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Long-Term Greenspace Exposure and Progression of Arterial Stiffness: The Whitehall II Cohort Study

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BACKGROUND: Arterial stiffness, and its progression with age, is an important indicator of cardiovascular aging. Greenspace exposure may protect against arterial stiffness by promoting physical activity, fostering social cohesion, and reducing stress and exposure to air pollution and noise.

OBJECTIVES: The aim of this study was to investigate the association of long-term exposure to outdoor greenspace with arterial stiffness and its progression over time.

METHODS: This prospective cohort study was based on 4,349 participants (55–83 years of age) of the Whitehall II Study, United Kingdom. Arterial stiffness was assessed in two medical examinations (2007–2009 and 2012–2013) by measuring the carotid–femoral pulse wave velocity (cf-PWV). Residential surrounding greenspace was characterized using satellite-based indices of greenspace including normalized difference vegetation index (NDVI), enhanced vegetation index (EVI), and vegetation continuous fields (VCF) across buffers of 500 and 1,000 m surrounding the participants' residential locations at each follow-up. The association between the greenspace indicators and baseline cf-PWV and 4-year progression of cf-PWV was assessed using linear mixed-effects models with the participant as a random effect, controlling for demographic, lifestyle, and (individual and area) socioeconomic factors.

RESULTS: No statistically significant associations were observed between residential surrounding greenspace and baseline or 4-y progression of cf-PWV; interquartile range (IQR) increases in NDVI, EVI, and VCF in the 500-m buffer were associated with −0.04 m/s [95% confidence interval (CI): −0.12, 0.04], −0.03 m/s (95% CI: −0.10, 0.05), and −0.02 m/s (95% CI: −0.08, 0.04) in baseline cf-PWV and 0.06 m/s (95% CI: −0.02, 0.14), 0.05 m/s (95% CI: −0.03, 0.14), and 0.00 m/s (95% CI: −0.09, 0.09) in 4-y progression in cf-PWV, respectively. The associations were similar when using 1,000-m buffers.

CONCLUSIONS: We did not observe any consistent association between residential surrounding greenspace and arterial stiffness. https://doi.org/10.1289/EHP6159

Introduction

The older population (60 years of age and over) is rapidly growing worldwide, doubling from 962 million older adults in 2017 to 2.1 billion by 2050 (United Nations Department of Economic and Social Affairs 2017). Among older adults, a main contributor to the burden of disease is cardiovascular disease (CVD) (Prince et al. 2015). The risk of CVD increases with age due to the aging of the cardiovascular system (Prince et al. 2015). One of the most important traits of cardiovascular aging is arterial stiffness and its progression with age (McEniery et al. 2005). Arterial stiffness occurs when the vessel wall increasingly loses elasticity (O'Neill et al. 2017) and is a strong predictor of incident cardiovascular events and mortality (Vlachopoulos et al. 2010).

Recent studies have aimed to identify modifiable factors that may decrease arterial stiffness, such as increased physical activity (Ahmadi-Abhari et al. 2017), healthy weight (Brunner et al. 2015), and reduced air pollution (Ljungman et al. 2018) and noise (Foraster et al. 2017). A potentially protective factor that has not yet been considered is greenspace. Greenspace is any open piece of land that is "partly or completely covered with grass, trees, shrubs, or other vegetation" and includes, among others, parks, forests, and community gardens (U.S. EPA 2018). Greenspace may protect against arterial stiffness by increasing physical activity, reducing stress, fostering social engagement, and reducing exposure to air pollution and noise (Markevych et al. 2017). Previous studies have shown an association between higher exposure to greenspace and lower risk of cardiovascular morbidity and mortality, though most studies were cross-sectional, and the strength of the evidence remained mixed (Fong et al. 2018; James et al. 2015). However, the mechanism of the relationship between exposure to greenspace and cardiovascular outcomes is not well understood. The association with arterial stiffness, a preceding condition of CVD, has not been investigated yet.

Therefore, the aim of the present longitudinal study was to investigate the association between long-term exposure to residential surrounding greenspace and arterial stiffness and its progression over time.

Methods

Study Population

The present study is based on data collected by the Whitehall II cohort study. In 1985, British civil servants 35 to 55 years of age from 20 government departments in London were invited to participate in the study (Marmot and Brunner 2005). The cohort started with 10,308 participants who were invited for clinical

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examinations and questionnaires every 5 y, irrespective of participation in the previous follow-up. We used data collected in the follow-ups in which arterial stiffness was measured (2007–2009 and 2012–2013) and included all participants living in Great Britain at the time of arterial stiffness measurements with data available on arterial stiffness and covariates for at least one of the follow-ups. Consequently, our study sample included three groups: participants of both the 2007–2009 and 2012–2013 follow-ups, participants of only the 2007–2009 follow-up, and participants of only the 2012–2013 follow-up. Research ethics approvals were received from the University College London (UCL) Medical School Committee on the Ethics of Human Research, and participants gave written informed consent at each follow-up.

Exposure Assessment

Exposure to greenspace was characterized by outdoor greenspace surrounding the residential location of each participant. Each participant's residential location was geocoded at each follow-up based on the postcode centroid of their residential address at that follow-up. The geocodes of the postcode centroids were obtained from the postcode directory of the corresponding year, provided by the Office for National Statistics (Office for National Statistics 2017). In 2011, a postcode held a median of 14 [interquartile range (IQR): 20] households (Office for National Statistics 2013).

Residential surrounding greenspace was assessed using three satellite-based indicators of outdoor greenspace: *a*) normalized difference vegetation index (NDVI), which is an indicator based on land surface reflectance of visible (red) and near-infrared parts of the spectrum. It ranges between -1 and 1, with higher values indicating more greenspace (i.e., photosynthetically active vegetation); *b*) the enhanced vegetation index (EVI), which is considered an improvement on NDVI due to minimized soil background influences and higher responsiveness to canopy structural variations (MODIS 2017); and *c*) vegetation continuous fields (VCF), which is an estimate of the percentage of land (in each image pixel) covered by woody vegetation with a height equal to or greater than 5 m (Hansen et al. 2003). The NDVI, EVI, and VCF maps had a spatial resolution of 250 m by 250 m (Didan 2015).

