fashion and readings were taken over a 10–15 s duration. ASI acts as a clinical marker of large artery stiffness and has been shown to be moderately correlated with pulse wave velocity and augmentation index. ASI is measured from a single peripheral pulse waveform. The carotid-to-femoral pulse transit time was calculated from the dicrotic waveform as the time difference between a forward component when the pressure is transmitted from the left ventricle to the finger and a reflected or backward component as the wave is transmitted from the heart to lower body via the aorta (Woodman et al., 2005). ASI was calculated in metres per second as: H/PTT, where H is the participant's height, and PTT is the pulse transit time or the peak-to-peak time between the first (systolic) and second (diastolic) wave peaks in the dicrotic waveform (Woodman et al., 2005). We excluded extreme outlier ASI values from our analyses defined as mean ± 5*standard deviation.

2.3. Urban exposures – Walkability and greenness

We developed the UK Biobank Urban Morphometrics Platform (UKBUMP), an individual-level built environment database of health-specific urban exposures within residential street catchments of UK Biobank participants' geocoded home address (catchments being measured at various spatial scales). Cohort participant's home address was first geocoded in terms of X, Y coordinates and spatial and network modelling were performed upon multiple UK-wide dataset (including UK-wide AddressBase Premium data of Ordnance Survey GB (OS GB), remotely sensed data, digital terrain topographical models and other datasets), and subsequently linked to anonymized UK Biobank participant IDs. The spatial database comprised approximately 750-plus built environment exposure metrics of density, destination accessibility, design and morphology, and physical environment; details elsewhere

(Sarkar et al., 2015a).

We developed a walkability index to characterize walkability at neighbourhood level, measured using a 1 Km street network catchment (equivalent to approximately 10-minute walk) based on each UK Biobank participant's geocoded home address. As described previously (Sarkar et al., 2018a), the walkability index was defined as a function of density (residential, retail and public transit), street-level design, and destination accessibility. These three dimensions reflect findings from prior literature linking urban design attributes to utilitarian walking and physical activity (Glazier et al., 2014). UK-wide land use and street centerlines were extracted from the Ordnance Survey AddressBase Premium and Integrated Transport Network database and the densities (in units/Km^2) were expressed as the number of residential units, retail outlets and public transport stops within 1-Km street buffer of a participant's geocoded home address: $D_i^{1Km} = \frac{n_{lu}}{A}$; where D_i^{1Km} represents the density of a land use (residential/retail/public transport) for participant i within 1-Km street catchment, A is its area and n_{lu} is the number of units of a specific land use. Residential density included the combined density of detached, semi-detached, terraced housing units and self-contained flats. Similarly, the number of retail outlets and public transport (bus stops and train stations) were measured. Street-level configuration, a proxy of movement density was modelled as the graph-theoretic metric of betweenness centrality, a measure of the through-movement potential at this scale based on the topology of street networks. It is proportional to the simulated count of movements passing through a link from and to all other parts of the network, assuming that journeys in the network follow the shortest angular path connecting any pair of nodes in the network. We extracted and cleaned approximately 5 million street links within a 50-kilometre radius of each of the UK Biobank assessment centres and performed network analyses with the spatial design network analysis (sDNA) software (Cooper et al., 2012; Sarkar et al., 2017). Betweenness was modelled at multiple spatial scales between 400 m to 50 Km, to capture micro-, meso- and macro-level effects of surrounding urban features on psycho-social behaviour. A second street network measure, destination accessibility, was defined as the mean street distance of a participant's home address to eleven common destinations including community hall/facility (land use code CC04), community library (CL03), recreation and leisure (CL07), educational institutions (CE01, CE02, CE03, CE04), retail service agents and post office (CR02), pubs/bars/night clubs (CR06), restaurant/cafeteria (CR07) and places of worship (ZW). It was measured in ArcGIS Network Analyst using the nearest facility algorithm and expressed as:

$$DA_i = \frac{\sum (ND_{CC04} + ND_{CL03} + ND_{CL07} + ND_{CE01} + ND_{CE02} + ND_{CE03} + ND_{CE04} + ND_{CR02} + ND_{CR06} + ND_{CR07} + ND_{ZW})}{11}$$

where DA_i represents the destination accessibility for participant i and ND is street network distance to the nearest destination. The metrics of density, design and destination were transformed to deciles and neighbourhood walkability within a 1-Km catchment for a participant i was defined as:

$$Walkability_i^{1Km} = [Resid_{dec} + Retail_{dec} + PT_{dec} + Betweenness_{dec} + (10 - Destinations_{dec})];$$

where '$Resid_{dec}$', '$Retail_{dec}$', 'PT_{dec}' and '$Betweenness_{dec}$' represent respectively the standardized deciles of residential unit density, retail density, public transport density, and street-level betweenness, with higher values indicating higher contributions to walkability. '$Destinations_{dec}$' represents deciles of destination accessibility and was negatively coded, given an inverse relationship between street distance to destinations and walkability. The composite index ranges between 5 and 50, with larger values representing greater walkability.

