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A feasibility study on the association between residential greenness and neurocognitive function in middle-aged Bulgarians

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Recent research has indicated that exposure to residential vegetation ("greenness") may be protective against cognitive decline and may support the integrity of the corresponding brain structures. However, not much is known about these effects, especially in less affluent countries and in middle-aged populations. In this study, we investigated the associations between greenness and neurocognitive function. We used a convenience sample of 112 middle-aged Bulgarians and two cognitive tests: the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB) and the Montreal Cognitive Assessment (MoCA). In addition, structural brain imaging data were available for 25 participants. Participants' home address was used to link cognition scores to the normalised difference vegetation index (NDVI), a measure of overall neighbourhood vegetation level (radii from 100 to 1,000 m). Results indicated that higher NDVI was consistently associated with higher CERAD-NB and MoCA scores across radial buffers and adjustment scenarios. Lower waist circumference mediated the effect of NDVI on CERAD-NB. $NDVI_{100\text{-}m}$ was positively associated with average cortical thickness across both hemispheres, but these correlations turned marginally significant ($P<0.1$) after correction for false discovery rate due to multiple comparisons. In conclusion, living in a greener neighbourhood might be associated with better cognitive function in middle-aged Bulgarians, with lower central adiposity partially accounting for this effect. Tentative evidence suggests that greenness might also contribute to structural integrity in the brain regions regulating cognitive functions. Future research should build upon our findings and investigate larger and more representative population groups.

KEY WORDS: cognitive function; green spaces; MRI; natural outdoor environments; neurodevelopment

Dementia is characterised by objective impairment in cognitive domains, such as deficits in memory and executive functions (1). The continuum of cognitive decline ranges from Alzheimer's disease, which accounts for 60 to 70 % of cases (1), to prodromal forms like mild cognitive impairment, which affects 10–20 % of those aged 65 years and older (2). Dementia affects 47 million people worldwide and imposes a heavy burden on society (≈$818 billion in 2015), especially in low- and middle-income countries, where nearly 60 % of people with dementia live (1). Less is known about the economics of mild cognitive impairment, but it is also associated with substantial costs (3).

Widely recommended interventions to prevent or delay cognitive decline include management of cerebrovascular risk factors (e.g. the metabolic syndrome constellation), promotion of physical and mental activity, and social interaction (2, 4, 5). At the same time, various characteristics of the living environment have the potential to shape risk factors and health-enhancing behaviours. For instance, neighbourhood green vegetation (i.e., street trees, urban parks, and gardens – "greenness" in short) can mitigate air pollution and noise (6), two risk factors which can instigate neuroendocrine stress, inflammatory response, and alterations in neurotransmitter signalling in the brain regions (e.g. prefrontal cortex) responsible for regulation of cognitive functions (7, 8). Green environments require little top-down processing and provide opportunities for the restoration and recovery of the neurocognitive apparatus involved in sustaining directed attention (9–11). According to Browning and Alvarez's Scanning for Threats theory (12), green environments can dampen the brain's tendency to scan the surrounding environment for potential threats or dangers, which typically triggers sympathetic activation, and therefore protect the limbic system involved in danger signalling. Green spaces such as parks can engage local residents in outdoor physical activity and social interaction (6). From the clinical perspective, greenness appears protective against cardiovascular and cerebrovascular risk, as it can reduce high blood pressure (13, 14), cholesterol levels (15), and obesity (16), although the evidence remains

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inconclusive (17). In addition, emerging neuroscientific findings show that higher neighbourhood greenness might support structural integrity of those brain regions which are often associated with cognitive decline (18, 19). It is therefore conceivable that living in an environment with high amount of greenness may be conducive to health-enhancing experiences and behaviours and thus contribute to offsetting cognitive impairment.

Despite these encouraging findings, however, not much is known about the effects of greenness on neurocognitive function, especially in less affluent countries and in middle-aged populations, in whom subtle precursors of cognitive impairment have been studied poorly (1, 6). The aim of this exploratory study was therefore to address these gaps in literature in a sample of middle-aged Bulgarians whose home address could be linked retrospectively to performance on several cognitive tests and in a subsample whose structural brain imaging data were available. The intent was to evaluate the feasibility of a future large-scale research in Bulgaria and other countries.