Moderate Resolution Imaging Spectroradiometer (MODIS) images of NDVI and EVI were obtained over a 16-d period. To maximize the contrast in exposure, we looked for images with the least cloud cover obtained between May and June (i.e., the maximum vegetation period of the year in our study region) of the relevant years both at baseline and the follow-up (Figure S1; Table S1). MODIS images of VCF were provided as annual values. We downloaded annual images of a relevant year to the baseline and follow-up (Figure 1; Table S1). All images were obtained from the Data Pool website of the NASA Land Processes Distributed Active Archive Center.

Estimates of residential surrounding greenspace were averaged across buffers of 500 and 1,000 m around the corresponding postcode centroid of the address at each follow-up, consistent with our previous studies on Whitehall II participants (de Keijzer et al. 2018, 2019b, 2019a). We selected the 500-m buffer to encompass the direct environment around the home and the 1,000-m buffer to cover the general walking distance to places near the home (Stockton et al. 2016). Buffers smaller than 500 m were not feasible given the size of the postcode areas and the resolution of our NDVI, EVI, and VCF maps. To summarize, we abstracted estimates for three vegetation indices across two buffer sizes at two follow-ups resulting in up to $12 (3 \times 2 \times 2)$ exposure estimates per participant.

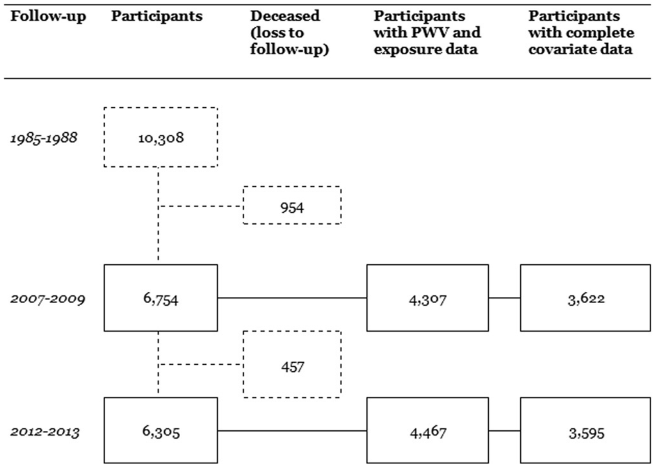

Figure 1. Flowchart of the study population.

Arterial Stiffness

Arterial stiffness was assessed in the clinical examinations of 2007–2009 and 2012–2013. Appointments were in the morning or afternoon. They were set to ensure that the time between two clinical examinations was similar for all participants. Participants followed the same examination sequence, starting with a blood test in fasting conditions, refreshment, and then the clinical measures. Arterial stiffness was assessed by measuring the carotid–femoral pulse wave velocity (cf-PWV), which is considered a gold-standard measure (Laurent et al. 2006; O'Neill et al. 2017). Applanation tonometry was used to assess cf-PWV between the carotid and femoral sites (SphygmoCor®, AtCor Medical) (Ahmadi-Abhari et al. 2017; O'Neill et al. 2017). cf-PWV (m/s) was calculated by dividing the path length over the transit time (Ahmadi-Abhari et al. 2017; O'Neill et al. 2017; Wilkinson et al. 1998). The path length was calculated by subtracting the carotid–sternal notch distance from the femoral–sternal notch distance. The transit time was defined as the difference between the heart–carotid and heart–femoral blood transmission times (i.e., the time difference between the peak of the R-wave on electrocardiogram and the foot of the pulse waveform captured by the tonometer at the site of the carotid or femoral pulse) (Ahmadi-Abhari et al. 2017). To ensure assessment accuracy, in each follow-up, cf-PWV measurements were taken twice, or three times if the difference in cf-PWV between the first two measurements was larger than 0.5 m/s. The median variance between the PWV measurements within the subject was 0.15 m/s in the follow-up of 2007–2009 and 0.21 m/s in the follow-up of 2012–2013. The mean of these measurements in each follow-up was used in the analyses (Ahmadi-Abhari et al. 2017; O'Neill et al. 2017). In addition, to assess the short-term repeatability of the measurements, PWV measurements were repeated in a sample of participants within 30 d after the first PWV measurements (Ahmadi-Abhari et al. 2017). For the follow-up of 2007–2009, the measurements were repeated for 125 participants, and the median difference of the repeats was 0.83 m/s (IQR: 0.43–1.40). For the follow-up of 2012–2013, the measurements were repeated for 114 participants, and the median difference of the repeats was 0.89 m/s (IQR: 0.41–1.47).