We modelled exposure to residential greenness using Normalized Difference Vegetation Index (NDVI), an objective index of relative overall greenness associated with vegetation cover derived from remotely sensed data and used as a standard green metric in previous epidemiological studies (Rhew et al., 2011). NDVI acts as an indicator of green quality and intensity and is measured from the differential spectral signatures of chlorophyll in healthy vegetation; i.e. absorbance and reflectance in the visible (red) and near-infrared wavelengths of the electromagnetic spectrum (Weier and Herring, 2000). The difference is captured as:

$$NDVI = \frac{(NIR - RED)}{(NIR + RED)};$$

where NIR and RED are detected spectral reflectance in near-infrared and red wavelength regions. The index ranges between −1 and 1, with higher values indicating higher density of healthy green vegetation. In this study, NDVI was measured from 0.50-metre resolution multispectral colour infrared (CIR) data collected by Bluesky (Bluesky International Limited, UK) and derived from Vexcel UltraCamD and Leica ADS4 sensors, with spatial accuracy of 1 m, mounted underneath survey aircraft. After excluding large water bodies, summer-time images of similar temporal scales were extracted and mean NDVI within a 0.5-kilometre radial catchment of UK Biobank participants' home address were measured. The criteria of 0.5Km catchment was chosen from our previous studies in the cohort (Sarkar, 2017; Sarkar et al., 2018b) and other research reports (Sarkar et al., 2015b; Villeneuve et al., 2012; Wolch et al., 2011).

Among the other physical environment variables, terrain variability was measured from a 5-m resolution BlueSky digital terrain model in terms of standard deviation in slope within a 0.5-kilometre residential catchment. Traffic intensity in the road nearest to the residential address was measured from the traffic count data of the Road Traffic Statistics Branch of Department of transport and expressed as the average total number of motor vehicles per day.

2.4. Statistical analysis

Linear regression models with robust estimators were developed to examine the associations of walkability and NDVI greenness with arterial stiffness coded as a continuous variable. Separate single-exposure models were constructed with walkability and NDVI greenness coded as continuous (per interquartile range (IQR) increment) as well as categorical (four-factor quartile) variables. The selection of model covariates and confounders (socio-demographics, lifestyle and diet, comorbidities and family history of disease and other environment) were informed *a priori* by assumed causal relationship and literature on

cardiovascular risk factors (de Keijzer et al., 2020; Lane et al., 2017; Piepoli et al., 2016). They were introduced sequentially in batches after accounting for a parsimonious fit. We assessed multi-collinearity at each stage using variance inflation factors (VIF). Model 1 adjusted for socio-odemographic variables: sex (coded as female and male); age-groups (<50, 50–59 and ≥ 60 years); ethnicity(British and others); highest educational attainment (five-factor variable coded as none; O levels/GCSEs/CSEs; A levels/AS levels; NVQ/HND/HNC/other professional; and college or university degree); employment status (employed; retired; and unemployed/home maker/others); and average household income before tax (four-factor variable coded as <£18,000, £18,000–30,999, £31,000–51,999, ≥£52,000). Model 2 additionally adjusted for lifestyle and dietary risk factors including smoking status (three-factor variable coded as never, previous and current); alcohol intake frequency (never/special occasions only, 1–2 times a week, 3–4 times a week, daily/almost daily); residential tenureship (own outright, own with mortgage, rent); number of stressful life events (coded as none, 1, 2 and ≥3); salt intake (four-factor variable coded as never/rarely, sometimes, usually, always); processed meat intake (never, <1 times a week or once a week, 2–4 times a week, 5–6 times a week or more); and fresh fruits intake (none, ≤1 table spoonful, 2 table spoonful, and ≥3 table spoonful). Model 3 further adjusted for doctor-diagnosed comorbidities and family history of diseases comprising body-mass index (three-factor variable coded as normal weight, overweight, obese); cardiovascular disease status (four factor variable coded as none, only high blood pressure, only heart attack/angina/stroke, and high blood pressure and heart attack/angina/stroke); diabetes diagnosed by doctor (none, yes); antihypertensive medication use (none, yes); and parental cardiovascular diseases (three-factor variable coded as none, either parent, both parents). The fully-adjusted model (Model 4) additionally adjusted for other environment variables, namely terrain variability categorized as quartiles; traffic intensity on the nearest road (≤500, >500 vehicles/day); and Townsend's deprivation index expressed as quintiles (Norman, 2010). We also developed multiple-exposure models with both walkability and NDVI greenness in the same models, using the same schema for adjustment.

As further sensitivity analyses, we performed the following analytical procedures: (1) We reran our multiple-exposure models employing multiple imputation by chained equations (MICE) in Stata to impute for missingness across covariates. For all participants with data on ASI, walkability and NDVI greenness (N = 135,447), we included all covariates, exposures and outcome to impute missing data on ethnicity, highest educational attainment, employment status, household income, smoking status, alcohol consumption, stressful life events, residential tenureship, salt intake, processed meat intake, fresh fruit intake, BMI status, cardiovascular disease status, antihypertensive medication use, parental cardiovascular diseases, terrain, traffic intensity and Townsend's deprivation index. A set of 20 imputation datasets were created (Sterne et al., 2009). (2) We reran the fully-adjusted models for a subset of vulnerable participants who had hypertension, cardiovascular diseases or who were taking blood pressure medication. (3) We examined effect-modifications by sex and age. To disentangle the effect of walkability upon the association between green exposure and ASI, we also tested the interaction between walkability and NDVI greenness. (4) We further tested the interactive effects of walkability and income groups on the association between greenness and ASI. (5) We developed restricted cubic spline (RCS) models to examine dose–response relationship that reveal variations in arterial stiffness across walkability and greenness exposure continuums, with Harrell's knots being placed at 10, 50 and 90 percentiles of the exposure data. (6) As an additional analysis, we disaggregated the effects in to between-city and within-city effects (Miller et al., 2007). To examine the between-city effect, we estimated the city-mean exposure by averaging exposure values for all participants residing in the same city. For the within-city effect, we subtracted the city-mean exposure from individual exposure to estimate the deviation of an individual's exposure value to the city-mean value. Both variables were

Table 1
Characteristics of UK Biobank target sample (N = 169,704).