PARTICIPANTS AND METHODS

Study design and sampling

The present cross-sectional study takes advantage of data originally collected to investigate vascular risk factors for possible mild cognitive impairment in middle-aged individuals (20). The data were collected between 2014 and 2016 in the District of Plovdiv, Bulgaria. Participants were examined at the Departments of Neurology and Endocrinology at "St George" University Hospital, Plovdiv. We included literate volunteers aged between 45 and 55 years and excluded patients with decompensated chronic diseases (other than hypertension/diabetes), psychiatric disorders (e.g. depression), dementia, addiction to alcohol/drugs, and those taking medication that could influence carbohydrate/lipid metabolism.

The participants were asked to complete a questionnaire asking about basic demographic, lifestyle, and health-related factors. They also underwent a clinical examination and neuropsychological evaluation. Residential addresses needed for assignment of geographic variables were obtained from participants' medical records. Participants had lived in their current home for at least five years.

From the database of 120 individuals we excluded those with missing outcome data and unsuccessfully geocoded residential address, which left us with a sample of 112 participants. Brain magnetic resonance imaging (MRI) was performed in a subsample of 25 participants, and these data were used for an exploratory analysis.

Informed consent was obtained from all participants prior to participation in the study. The study protocol adhered to the Declaration of Helsinki and was approved by the University Ethics Committee.

Cognitive function assessment

Participants were examined by a trained clinical neuropsychologist. Overall level of cognitive function was assessed with two validated neuropsychological tests. The main outcome was the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB). CERAD-NB was developed to be a reliable and standardized tool for measuring primary cognitive manifestations of Alzheimer's disease (21) and has already been used to study environmental determinants of cognitive function (22). It consists of the following subtests: Verbal Fluency (VF), modified Boston Naming Test (BNT), Constructional Praxis (CP), Word List Memory (WLM), Word List Recall (WLR), and Word List Recognition (WLRc). They tap different aspects of memory deficits, such as verbal productivity, semantic memory, visual perception, immediate and delayed memory, learning ability of non-associated verbal material, and visual-constructive abilities (23). Each subtest was scored based on the sum of points from successfully completed answers. The total score (0 to 100) from these subtests was calculated according to the method proposed by Chandler et al. (23).

For comparison, we used another supplementary screening tool for mild cognitive impairment, the Montreal Cognitive Assessment (MoCA) (24). MoCA is often used to differentiate cognitive impairment from normal cognitive aging (25).

Structural brain imaging

High resolution anatomical images were acquired for 25 participants using the MAGNETOM Aera 1.5T magnetic resonance scanner (Siemens Healthcare, Erlangen, Germany) (26). Image outputs were visually inspected for any artefacts by an experienced neuroradiologist. A subsequent automated morphometric analysis of raw brain scans allowed investigation of the relationships between residential greenness and brain structure. Structural MRI T1 MPRAGE 3D images (acquisition matrix 232/256, slice thickness 0.9 mm, 192 slices, voxel size T 0.9 mm, TE 4,28 TR 1620, FoV 240*265, TI 918) were automatically processed using Freesurfer v. 5.3.0 (Laboratory for Computational Neuroimaging at Athinoula A. Martinos Center for Biomedical Imaging, Harvard University, Charlestown, MA, USA). Post-processing (surface-based methods) consisted of several steps to obtain cortical thickness values for brain regions of interest (27–29) based on the Desikan Atlas (30). Cortical thickness values were extracted and used for subsequent investigation of the relationships between residential greenness and brain structure. Our hypothesis was that higher residential greenness would be associated with greater cortical thickness in several brain regions. Informed by previously reported relations of brain structure with cognitive function (31, 32) and greenness exposure (18, 19), we narrowed the

scope down to the following regions of interest in both hemispheres:

- Frontal lobe – superior frontal gyrus; rostral and caudal middle frontal gyrus; inferior frontal gyrus (pars opercularis, pars triangularis, and pars orbitalis); lateral and medial orbitofrontal gyrus; precentral gyrus; and paracentral gyrus;
- Parietal lobe – precuneus;
- Temporal lobe – fusiform gyrus, entorhinal cortex, parahippocampal gyrus;
- Occipital lobe – cuneus;
- Amygdala and hippocampus;
- Insular cortex.