Covariates

Covariate data included data on demographic characteristics, lifestyle factors, individual and neighborhood socioeconomic status (SES), and cardiovascular covariates. The demographic characteristics included age (continuous in years, reported at the first visit in the study period), sex (male or female), and ethnicity (white or nonwhite). The indicators of lifestyle were recorded by questionnaire at each follow-up and included smoking status (current, past, or never), alcohol consumption (frequency of alcohol consumption in the past 12 months; less than daily, (almost) daily, or twice a day or more), and diet (frequency of intake of fruit and vegetables; less than twice a day, or twice a day or more). For SES, the individual indicators were educational attainment (reported in the follow-up of 1997–1999) and employment grade (reported at each follow-up). Educational attainment was categorized as lower secondary school degree or less (low), higher secondary school degree (middle), and university or higher degree (high), following previous Whitehall II studies (de Keijzer et al. 2018, 2019b; Trudel et al. 2016). Employment grade was based on the British civil service grades of employment and categorized as clerical (low), professional and executive (middle), and administrative (high) (Trudel et al. 2016). The neighborhood-level SES indicators were country-specific tertiles of the income and employment domains of the Index of Multiple Deprivation (IMD) according to the 2001 Census (Noble et al. 2006). The IMD data were collected at the Lower Layer Super Output Area (LSOA) level, which is the smallest spatial scale for which the IMD data is available. LSOAs are administrative areas, created by grouping postcodes based on similar social demographics and proximity. LSOAs have around 650 households and could represent a neighborhood (Stockton et al. 2016). To account for the possibility of changing the LSOA because of moving, we collected the IMD data at each follow-up based on the LSOA of the participant in the corresponding follow-up. The income and employment domains of the IMD were selected to be included in our analysis, as these domains were comparable between England, Wales, and Scotland (Abel et al. 2016). For cardiovascular covariates, the diastolic and systolic blood pressure (DBP and SBP, respectively) were measured in the medical examination at each follow-up at the time of the cf-PWV measurement. We calculated the mean arterial pressure (MAP) in mmHg as $(2\times \text{DBP}+\text{SBP})/3$.

Statistical Analyses

Main analyses. The main analyses were based on complete cases, including participants with complete data on the outcome, exposure, and covariates. We examined the association of the greenspace indicators with arterial stiffness and its progression over time using linear mixed-effects models to take into account the repeated measurements for each participant. We included the person as random effect and the repeated measurements of cf-PWV as outcome (de Keijzer et al. 2018, 2019b). A measure of exposure to greenspace (i.e., NDVI, EVI, or VCF; one at a time; at each follow-up) was included as a fixed-effect predictor, capturing the cross-sectional association between greenspace and cf-PWV at baseline. Furthermore, to estimate the association with progression of arterial stiffness, an interaction term between the greenspace indicator and time was included as another fixed effect predictor to estimate the difference in 4-y progression in cf-PWV associated with an increase in greenspace (Ahmadi-Abhari et al. 2017; O'Neill et al. 2017). The time indicator was the time interval in years between the two follow-ups, standardized to 4 y (i.e., the follow-up time was divided by 4, the mean interval between the follow-ups). The association with greenspace was reported per IQR increase in each indicator of greenspace, based on all study participants.

We adjusted the models for an increasing number of confounders that were selected *a priori* based on previous Whitehall II studies on PWV (Ahmadi-Abhari et al. 2017; Brunner et al. 2015; O'Neill et al. 2017; Trudel et al. 2016), studies on the environment and PWV (Foraster et al. 2017; Lenters et al. 2010; Ljungman et al. 2018), and studies on the health effects of greenspace exposure (de Keijzer et al. 2018, 2019b; Dzhambov et al. 2018) (Figure S2). We did not adjust for factors that could be hypothesized to be on the pathway between greenspace exposure and arterial stiffness such as physical activity (Ahmadi-Abhari et al. 2017; Barnett et al. 2017; Dalton et al. 2016). The age- and sex-adjusted model (Model 1) was only adjusted for age and sex. The minimally adjusted model (Model 2) was adjusted for age, age squared, sex, ethnicity, MAP, diet, alcohol consumption, and smoking status. The fully adjusted model (Model 3) was the minimally adjusted model further adjusted for the socioeconomic indicators: educational attainment, employment grade, the IMD income tertiles, and IMD employment tertiles. MAP, a measure of flow, resistance, and pressure in arteries in one heartbeat, is considered to be an important confounder for associations with arterial stiffness and thus important to adjust for (Fortier et al. 2018; London and Pannier 2010; Willum-Hansen et al. 2006). This is in accordance with previous studies of the association between environmental exposures and PWV (Baumgartner et al. 2018; Foraster et al. 2017) and previous Whitehall II studies on cf-PWV (Ahmadi-Abhari et al. 2017; Johansen et al. 2012; O'Neill et al. 2017).

We explored the linearity of the dose–response relationship between greenspace exposure and arterial stiffness using generalized additive models for each indicator of greenspace exposure, both in unadjusted and fully adjusted models. We did not observe any strong indication for a nonlinear dose–response relationship between greenspace exposure and arterial stiffness (Figure S3).

To summarize, we have used a random intercept mixed model:

$$y_{ij} = \mu + \alpha_i + \beta_0 x_{i0} + \beta_1 t + \beta_2 x_{i1} t + \sum \beta_c x_{cij} + \varepsilon_i,$$

where y_{ij} corresponds to the measure of PWV of the ith participant at the follow-up jth, μ is the intercept, α_i is the random effect of the ith subject, β_0 is the regression coefficient associated to the greenspace indicator at the first follow-up, x_{i0} corresponds to the greenspace indicator (NDVI, EVI, or VCF) of the ith participant at the 2007–2009 follow-up centered with respect to the mean of the sample and divided by its IQR, t corresponds to the years between first and second follow-up divided by 4, β_1 is the regression coefficient associated with the time variable at the average value of the greenspace variable, β_2 is the regression coefficient associated with the greenspace indicator associated at the second follow-up with respect to the first one, x_{i1} corresponds to the greenspace indicator (NDVI, EVI, or VCF) of the ith participant at the 2012–2013 follow-up centered with respect the mean of the sample and divided by its IQR, x_{cij} are the covariates of the main models and β_c their corresponding regression coefficients, and ε_{ij} is the usual random error.

Sensitivity analyses. First, to test the robustness of our findings to the selection of the confounders, we further adjusted the models for *a*) marital status; *b*) cardiometabolic factors including heart rate, high-density lipoprotein cholesterol (HDL), and triglycerides; and *c*) cardiometabolic factors (as stated in *b*) plus use of antihypertensive, lipid-lowering, and diabetes medication. Marital status (married/cohabiting or other) was recorded by questionnaire at each follow-up. Cardiometabolic factors (i.e., heart rate in bpm, systolic blood pressure in mmHg, HDL cholesterol in mmol/L, and triglycerides levels in mmol/L) were measured in the clinical examination at each follow-up. The data on use of antihypertensive, lipid-lowering, and diabetes medication (yes or no) were collected by questionnaire at each follow-up. Moreover, to examine potential confounding by other environmental factors, we further adjusted for road area density, path area density, and domestic building density (one at a time). We determined the proportion of road area, path area, and domestic buildings area as percentages of the total area in the LSOA at each follow-up. These data were obtained from the Generalised Land Use Database 2005 from the Office for National Statistics (Office for National Statistics 2010). This analysis was restricted only to participants living in England, as the land use information was only available for England.