Participant characteristics	N	
Socio-demographics:		
Age in years (Mean, SD)	169,704	56.8 (8.2)
Gender N (%): Female	169,704	91,993 (54.2)
Male		77,711 (45.8)
Ethnicity N (%): British	168,590	142,502 (84.5)
Others: (Black, Asian, Irish, others)		26,088 (15.5)
Highest educational qualification N (%): None	167,429	26,053 (15.6)
College or University degree		56,672 (33.9)
O levels/GCSEs/CSEs		45,542 (27.2)
A levels/AS levels		19,079 (11.4)
NVQ/HND/HNC/Other professional		20,083 (12.0)
Employment status N (%): Employed	167,503	93,890 (56.1)
Retired		58,388 (34.9)
Unemployed, home maker, others		15,225 (9.1)
Household income: <£18 000	144,791	32,748 (22.6)
£18 000–£30 999		36,878 (25.5)
£31 000–£51 999		37,327 (25.8)
≥£52 000		37,838 (26.1)
Lifestyle & dietary risk factors:		
Smoking status N (%): Nonsmoker	168,646	93,230 (55.3)
Previous smoker		58,338 (34.6)
Current smoker		17,078 (10.1)
Alcohol intake frequency N (%): Never/special occasions only	169,154	54,989 (32.5)
1–2 times/week		42,422 (25.1)
Daily − 3–4 times/week		71,743 (42.4)
Residential tenureship N (%): Own outright	166,561	88,709 (53.3)
Mortgage		59,424 (35.7)
Rent		18,428 (11.1)
Number of stressful life events N (%): None	167,969	89,996 (53.6)
One		55,895 (33.3)
Two		17,394 (10.4)
>Two		4,684 (2.8)
Salt added to food N (%): Never/rarely	169,269	94,129 (55.6)
Sometimes		47,431 (28.0)
Usually		19,443 (11.5)
Always		8,266 (4.9)
Processed meat intake N (%): None	168,845	16,487 (9.8)
Once a week		99,065 (58.7)
2–4 times a week		46,261 (27.4)
>4 times a week		7,032 (4.2)
Fresh fruit intake N (%): None	168,532	10,262 (6.1)
≤ one table spoonful		50,549 (30.0)
Two table spoonful		47,542 (28.2)
≥ three table spoonful		60,179 (35.7)
Co-morbidities:		
Body-mass index status N (%): Normal weight	169,493	55,873 (33.0)
Overweight		71,638 (42.3)
Obese		41,982 (24.8)
Cardiovascular status N (%): None	168,851	118,273 (70.1)
Only high blood pressure		41,041 (24.3)
Only heart attack/angina/stroke		4,482 (2.7)
High blood pressure and heart attack/angina/stroke		5,055 (3.0)
Diabetes N (%): None	169,704	159,834 (94.2)
Yes		9,870 (5.8)
Antihypertensive medication use N (%): None	169,411	133,186 (78.6)
Yes		36,225 (21.4)
Parental cardiometabolic diseases N (%): none	148,339	39,679 (26.8)
Either parent		69,058 (46.6)
Both parents		39,602 (26.7)
Physical environment:		
Terrain variability within 500 m (degrees) N (%): Q_1 (Low)	163,114	49,367 (30.3)
Q_2		43,584 (26.7)
Q_3		36,388 (22.3)
High (Q_4)		33,775 (20.7)
Traffic intensity in the nearest road (count) N (%): ≤500	167,571	157,393 (93.9)
>500		10,178 (6.1)
Townsend deprivation index (Mean, SD)	169,431	−1.1 (3.0)

(*continued on next page*)

Table 1 (*continued*)

Participant characteristics	N	
Exposures		
Neighbourhood walkability[a] (1000 m catchment) (Mean, SD)	163,394	27.2 (10.0)
Greenness[b] (500 m catchment) (Mean NDVI, SD)	135,863	0.2 (0.1)
Outcomes		
Arterial stiffness index, m/s (Mean, SD)	169,704	9.3 (3.1)

[a] Neighbourhood walkability composite index ranges between 5 and 50, with larger values representing greater walkability.

[b] Greenness ranges between −1 and 1, with higher values indicating higher density of green vegetation.

included in the fully adjusted model. All analyses were conducted in Stata 16. Beta (β) with two-tailed 95% confidence intervals are presented.

3. Results

Our target sample comprised 169,704 UK Biobank participants recruited between April 04, 2006 and October 1, 2010, comprised of individuals with valid data on arterial stiffness after excluding extreme values (n = 82). After excluding participants with missing data on sociodemographic covariates (n = 26,819), lifestyle and dietary risk factors (n = 2,403), comorbidities and family history (15,986), other environment (5,534) and our primary exposures of walkability and greenness (19,967), N = 98,995 participants remained for the fully-adjusted complete case analyses. The mean age of our target sample was 56.8 years (SD = 8.2), of which 91,993 (54.2%) were female. Mean arterial stiffness index (ASI) was 9.3 m/s (SD = 3.1). 24.3% of the target sample had high blood pressure, 2.7% suffered from heart attack or angina or stroke, while 3.0% had high blood pressure as well as cardiovascular disease. Mean walkability index within a 1000-metre street catchment was 27.2 (SD = 10.0, IQR = 16.0). Mean greenness measured by NDVI within a 0.5 Km buffer was 0.2 (SD = 0.1, IQR = 0.24). The Pearson's correlation coefficient between walkability and NDVI greenness was −0.04 for the full sample. The descriptive characteristics of our UK Biobank target sample are shown in Table 1.