Residential greenness

Residential greenness was operationalised as the normalised difference vegetation index (NDVI) (33), commonly employed as a proxy for overall vegetation level (6, 19, 34, 35). It ranges from -1 to +1, where positive values closer to 1 indicate high greenness (36). NDVI was calculated based on the difference of Earth's surface reflectance in two vegetation-informative wavelengths, visible red (RED) and near infrared (NIR) light: NDVI=(NIR-Red)/(NIR+RED). For these calculations, we used a single cloud-free Landsat 8 Operational Land Imager satellite image at a resolution of 30x30 m, obtained on 9 July 2015 to capture maximum summertime greenness within the timeframe of data collection (retrieved from: https://earthexplorer.usgs.gov/). Informed by expert recommendations, negative pixel values were removed from the raster before NDVI assignment to partial out the effect of water bodies in the residential area, which may also be beneficial for neurodevelopment (6). Mean NDVI was abstracted in the radii of 100 m, 300 m, 500 m, and 1000 m around the residence (37). Geographic data were managed and calculated using QGIS 3.8.0 (OSGeo, Chicago, IL, USA) and ArcGIS 10.3 (ESRI, Redlands, CA, USA).

Other covariates

Relying on available literature, we determined additional covariates that could attenuate or otherwise modify the effect of NDVI on neurocognitive function, and used them in several alternative statistical models adjusting for their effect. We had self-reported data on participants' sex, age, education (secondary school or university), smoking (pack-years of smoking), and alcohol consumption (yes or no).

Waist circumference was measured according to the WHO protocol (38). Morning blood pressure was measured according to the American Heart Association guidelines using a calibrated aneroid sphygmomanometer with standard cuff-size (39).

Morning venous blood samples were drawn in a sitting position after an overnight fast and collected by nurses using standard serum-separating vacutainers. The samples were analysed for total cholesterol and blood glucose using enzymatic methods and automated biochemical analysers.

Nitrogen dioxide (NO_2) levels were taken from a map with a resolution of 100 x 100 m generated from a global land use regression model using data from air quality monitoring stations, satellite readings, and other common geographic variables related to air pollution (40).

Road traffic day-evening-night noise (L_{den}) levels were available for participants residing in the city of Plovdiv (n=83), which has a strategic noise map (41) in line with the EU Directive 2002/49/EC (42). L_{den} was modelled for the year 2016 using the CNOSSOS-EU noise model (43). Each address was inspected visually on a noise contour map, and building façades were assigned L_{den} in 5-dB exposure bins (from 55 to 80 dB). For the analyses, we considered L_{den} at the least exposed façade, because it provided greater exposure contrast between participants' addresses. Population in the 500-m radius around home and the city of residence (Plovdiv vs other) was taken as a proxy for urbanicity (44).

Statistical analysis

Inspection of the dataset indicated that no covariate had more than 10 % of missing values. The values were missing at random and were imputed using the expectation-maximisation algorithm (45). The outcome variables had normal or close-to-normal distributions and were therefore analysed with parametric methods (46).

Descriptive statistics and correlations were used to identify general patterns of association between the data. We then employed multivariate linear regression models to investigate the relationships of NDVI with CERAD-NB and MoCA total scores. We also looked at specific CERAD subtests. The main model (Model 1) was adjusted for sex, age, education, city, and population in the 500 m radius. We also designed alternative models to test whether additional covariates or putative mediators would attenuate the effect of NDVI. They were all based on Model 1 but also included the following covariates: smoking and alcohol consumption (Model 2); waist circumference, systolic blood pressure, total cholesterol, and blood glucose (Model 3); NO_2 (Model 4); and L_{den} (Model 5). To control for co-exposure to NO_2 as a confounding variable that highly correlated with NDVI (tolerance<0.2 and Variance Inflation Factor >5), we first regressed NO_2 against NDVI in the respective radius and then used model residuals as a covariate in Model 4 (47).

Next we tested single mediation models linking $NDVI_{100\text{-}m}$ to CERAD-NB total score via the following putative mediators: waist circumference, systolic blood pressure, total cholesterol, glucose, and NO_2. L_{den} was not measured on a truly continuous scale and was not suitable for mediation modelling. We used the PROCESS 2.16 macro (48). 95 % CIs of indirect effects were estimated with bias-corrected bootstrapping (5000 samples).