Second, we assessed the impact of missing covariate data by repeating the main analyses with multiple imputation for missing covariate values. Multiple imputation was conducted by chained equations carrying out 25 imputations with 10 cycles for each imputation that generated 25 complete datasets (as described in Table S2) (de Keijzer et al. 2018). The standard combination rules for multiple imputations were used to analyze the datasets (Spratt et al. 2010).

Third, we used an inverse-probability-weighting approach (Weuve et al. 2012) to test for the influence of differential loss to follow-up on our findings. This analysis was restricted to participants with a baseline observation (i.e., participants of follow-up of 2007–2009; $n = 3{,}622$). To estimate the probability of participation also at follow-up (i.e., at follow-up of 2012–2013), we developed predictive logistic regression models with the outcome being the participation at follow-up (yes/no) and, as predictor variables, those characteristics that were related to the outcome (i.e., loss to follow-up), including age, sex, ethnicity, educational attainment, employment grade, subjective general health status (excellent, very good, good, fair, or poor, assessed by questionnaire), smoking status, weight status (characterized by body mass index in $\mathrm{kg/m^2}$, assessed at clinical examination), low-density lipoproteins cholesterol level (in mmol/L, assessed at clinical examination), residential surrounding greenspace (EVI in the 1,000-m buffer), and cf-PWV. Subsequently, we defined the weight for each participant as the inverse of the participant's predicted probability of completing the follow-up of the study and applied these weights in the main models.

Fourth, our greenspace estimates were obtained across circular buffers around the residential location, assuming that such a buffer could represent the living environment (i.e., the neighborhood) for each participant. To assess the impact of this assumption, we also calculated the average NDVI, EVI, and VCF across an administrative area, namely, the LSOAs corresponding to the residential postcode of each participant at each follow-up. We then repeated the main analysis using the greenspace indicators across the LSOA.

Fifth, to take into account seasonal variability in vegetation, and hence NDVI and EVI, we also downloaded MODIS images from December (i.e., a period of minimum vegetation in our study region) of the relevant years to each follow-up (Table S1) and abstracted the average NDVI and EVI across 500-m and 1,000-m buffers. We repeated the analysis using an average of this winter estimate and the summer estimate (i.e., the estimate used in the main analyses, obtained in May–June). As the VCF estimates were obtained from annual maps, seasonality was already included.

Lastly, moving homes (indicated by a change in postcode) could have resulted in some exposure misclassification because we did not have data on the exact time that the participants moved home between the two follow-ups. In addition, the investigated associations could have been modified by rurality, country, and ethnicity. We repeated the analysis *a*) excluding participants who changed postcode during the follow-up period, *b*) excluding rural areas, *c*) including only participants who lived in England, and *d*) excluding nonwhite participants. The indicator of rurality was based on the definition of rural areas by the Organisation for Economic Co-operation and Development as administrative units with a population density lower than 150 inhabitants per $\mathrm{km^2}$ (OECD 2011). Each participant was classified to be living in a rural area (yes/no) at each follow-up using data on the population density obtained at the LSOA level from the 2001 Census data (National Records of Scotland 2001; Office for National Statistics 2001). The information about the country of residence was obtained from the postcode. Due to the low number of participants living in rural areas ($<10\%$), living outside of England ($<2\%$), and nonwhite participants ($<7\%$), we could not stratify the analyses by rurality, country, or ethnicity.

Stratified analyses. We investigated effect modification by sex and SES by stratifying the studied associations by sex, education, and an indicator of area deprivation (tertiles of the IMD income domain). We used the likelihood ratio test to statistically test the multiplicative interaction between each of the aforementioned potential effect modifiers and indicators of greenspace exposure (one at a time).

Results

The study population included a total of 5,316 participants (55 to 83 years of age) who had data available on cf-PWV and greenspace exposure (Table 1; Figure 1). The participants' demographic, lifestyle, and socioeconomic characteristics are described in Table 1. Over 73% of the study population was male, and over 90% was white (Table 1). The median cf-PWV increased from 8.1 m/s in 2007–2009 to 8.7 m/s in 2012–2013 (Table 1). Furthermore, exposure to greenspace did not change noticeably over the study period (Table 1). The estimates of NDVI and EVI were strongly correlated with each other (correlation >0.9) but weakly correlated with the estimates of VCF (correlation >0.3) (Table S3).

Of the 5,316 participants, the main analyses were based on 4,349 participants with complete covariate data, of whom 755 participants only participated in the follow-up of 2007–2009, 727 only participated in 2012–2013, and 2,867 participated in both follow-ups. To clarify, the analyses included $755 + 2{,}867 = 3{,}622$ participants in 2007–2009 and $727 + 2{,}867 = 3{,}594$ participants in 2012–2013 (Figure 1).