Results of the single exposure regression models are presented in Tables 2a and 2b. After full adjustments, each IQR increment in walkability was inversely associated with arterial stiffness (β = −0.060 m/s; 95% CI: −0.09 to −0.03; p < 0.001). Each IQR increment in NDVI greenness was also inversely associated with ASI (β = −0.222; −0.25 to −0.19; p < 0.001). These results remained consistent in the models using categorical exposures. In reference to the lowest walkability quartile, those in the highest quartile had lower ASI (β = −0.074 m/s, −0.13 to −0.02, p = 0.006), while participants in the third and fourth NDVI greenness quartiles had lower ASI (β = −0.081, −0.14 to −0.02, p = 0.011 in the third and β = −0.288, −0.35 to −0.22, p < 0.001 for the fourth in reference to the first NDVI quartile). The results of multiple-exposure models, including both walkability and NDVI greenness, are presented in Table 3. Each IQR increment in walkability and NDVI greenness was associated with lower ASI (β = −0.07 m/s, −0.10 to −0.04, p < 0.001 and β = −0.229, −0.26 to −0.20, p < 0.001

Table 2a
Association between residential walkability within 1-Km street catchment and arterial stiffness among UK Biobank participants.

	Model 1[a] N = 137,636 β (95% CI) p-value	Model 2[b] N = 135.357 β (95% CI) p-value	Model 3[c] N = 119,985 β (95% CI) p-value	Model 4[d] N = 118,680 β (95% CI) p-value
Walkability index (per IQR increment)	−0.039 (−0.06,−0.01) 0.002	−0.064 (−0.09,−0.04) < 0.001	−0.056 (−0.08,−0.03) < 0.001	−0.060 (−0.09,−0.03) < 0.001
Walkability index quartiles: Low (Q_1)–Ref	1	1	1	1
Q_2	0.010 (−0.04,0.06) 0.655	0.003 (−0.04,0.05) 0.888	0.025 (−0.02,0.07) 0.301	0.026 (−0.02,0.08) 0.290
Q_3	−0.019 (−0.06,0.03) 0.394	−0.043 (−0.09,0.00) 0.059	−0.035 (−0.08,0.01) 0.139	−0.032 (−0.08,0.02) 0.197
High (Q_4)	−0.054 (−0.10,−0.01) 0.018	−0.091 (−0.14,−0.05) < 0.001	−0.073 (−0.12,−0.03) 0.002	−0.074 (−0.13,−0.02) 0.006

Note: Separate models are constructed for exposures coded as continuous variable and as categorical variable.

[a] Model 1 adjusted for sociodemographic variables (sex, age-groups, ethnicity, highest educational attainment, employment status and average household income before tax).

[b] Model 2 adjusted for sociodemographic variables plus lifestyle and dietary risk factors (smoking status, alcohol intake frequency, residential tenureship, number of stressful life events, salt intake, processed meat intake, and fresh fruits intake).

[c] Model 3 adjusted for sociodemographic variables, lifestyle and dietary risk factors plus doctor-diagnosed comorbidities and family history of diseases (body-mass index, cardiovascular disease status, diabetes diagnosed by doctor, antihypertensive medication use, and parental cardiovascular diseases).

[d] Model 4 adjusted for sociodemographic variables, lifestyle and dietary risk factors, doctor-diagnosed comorbidities and family history of diseases plus other environment variables (terrain variability, traffic intensity on the nearest road and Townsend's deprivation index).

Table 2b
Association between residential greenness within 500 m catchment and arterial stiffness among UK Biobank participants.

	Model 1[a] N=114,555 β (95% CI) p-value	Model 2[b] N=112,766 β (95% CI) p-value	Model 3[c] N=100,038 β (95% CI) p-value	Model 4[d] N=99,206 β (95% CI) p-value
NDVI greenness (per IQR increment)	−0.217 (−0.25,−0.19) <0.001	−0.213 (−0.24,−0.18) <0.001	−0.22 (−0.25,−0.19) <0.001	−0.222 (−0.25,−0.19) <0.001
NDVI greenness quartiles: Low (Q_1)–Ref	1	1	1	1
Q_2	0.024 (−0.04,0.09) 0.443	0.031 (−0.03,0.09) 0.331	0.028 (−0.04,0.09) 0.399	0.027 (−0.04,0.09) 0.424
Q_3	−0.082 (−0.14,−0.02) 0.005	−0.075 (−0.13,−0.02) 0.012	−0.068 (−0.13,−0.01) 0.030	−0.081 (−0.14,−0.02) 0.011
High (Q_4)	−0.278 (−0.34,−0.22) <0.001	−0.275 (−0.33,−0.22) <0.001	−0.285 (−0.35,−0.22) <0.001	−0.288 (−0.35,−0.22) <0.001

Note: Separate models are constructed for exposures coded as continuous variable and as categorical variable.

[a] Model 1 adjusted for sociodemographic variables (sex, age-groups, ethnicity, highest educational attainment, employment status and average household income before tax).

[b] Model 2 adjusted for sociodemographic variables plus lifestyle and dietary risk factors (smoking status, alcohol intake frequency, residential tenureship, number of stressful life events, salt intake, processed meat intake, and fresh fruits intake).

[c] Model 3 adjusted for sociodemographic variables, lifestyle and dietary risk factors plus doctor-diagnosed comorbidities and family history of diseases (body-mass index, cardiovascular disease status, diabetes diagnosed by doctor, antihypertensive medication use, and parental cardiovascular diseases).

[d] Model 4 adjusted for sociodemographic variables, lifestyle and dietary risk factors, doctor-diagnosed comorbidities and family history of diseases plus other environment variables (terrain variability, traffic intensity on the nearest road and Townsend's deprivation index).

Table 3
Associations of residential walkability and greenness with arterial stiffness among UK Biobank participants in multiple-exposure analyses.

	Model 1[a] N = 114,313 β (95% CI) p-value	Model 2[b] N = 112,529 β (95% CI) p-value	Model 3[c] N = 99,827 β (95% CI) p-value	Model 4[d] N = 98,995 β (95% CI) p-value
Walkability index (per IQR increment)	−0.042 (−0.07,−0.01) 0.002	−0.065 (−0.09,−0.04) < 0.001	−0.055 (−0.08,−0.03) < 0.001	−0.07 (−0.10,−0.04) < 0.001
Walkability index quartiles: Low (Q_1)–Ref	1	1	1	1
Q_2	0.018 (−0.03,0.07) 0.470	0.013 (−0.04,0.06) 0.601	0.039 (−0.01,0.09) 0.149	0.037 (−0.02,0.09) 0.169
Q_3	−0.015 (−0.06,0.03) 0.554	−0.037 (−0.09,0.01) 0.143	−0.029 (−0.08,0.02) 0.268	−0.032 (−0.09,0.02) 0.243
High (Q_4)	−0.048 (−0.10,0.00) 0.054	−0.086 (−0.14,−0.04) 0.001	−0.062 (−0.11,−0.01) 0.017	−0.083 (−0.14,−0.03) 0.005
NDVI greenness (per IQR increment)	−0.219 (−0.25,−0.19) < 0.001	−0.217 (−0.25,−0.19) < 0.001	−0.224 (−0.26,−0.19) < 0.001	−0.229 (−0.26,−0.20) < 0.001
NDVI greenness quartiles: Low (Q_1) – Ref	1	1	1	1
Q_2	0.022 (−0.04,0.08) 0.488	0.025 (−0.04,0.09) 0.432	0.024 (−0.04,0.09) 0.479	0.021 (−0.04,0.09) 0.525
Q_3	−0.075 (−0.13,−0.02) 0.012	−0.064 (−0.12,−0.01) 0.032	−0.059 (−0.12,0.00) 0.062	−0.074 (−0.14,−0.01) 0.020
High (Q_4)	−0.277 (−0.34,−0.22) < 0.001	−0.276 (−0.34,−0.22) < 0.001	−0.285 (−0.35,−0.22) < 0.001	−0.293 (−0.36,−0.23) < 0.001

Note: Separate models are constructed for exposures coded as continuous variable and as categorical variable.

[a] Model 1 adjusted for sociodemographic variables (sex, age-groups, ethnicity, highest educational attainment, employment status and average household income before tax).

[b] Model 2 adjusted for sociodemographic variables plus lifestyle and dietary risk factors (smoking status, alcohol intake frequency, residential tenureship, number of stressful life events, salt intake, processed meat intake, and fresh fruits intake).

[c] Model 3 adjusted for sociodemographic variables, lifestyle and dietary risk factors plus doctor-diagnosed comorbidities and family history of diseases (body-mass index, cardiovascular disease status, diabetes diagnosed by doctor, antihypertensive medication use, and parental cardiovascular diseases).

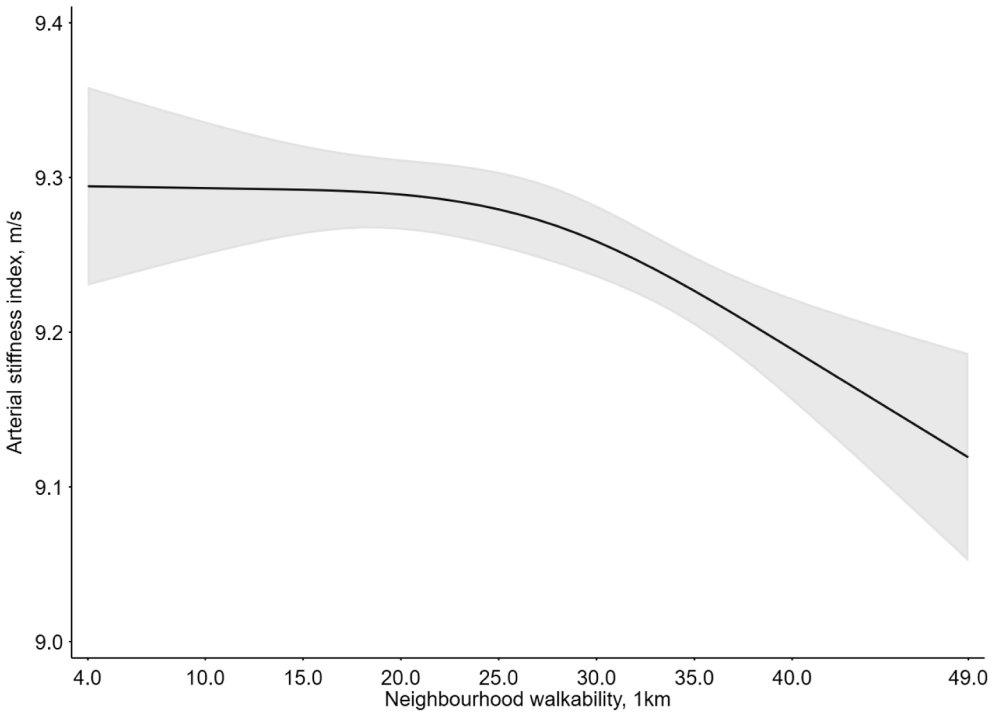
[d] Model 4 adjusted for sociodemographic variables, lifestyle and dietary risk factors, doctor-diagnosed comorbidities and family history of diseases plus other environment variables (terrain variability, traffic intensity on the nearest road and Townsend's deprivation index).

respectively). In reference to participants in the lowest walkability quartile, those in the highest quartile had lower ASI (β = −0.083 m/s, −0.14 to −0.03, p = 0.005). In the case of NDVI greenness, participants in the third and fourth NDVI greenness quartiles had lower ASI compared to those in the first quartile (β = −0.074 m/s, −0.14 to −0.01, p = 0.020 and β = −0.293, −0.36 to −0.23, p < 0.001 respectively). The VIF values of all our models were<5.09 indicating low multi-collinearity.