Main Analyses

The results of the age- and sex-adjusted models, minimally adjusted models, and fully adjusted models are presented in Table 2. An increase in residential surrounding greenspace (NDVI, EVI, or VCF in a 500- or 1,000-m buffer) was associated with less arterial stiffness (i.e., a lower cf-PWV) at baseline, although the associations were nonsignificant after adjustment for ethnicity, MAP, and lifestyle factors (Model 2) and further attenuated after adjustment for SES (Model 3; Table 2). Furthermore, no significant association was observed between residential surrounding greenspace and the progression of arterial stiffness. In the fully adjusted model, a 1-IQR increase in NDVI, EVI, and VCF in the 500-m buffer was associated with -0.04 m/s [95% confidence interval (CI): -0.12, 0.04], -0.03 m/s (95% CI: -0.10, 0.05), and -0.02 m/s (95% CI: -0.08, 0.04) in the baseline cf-PWV and with 0.06 m/s (95% CI: -0.02, 0.14), 0.05 m/s (95% CI: -0.03, 0.14), and 0.00 m/s (95% CI: -0.09, 0.09) increase in 4-y progression in cf-PWV (Model 3; Table 2). The results were comparable when using greenspace estimates across the 500- and 1,000-m buffer (Table 2).

Sensitivity Analyses

The associations between the greenspace indicators and baseline and 4-y progression in cf-PWV remained statistically nonsignificant after further adjustment for marital status or cardiometabolic factors including heart rate, HDL, triglycerides, and use of antihypertensive, lipid-lowering, and diabetes medication (Table S4). In addition, further adjustment for road area density, path area density, and

Table 1. Descriptive characteristics of the study population per follow-up.

	2007–2009	2012–2013
Variable	*n* (%) or M (Q1–Q3)	*n* (%) or M (Q1–Q3)
Participants (*n*)	4,307	4,467
Age (y)		
M (Q1–Q3)	64.4 (60.5–70.1)	68.3 (64.5–73.7)
Missing values [*n* (%)]	0 (0)	0 (0)
Sex [*n* (%)]		
Male	3,209 (74.5)	3,298 (73.8)
Female	1,098 (25.5)	1,169 (26.2)
Missing values	0 (0)	0 (0)
Ethnicity [*n* (%)]		
White	3,961 (92)	4,133 (92.5)
Nonwhite	346 (8)	334 (7.5)
Missing values	0 (0)	0 (0)
Educational attainment [*n* (%)]		
≤Lower secondary school	1,194 (31.8)	1,251 (32.1)
Higher secondary school	1,070 (28.5)	1,108 (28.4)
University or higher	1,486 (39.6)	1,539 (39.5)
Missing values	557 (13)	569 (13)
Employment grade [*n* (%)]		
Low	2,087 (49.7)	2,206 (50.3)
Middle	1,749 (41.7)	1,820 (41.5)
High	362 (8.6)	360 (8.2)
Missing values	109 (3)	81 (2)
Area SES		
Income		
Score: 0 to 1 [M (Q1–Q3)]	0.1 (0–0.1)	0.1 (0–0.1)
Missing values [*n* (%)]	4 (0)	1 (0)
Employment		
Score 0 to 1 [M (Q1–Q3)]	0 (0–0.1)	0 (0–0.1)
Missing values [*n* (%)]	4 (0)	1 (0)
Alcohol consumption		
Less than daily	2,242 (53.1)	2,273 (53.2)
(Almost) daily	1,740 (41.2)	1,766 (41.3)
Twice a day or more [*n* (%)]	240 (5.7)	237 (5.5)
Missing values [*n* (%)]	85 (2)	191 (4)
Fruit and vegetable intake		
Less than twice a day [*n* (%)]	2,513 (59)	1,797 (40.8)
Twice a day or more	1,744 (41)	2,611 (59.2)
Missing values [*n* (%)]	50 (1)	59 (1)
Smoking status [*n* (%)]		
Current	2,074 (49)	1,986 (47)
Past	1,948 (46.1)	2,105 (49.8)
Never	208 (4.9)	134 (3.2)
Missing values	77 (2)	242 (5)
Country [*n* (%)]		
England	4,221 (98)	4,379 (98)
Missing values	0 (0)	0 (0)
Rurality [*n* (%)]		
Rural	422 (9.8)	427 (9.6)
Missing values	4 (0)	0 (0)
M (Q1–Q3)		
Carotid–femoral pulse wave velocity (ms)	8.1 (7.1–9.5)	8.7 (7.4–10.4)
Mean arterial pressure (mmHg)	89 (82.3–96.3)	93.3 (86.3–100.7)
Index: –1 to 1		
NDVI		
500-m buffer	0.63 (0.54–0.71)	0.60 (0.52–0.67)
1,000-m buffer	0.64 (0.55–0.72)	0.61 (0.54–0.69)
EVI		
500-m buffer	0.37 (0.3–0.47)	0.36 (0.3–0.44)
1,000-m buffer	0.39 (0.32–0.50)	0.38 (0.32–0.47)
Percentage		
VCF		
500-m buffer	20.1 (14.8–26.4)	19.1 (14.9–23.9)
1,000-m buffer	20.4 (15.5–25.9)	19.4 (15.6–23.7)

Note: Data presented as number of participants (*n*) and percentage (%) or median (M) and first quartile and third quartile (Q1–Q3). EVI, enhanced vegetation index; NDVI, normalized difference vegetation index; VCF, vegetation continuous fields.

domestic building density did not considerably change the association between the greenspace indicators and the progression in cf-PWV; however, the association with baseline cf-PWV became slightly stronger when adjusting for road or domestic building density (Table S5); an IQR increase in NDVI in the 1,000-m buffer was associated a reduction in baseline cf-PWV of $-0.11\ \mathrm{m/s}$ (95% CI: -0.21, -0.01) when adjusting for domestic building density and $-0.12\ \mathrm{m/s}$ (95% CI: -0.23, -0.01) when adjusting for road density (Table S5). However, the association with NDVI in the 500-m buffer, EVI, or VCF did not reach statistical significance.