We imputed missing data across all covariates achieving an enhanced sample size of N = 135,477 participants and found consistent results as reported in our primary analyses (see *Appendix*, Table 1). On rerunning our models by restricting analyses for a subset of vulnerable participants who were hypertensive or with prior doctor-diagnosed cardio-vascular disease or taking anti-hypertensive medication, the negative association of greenness with ASI became slightly more pronounced, while walkability had null association. In reference to the lowest NDVI quartile, those in the third (β = −0.124 m/s, −0.25 to 0.002, p = 0.053) and highest (β = −0.328, −0.46 to −0.20, p < 0.001) exposure quartiles had lower ASI (see *Appendix*, Table 2). The restricted cubic spline models showing the dose–response relationship of arterial stiffness across walkability and greenness exposure continuums are shown in Fig. 1. The models, employing three Harrell's knots, deciphered a non-linear trend with a consistent negative association between ASI and walkability (p-value for non-linearity = 0.045), and NDVI greenness (p-value for non-linearity < 0.001). Results of sub-group level analyses are shown in Fig. 2. For NDVI greenness, there are significant sex and age group effects, with relatively higher beneficial associations reported among women (p < 0.001) and older adults aged ≥ 60 years (p = 0.011). We found evidence of multiplicative interaction between greenness and walkability on ASI (p < 0.001), with the beneficial associations of greenness upon ASI being more pronounced in the higher walkability quartiles. In the highest walkability quartile (Q4), in reference to the lowest NDVI greenness exposure quartile, those in the third and fourth quartiles had significantly lower ASI (β = −0.149, 95% CI = −0.28 to −0.02, p = 0.022 for the third green quartile and β = −0.191, 95% CI = −0.33 to −0.05, p = 0.006 for the highest green quartile; see Fig. 2). Models testing the combined effects of walkability quartiles and income groups upon the association between greenness and ASI are presented in *Appendix*, Supplementary Fig. 1. The beneficial association between greenness and ASI was most pronounced for participants in the low income (<£18,000 per year) and medium walkability (second and third quartiles) groups. The between-city and within-city effects for both walkability (β = −0.011 m/s, −0.018 to −0.004, p = 0.001 and β = −0.003, −0.005 to −0.001, p = 0.001 respectively) and NDVI greenness (β = −1.308 m/s, −1.51 to −1.11, p < 0.001 and β = −0.683, −0.861 to −0.506, p < 0.001 respectively) remained significant in our multiple-exposure model (not shown in Table).

4. Discussion

In a UK-wide population cohort of middle-aged adults, residential walkability and greenness were found to be inversely associated with arterial stiffness. Subsequent to full adjustments, participants in the highest walkability exposure quartile had significantly lower ASI in reference to the lowest exposure quartile. Consistently, participants in the third and fourth greenness exposure quartiles had lower ASI compared to those in the first quartile. The RCS models showed consistent inverse non-linear associations of walkability and NDVI greenness with arterial stiffness. The results remained robust after imputing data on missing covariates. The observed inverse association between NDVI greenness and arterial stiffness is consistent with results from the few prior studies, which were conducted at smaller scale and with exposure measured at lower spatial resolution. A recent UK study of 4,000 participants found that each IQR increment in residential surrounding NDVI greenness assessed at a spatial resolution of 250 m was associated with lower pulse wave velocity (β = −0.04 m/s, 95% CI: −0.12 to 0.04), though the result remained non-significant (de Keijzer et al., 2020). Another study, of 3,000 participants in India, reported elevated central pulse pressure per IQR decrease in NDVI greenness (β = 3.1 mmHg, 95% CI: 2.0 to 4.1) (Lane et al., 2017). Similarly another recent US study reported that ASI measured in terms of augmentation index reduced by 3.8% as per each 0.1 increment in NDVI greenness in an analytic sample of 65 participants (Riggs et al., 2021). To our knowledge, our study is the first to examine the associations between individual-level residential walkability and arterial stiffness, reporting inverse associations for a large national sample of ~ 100,000. The observed beneficial associations corroborates the few previous studies to have examined the impacts of walkability on standard circulatory