The baseline associations between exposure to residential surrounding greenness and arterial stiffness at the first visit did not change notably when using multiple imputation for missing covariates (Table S6), inverse probability weighting to account for differential loss to follow-up (Table S7), greenspace estimates across the LSOA (Table S8), the average of the summer and winter estimates of EVI and NDVI (Table S9), or when excluding participants who changed postcode during the follow-up period, when excluding rural areas, when including only participants living in England, and when excluding nonwhite participants (Table S10). In general, the associations were statistically nonsignificant but suggested a negative direction. In turn, the longitudinal associations between the greenspace indicators and progression in arterial stiffness over the follow-up were less consistent across the sensitivity analyses. For instance, the positive association between exposure to residential surrounding greenspace and progression in arterial stiffness appeared statistically significant for NDVI and EVI estimates across the LSOA (Table S8) and for NDVI and EVI when excluding nonwhite participants (Model 4; Table S10) but attenuated toward the null when using multiple imputation for missing covariates (Table S6) and when excluding participants living in rural areas (Model 2; Table S10).

Stratified Analyses

The results of the stratified analyses when using greenspace estimates across the 500-m buffer were similar to the results when using greenspace estimates across the 1,000-m buffer (Tables S11–S13). Overall, we found few statistically significant associations between exposure to residential surrounding greenspace and baseline and progression in arterial stiffness among strata of sex and SES.

The analyses stratified by sex suggested a borderline significant association between higher residential surrounding greenspace and lower baseline arterial stiffness among men, while this association appeared direct but nonsignificant among women (Figure 2; Tables S11–S13). The interaction terms with sex for this association were statistically significant for EVI but not for NDVI or VCF (Table S14). The interaction terms with sex in the association with the 4-y progression in cf-PWV were not statistically significant for any of the exposures (NDVI, EVI, or VCF) (Table S14).

Though not statistically significant, the stratified analyses by educational attainment suggested an association between increased exposure to NDVI and EVI and lower baseline cf-PWV in the lower educational group, which attenuated among higher educational groups (Figure 2; Tables S11, S12, and S14). The detrimental association with increased progression in arterial stiffness was also strongest among the lower compared to the higher educational groups. These suggestions of trends were not consistent for VCF (Table S13).

The analyses stratified by area income deprivation suggested similar trends for NDVI and EVI, with stronger beneficial associations with baseline cf-PWV among those living in more deprived areas compared to those living in less deprived areas, but also stronger detrimental associations with progression in cf-PWV among those living in more compared to less deprived areas

Table 2. Difference in pulse wave velocity (m/s) (95% confidence interval) at baseline and in 4-y progression associated with 1 interquartile range (IQR) increase in residential surrounding greenspace (NDVI, EVI, or VCF).

	500-m buffer			1,000-m buffer		
Model	IQR	Baseline cf-PWV	4-y progression in cf-PWV	IQR	Baseline cf-PWV	4-y progression in cf-PWV
NDVI						
1	0.163	−0.10 (−0.18, −0.03)	0.07 (−0.02, 0.15)	0.165	−0.12 (−0.2, −0.04)	0.06 (−0.02, 0.15)
2	0.163	−0.07 (−0.14, 0.01)	0.06 (−0.02, 0.14)	0.165	−0.08 (−0.15, 0.00)	0.06 (−0.03, 0.14)
3	0.163	−0.04 (−0.12, 0.04)	0.06 (−0.02, 0.14)	0.165	−0.05 (−0.14, 0.03)	0.06 (−0.03, 0.14)
EVI						
1	0.154	−0.08 (−0.15, 0.00)	0.07 (−0.02, 0.15)	0.162	−0.09 (−0.16, −0.01)	0.07 (−0.02, 0.15)
2	0.154	−0.05 (−0.12, 0.02)	0.05 (−0.03, 0.13)	0.162	−0.06 (−0.13, 0.01)	0.05 (−0.04, 0.13)
3	0.154	−0.03 (−0.10, 0.05)	0.05 (−0.03, 0.14)	0.162	−0.03 (−0.11, 0.04)	0.05 (−0.03, 0.14)
VCF						
1	10.35	−0.06 (−0.13, 0.00)	0.01 (−0.08, 0.10)	9.22	−0.07 (−0.14, −0.01)	0.04 (−0.05, 0.12)
2	10.35	−0.03 (−0.09, 0.03)	0.00 (−0.09, 0.09)	9.22	−0.04 (−0.10, 0.02)	0.02 (−0.07, 0.10)
3	10.35	−0.02 (−0.08, 0.04)	0.00 (−0.09, 0.09)	9.22	−0.03 (−0.09, 0.03)	0.02 (−0.07, 0.10)

Note: Results from complete case analyses ($n = 4{,}349$); linear mixed-effects models include the main effect of greenspace (baseline) and an interaction with time (4-y progression). Model 1, age and sex-adjusted model. Model 2, minimally adjusted model that includes Model 1 in addition to age squared, ethnicity, mean arterial pressure, diet, alcohol consumption, and smoking status. Model 3, fully adjusted model that includes Model 2 in addition to educational attainment, employment grade, IMD income tertiles, and IMD employment tertiles. cf-PWV, carotid–femoral pulse wave velocity; EVI, enhanced vegetation index; NDVI, normalized difference vegetation index; VCF, vegetation continuous fields.

(Figure 2; Tables S11–S12). However, these differences were not statistically significant (Table S14) and not consistent for VCF (Figure 2; Table S13).

Discussion

In this longitudinal study, we investigated the association between long-term exposure to greenspace and arterial stiffness, based on assessments of the exposure to greenspace at each follow-up using three different satellite-based indices of greenspace and repeated measurements of cf-PWV to assess the progression of arterial stiffness. While the results indicated that higher exposure to residential surrounding greenspace was associated with less arterial stiffness at baseline, the association did not attain statistical significance. In turn, the results of complete case analyses were suggestive of a positive association between higher exposure to residential surrounding greenspace and accelerated progression of arterial stiffness, however, these results were also statistically nonsignificant and not consistent in all sensitivity analyses. These associations may have been stronger among men and participants living in more

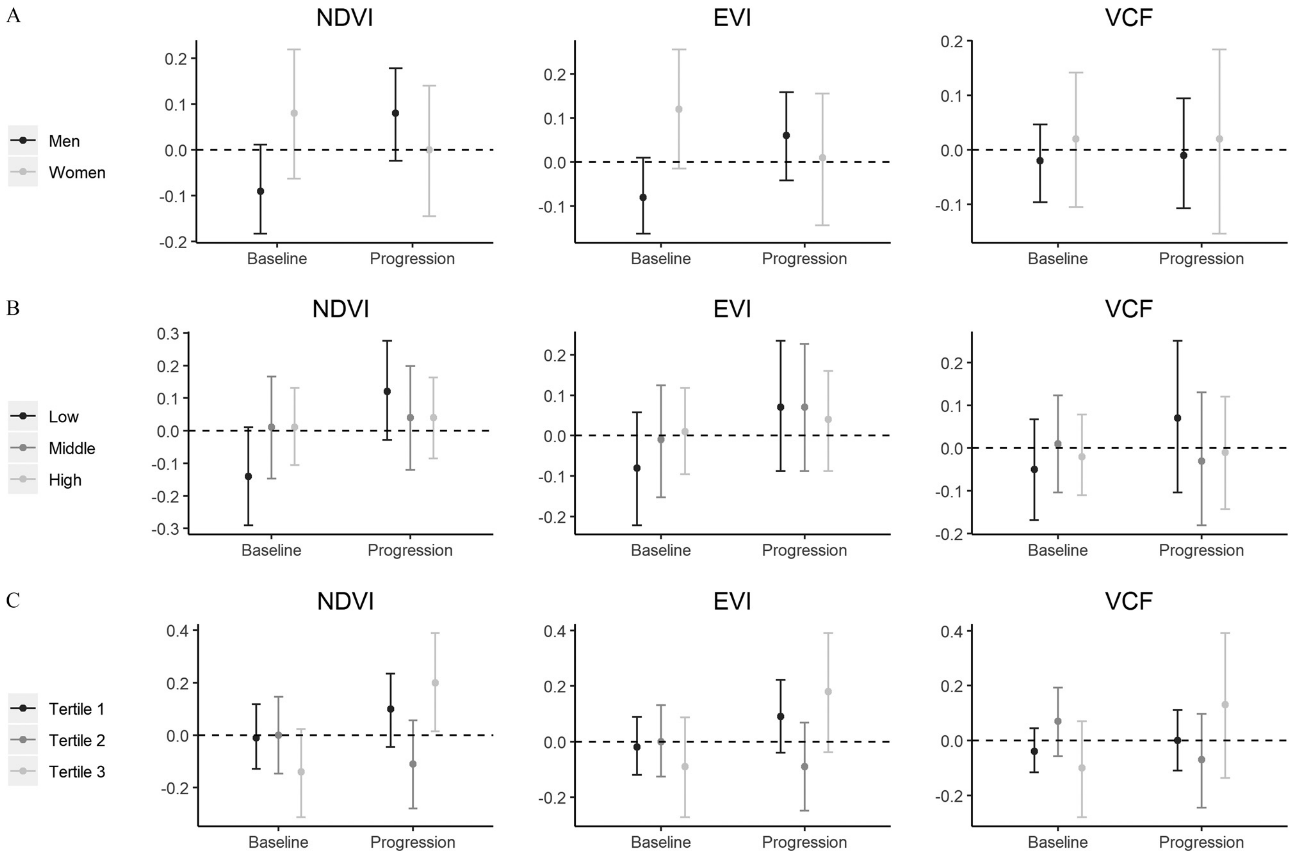

Figure 2. Difference in baseline (Baseline) and 4-year progression (Progression) in pulse wave velocity (m/s) (95% confidence interval) associated with one interquartile range increase in NDVI, EVI, or VCF in the 500-m buffer stratified by (A) sex, (B) education, and (C) area income deprivation. Note: EVI, enhanced vegetation index; NDVI, normalized difference vegetation index; VCF, vegetation continuous fields.

deprived areas. Our models were adjusted for a wide range of potential confounders, selected *a priori* based on previous relevant literature (Ahmadi-Abhari et al. 2017; Brunner et al. 2015; de Keijzer et al. 2018, 2019b; Dzhambov et al. 2018; Foraster et al. 2017; Lenters et al. 2010; Ljungman et al. 2018; O'Neill et al. 2017; Trudel et al. 2016). Moreover, in sensitivity analyses, we further adjusted for additional covariates, which did not notably change our findings.

The baseline estimates indicated the cross-sectional association between greenspace exposure at the first visit and the cf-PWV measurement in that visit. The lack of significant baseline associations may be partially because greenspace exposure at baseline could be a poor indicator of accumulated historical exposures, for instance, because of changes in residence, changes in green cover, or other changes. In addition, contrary to our hypothesis, we observed a positive association between greater exposure to residential surrounding greenspace and increased progression in arterial stiffness over the study period, although this association was not statistically significant and not consistent in all sensitivity analyses. Finding no consistent longitudinal association could have been influenced by the short follow-up period with only two assessment points of arterial stiffness about 4 y apart. In addition, this study was based on participants who had already been followed up for 22 y, while adults with worse health outcomes (including more arterial stiffness) are more likely to have been lost to follow-up before our study period.

Comparison with Previous Studies

To our knowledge, no previous study evaluated the association between long-term greenspace exposure and arterial stiffness. It is therefore not possible to compare our findings with those of previous studies. However, our findings are in contrast with several relevant studies. A cross-sectional study from India studied the association between greenspace exposure (as measured by NDVI) and biomarkers of vascular aging in adults $\geq$20 years of age (Lane et al. 2017). These biomarkers included SBP, DBP, central pulse pressure (cPP), and flow-mediated dilatation (FMD). Higher NDVI was associated with lower SBP, DBP, and cPP and higher FMD, indicating improved vascular aging.