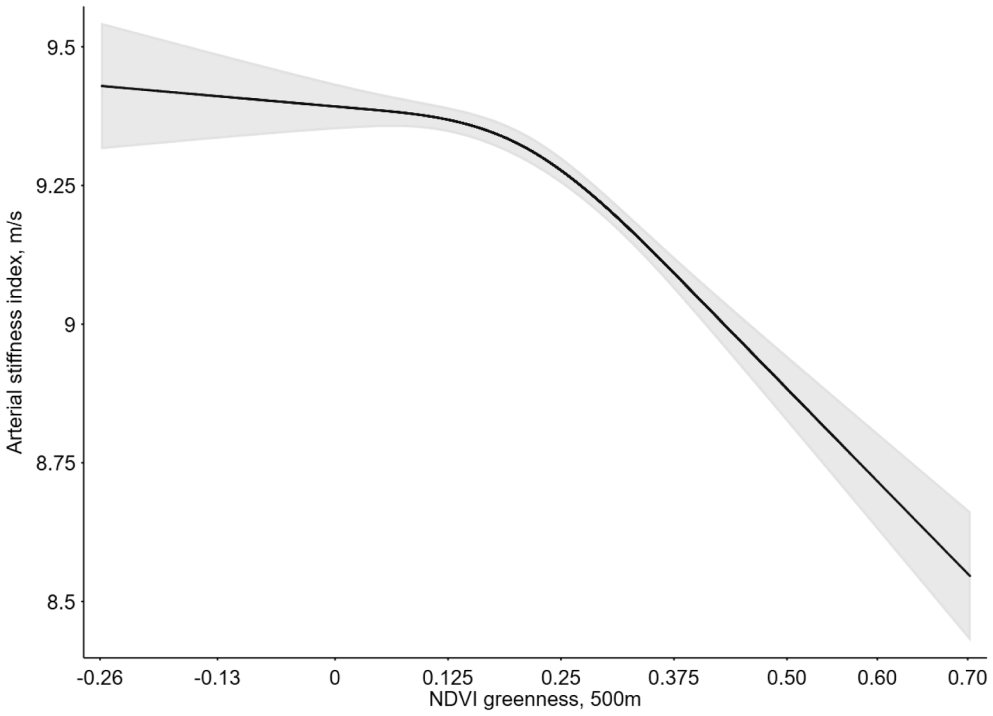


Fig. 1. Associations of residential walkability and greenness with arterial stiffness (ASI, m/s) allowing for non-linear effects. The continuous line represents the estimated mean arterial stiffness index while the shaded regions indicate 95% CIs. Separate models were fitted for residential walkability and greenness using restricted cubic splines with Harrell's knots, adjusting for socio-demographic covariates (age, sex, ethnicity, highest educational qualification, employment status, household income); lifestyle and dietary risk factors (smoking status, alcohol intake frequency, residential tenureship, number of stressful life events, salt intake, processed meat intake, and fresh fruits intake); doctor-diagnosed comorbidities and family history of diseases (BMI, cardiovascular disease status, diabetes, antihypertensive medication use and parental cardiovascular diseases); other environment variables (terrain variability, traffic intensity on nearest road and Townsend's deprivation index).

marker of blood pressure and hypertension (Chiu et al., 2016; Sarkar et al., 2018a).

The inverse associations of residential-level walkability and greenness with ASI may be explained via the physical activity-based pathway (Boreham et al., 2004; Gando et al., 2010; Tanaka et al., 1998). Residential built environments designed to be walkable (Sundquist et al., 2011; Van Dyck et al., 2010) and with adequate greenness (McMorris et al., 2015) have been found to promote physical activity. Previous evidence suggests that the beneficial associations of physical activity with arterial stiffness stem from improvements in metabolic profiles, being associated with lower blood glucose (Healy et al., 2007) and helping regulate lipoprotein lipase (LPL) activity (Hamilton et al., 2004). It has also been suggested that physical activity promotes arterial adaptation by improving cardiorespiratory fitness and associated enhanced blood flow and oxygen uptake (Boreham et al., 2004). Furthermore, the stress-inhibiting-potential of greener and more walkable residential environments may act as another plausible biological mechanism explaining our reported findings. Walkable salutogenic environments are generally associated with lower levels of oxidative stress (Yeager et al., 2018), being negatively associated with vascular aging and arterial stiffening (Patel et al., 2011). Our study further found evidence of multiplicative interaction between walkability and greenness,

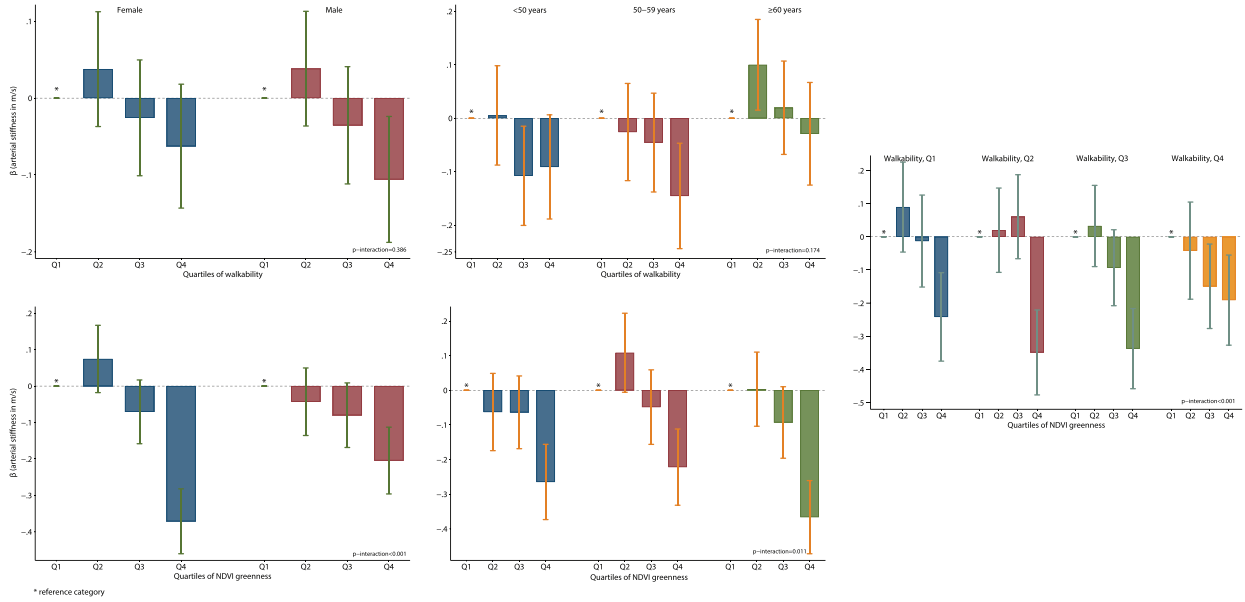


Fig. 2. Associations between quartiles of residential walkability and greenness and arterial stiffness (ASI, m/s) by sex, age-groups and walkability quartiles. Models adjusted for socio-demographic covariates (age, sex, ethnicity, highest educational qualification, employment status, household income); lifestyle and dietary risk factors (smoking status, alcohol intake frequency, residential tenureship, number of stressful life events, salt intake, processed meat intake, and fresh fruits intake); doctordiagnosed comorbidities and family history of diseases (BMI, cardiovascular disease status, diabetes, antihypertensive medication use and parental cardiovascular diseases); other environment variables (terrain variability, traffic intensity on nearest road and Townsend's deprivation index). p-values indicated significance of interaction between categories (quartiles) of walkability and greenness and population subgroups.

with the beneficial effects of greenness (both the third and fourth green quartiles) being significant in the highest walkability quartile. The results are of value especially to urban planners and designers in developing health-sustaining neighbourhoods with adequate provisions for green exposure as well as with a design that supports threshold levels of accessibility to key services and destinations to promote walking and physical activity. Such a dual synergistic approach to designing neighbourhoods is likely to help reap the health benefits of both exposures.

Strengths of the study include the use of a UK-wide cohort data of a large size and variability in population level characteristics and exposures. This enabled detection of effects, rigorous adjustment for confounders and range of sensitivity tests. Using a pulse waveform derived arterial stiffness index, adds value to the study in terms of being a more precise and rigorous marker of cumulative vascular ageing and predictor of CVD events than other commonly employed circulatory biomarkers, which are affected by other physiological factors and thereby prone to confounding fluctuations. Further, ASI is a more non-invasive metric, derived from the dichotic pulse wave form and hence easier to operationalize compared to the central pulse wave velocity, which is difficult to measure and requires participant training as the measurements need to be recorded in a supine position. Another novelty of the study stems from the use of highly characterized individual-level metrics for walkability and greenness. Our objectively assessed walkability index comprises detailed built environment metrics of density, design and destination accessibility, modelled from building footprint-level data (as opposed to land parcel-level data in many prior studies) and linked to participants' home address coordinates. The metric of NDVI greenness was modelled from multi-spectral BlueSky data and is of higher spatial resolution (0.50-metre) than has been employed in prior studies (for example, the 30-metre Landsat data or the 250-metre resolution MODIS data) (Sarkar et al., 2015b). As the CIR data is captured by low-flying aircraft, the sensing method overcomes the limitation of cloud cover and atmospheric distortions encountered in conventional remotely sensed data and thus makes our green-neighbourhood measure more accurate than in prior studies.

Among the limitations, a cross sectional observational design limits ascertainment of causality. Reverse causation cannot be completely ruled out although it is less likely that participants with high ASI will have systematically moved to neighbourhoods with high walkability and greenness. Moreover, participants had relatively high residential stability with a mean duration of residence in their current address of 17.7 years. Some exposure misclassification could have been possible as a result of temporal mismatch between outcome and exposure assessment; UK Biobank participants were assessed at baseline over the period 2006–2010 and the exposures were measured around the end of baseline (2010). Nonetheless, the built environment in major cities of the UK is highly urbanized and relatively stable and the impact of such mismatch on the reported effect estimates will unlikely to be significant. Another potential limitation may stem from the use of Pulse Trace device for measuring arterial stiffness on account of greater variability in ASI values relative to other available devices (DeLoach and Townsend, 2008). Although it is easier to operationalize in large population cohorts, it has been shown to have lower correlation with reference method and reproducibility in at least one study of a population of n=50 (Salvi et al., 2008). Lastly, the UK Biobank study had a low response rate of 5.5% and is likely to comprise healthier participants than the national population (healthy volunteer bias). However, given the large sample size and high internal validity, these are unlikely to affect the reported associations (Richiardi et al., 2013; Rothman et al., 2013).

5. Conclusion

Arterial stiffness is an important marker of early vascular ageing and a predictor of CVD and related mortality. In a very large UK-wide cohort, we found that residential walkability and greenness both had an inverse association with arterial stiffness, the results being robust to multiple adjustments and sensitivity tests. *Healthy cities by healthy design*, achieved via creating and retrofitting residential environments in cities to make them more walkable, accessible, green and salutogenic has the potential to affect the lives of millions of dwellers. Given the evidenced synergistic associations of beneficial exposures such as greenness and walkability with cardiovascular risks, per-capita green allocation in

residential neighbourhoods, design of green spaces and creation of walk-friendly neighbourhoods can be key planning strategies to be considered together. Furthermore, urban design may well be one of the most profound and long-lasting influences on public health, since the built environment influences multiple daily behaviours. Our study adds to the growing body of evidence that the detailed configuration of residential neighbourhoods is likely to be important for population-wide CVD health promotion. In particular, retrofitting neighbourhoods by designing more walkable and greener living environments can be a preventive intervention aimed at lowering the population distribution of vascular ageing and associated cardiovascular risks (Rose, 1992). From an urban planning perspective, policies that support strategic investments in healthy city infrastructures as well as monetize the intrinsic value of healthy places in promoting population health deserve further attention.

CRediT authorship contribution statement

Ka Yan Lai: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Software, Visualization. **Sarika Kumari:** Investigation, Writing – review & editing, Software, Validation, Visualization. **John Gallacher:** Conceptualization, Writing – review & editing. **Chris Webster:** Conceptualization, Investigation, Writing – review & editing, Resources, Funding acquisition. **Chinmoy Sarkar:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, Validation, Project administration, Supervision.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106960.

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