Furthermore, several studies investigated the association between greenspace and hypertension (Fong et al. 2018; James et al. 2015). However, few studied the association in middle-aged or older adults, and most studies were cross-sectional (Brown et al. 2016; Jia et al. 2018; Lim et al. 2017; Sarkar et al. 2018; Tamosiunas et al. 2014). In a study from the United States, higher NDVI at census block level was associated with lower odds of hypertension in 249,405 Medicare beneficiaries $\geq$65 years of age (Brown et al. 2016). Similarly, a study of 1,944 Chinese adults $\geq$40 years of age found lower odds of hypertension among participants with higher exposure to NDVI (Jia et al. 2018). However, results were mixed. In a cross-sectional study of 429,334 adults $\geq$38 years of age from the United Kingdom, nonlinear associations were found between greenspace (assessed as quartiles of NDVI) and odds of high blood pressure and hypertension, with beneficial associations for greenspace in the third quartile but not in the fourth quartile (Sarkar et al. 2018). In addition, proximity to greenspace was not associated with hypertension in two cross-sectional studies among 5,112 adults from Lithuania $\geq$45 years of age (Tamosiunas et al. 2014), or among 1,972 adults from Singapore $\geq$40 years of age (Lim et al. 2017).

Limitations

This study faced some limitations. First, the external generalizability of the findings needs confirmation by further studies because the Whitehall II study consisted of civil servants and underrepresented women and ethnic minorities. Second, to characterize arterial stiffness, only data on cf-PWV were available; thus, we could not evaluate the association with PWV at other sites of the cardiovascular tree, for which we might have observed other results. Nevertheless, cf-PWV has been regarded as "the most clinically relevant" marker of arterial stiffness (Laurent et al. 2006) and is a strong indicator of cardiovascular risk (Zhong et al. 2018), similar to brachial–ankle PWV (Tanaka et al. 2009). Plus, to assess progression of arterial stiffness, the follow-up period was just 4 y and only two measurement points. Third, our exposure assessment was based on satellite images that encompass all greenspace in a standardized way but did not consider the type of vegetation or land cover or the quality or actual use of the greenspace. Lack of data on the type and quality of greenspace could have resulted in exposure misclassification, potentially biasing associations towards or away from null, if, for example, the misclassification of the type of vegetation or quality was dependent on the neighborhood SES or was random. Furthermore, our exposure assessment focused on residential exposure, although the participants could have greenspace exposure at other locations such as work. Again, such an exposure misclassification could have resulted in over- or underestimation of the associations, for example, depending on whether working locations were related to systematically greater or lower exposure to greenspaces. Nevertheless, older adults may spend more time near home than younger population groups, for instance, due to retirement or reduced mobility. In the present study, over 60% of the participants were retired. Last, like any other observational study, we cannot rule out the possibility of residual confounding. Regarding health effects of greenspace exposure, residual SES confounding could be of particular concern. However, to minimize this possibility, we controlled our analyses for two individual- and two neighborhood-level indicators of SES. Additionally, we have provided the associations in each stratum of SES, in effect comparing participants with similar SES in each stratum. Furthermore, other environmental factors such as noise and the built environment may have affected the association between greenspace and arterial stiffness. Further adjusting the main analyses for the density of roads and domestic buildings did seem to strengthen the association between greater exposure to residential surrounding greenspace and reduced arterial stiffness at baseline, although we only observed a statistically significant association with NDVI in the 1,000-m buffer. The association with the progression of arterial stiffness was not notably affected by the adjustment for road or domestic building density.

Potential Underlying Mechanisms

Although in our current study, we did not observe any significant association between long-term exposure to residential surrounding greenspace and arterial stiffness, we consider it a plausible association that should be further investigated, as several pathways may underlie the association (Markevych et al. 2017). First, residing in neighborhoods with more greenspace has been, although not consistently, associated with increased physical activity and higher maintenance of physical activity levels in older adults (Barnett et al. 2017; Dalton et al. 2016), while physical activity may protect against progression of arterial stiffness (Ahmadi-Abhari et al. 2017). Furthermore, greenspace in the neighborhood may foster social support and cohesion, reduce feelings of stress, and improve mental health (de Vries et al. 2013; Gascon et al. 2015). In turn, better mental health, less stress, and improved social relationships may be associated with less arterial stiffness (Bomhof-Roordink et al. 2015; Midei and Matthews 2009; Seldenrijk et al. 2011); however, studies are scarce, and the direction of the association is unclear. Last, greater exposure to greenspace may be associated with reduced exposure to air pollution and noise (Dadvand et al. 2012, 2015), while higher levels of noise and air pollution may increase arterial stiffness (Foraster et al. 2017; Ljungman et al. 2018). In addition to air pollution, noise may also be an important mechanism underlying the association between greenspace exposure and arterial stiffness, which should be examined by future studies.

Conclusions

In a longitudinal study of adults who were 55 to 79 years of age at baseline, greater long-term exposure to residential surrounding greenspace was not found to be significantly associated with arterial stiffness or with the progression of arterial stiffness over 4 y.

Arterial stiffness is an important indicator of cardiovascular aging and has been strongly associated with cardiovascular morbidity and mortality (Vlachopoulos et al. 2010). Considering that the burden of disease in the older population is driven by CVD, and considering the rapid growth of the world's older population, it is of increasing importance to identify factors that foster cardiovascular health and, hence, healthy aging. Additionally, an increasing number of older adults are living in cities (United Nations 2015), where exposure to greenspace is limited. Although our findings did not suggest a significant association between exposure to residential surrounding greenspace and arterial stiffness, a substantial number of previous studies indicated that greenspace could contribute to the maintenance of cardiovascular health at older age. Given the biological plausibility of our evaluated association, we call for further longitudinal studies in other settings and climates and with longer follow-up periods while taking account of the specific characteristics of greenspace that could provide health benefits such as the type, size, quality, or access to greenspace. Moreover, special attention is needed for the pathways through which greenspace may impact arterial stiffness and for potential effect modification by sex and SES.

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