$NDVI_{100\text{-}m}$, which was found to be the best statistical predictor of cognitive function in the main analysis, was used for the analysis of cortical thickness in a subsample of 25 participants. We computed Pearson correlations with cortical thickness in the a priori selected brain regions of interest. To control for false discovery rate due to multiple comparisons (proportion of type I errors), we applied the Benjamini–Hochberg correction method (49).

Data were processed with SPSS Statistics for Windows v. 17 (SPSS Inc., Chicago, MI, USA), and associations were considered statistically significant at the $P<0.05$ level (2-tailed).

RESULTS

Sample characteristics and bivariate associations

Characteristics of the study sample are presented in Table 1. Mean age was 50 years and the majority of participants had higher education and were women. Bivariate Spearman correlations (Table 2) show that better cognitive function (i.e., higher CERAD score) was associated with higher greenness in the 100-m radius. NDVI within other radii did not seem to contribute to cognitive function or other biomedical variables. CERAD-NB was also associated with higher educational level, female sex, lower waist circumference, lower systolic blood pressure, and, surprisingly, higher NO_2 and L_{den}. Correlations between the geographic variables were in line with literature – higher greenness was inversely related to population density, NO_2, and L_{den}.

Table 1 Characteristics of the study sample

Characteristics	N=112
Sociodemographic factors	
Age, years (mean, SD)	49.99 (3.34)
Men (n, %)	41 (36.6)
Higher education (n, %)	82 (73.2)
Greenness	
$NDVI_{100\text{-}m}$ (median, IQR)	0.39 (0.10)
$NDVI_{300\text{-}m}$ (median, IQR)	0.40 (0.07)
$NDVI_{500\text{-}m}$ (median, IQR)	0.40 (0.08)
$NDVI_{1000\text{-}m}$ (median, IQR)	0.41 (0.09)
Cognitive function	
CERAD-NB (mean, SD)	82.45 (7.77)
MoCA (mean, SD)	26.01 (2.69)
Other covariates	
Pack-years of smoking (median, IQR)	7.00 (18.00)
Alcohol consumption (n, %)	76 (67.9)
Waist circumference, cm (mean, SD)	94.22 (15.03)
Systolic blood pressure, mmHg (mean, SD)	119.86 (12.51)
Total cholesterol, mmol/L (mean, SD)	5.87 (1.14)
Glucose, mmol/L (mean, IQR)	5.47 (1.15)
NO_2, $\mu g/m^3$ (mean, SD)	18.66 (4.03)
L_{den}>65 dB(A) (n, %)[a]	46 (41.1)
Residence in Plovdiv city (n, %)	83 (74.1)
$Population_{500\text{-}m}$ (median, IQR)	8381.17 (7108.51)

CERAD-NB – Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery; IQR – interquartile range; L_{den} – day-evening-nigh noise level; NDVI – normalised difference vegetation index; MoCA – Montreal Cognitive Assessment; NO_2 – nitrogen dioxide; SD – standard deviation; [a] L_{den} was only available for participants residing in the city of Plovdiv (n=83)

Associations between greenness and cognitive function

Table 3 shows multivariate correlations between NDVI and cognitive function. Higher NDVI was consistently associated with higher CERAD-NB and MoCA scores across the radii and adjustment models. This effect was most pronounced for $NDVI_{100\text{-}m}$. However, when we re-run the main model for each CERAD subtest individually, $NDVI_{100\text{-}m}$ significantly correlated only with verbal fluency (β=1.47; 95 % CI: 0.60, 2.34).

Single mediation models showed that higher NDVI was associated with higher CERAD-NB score through lower waist circumference across all radii (Table 4). None of the other factors acted as a mediator.

Greenness and cortical thickness

First we compared the participants with MRI data to the rest to check whether any selection bias was at play. Table 5 clearly shows that there were no materially important differences between the two groups, except for the significantly higher pack-years of smoking in the subsample of 25 participants with MRI.

The analysis of the brain regions of interest showed that $NDVI_{100\text{-}m}$ positively correlated with average cortical thickness across both hemispheres, more specifically in several gyri across the prefrontal cortex, bilateral fusiform gyrus, left precuneus and insula, and right cuneus (Table 6). These correlations largely survived adjustment for sex, age, education, city, and population in the 500-m radius (data not shown). However, none of them remained significant ($P<0.1$) after correction for false discovery rate (Table 6).

DISCUSSION

Overall findings

We found evidence that higher greenness was consistently associated with better performance on two distinct cognitive tests. This association was partly mediated by lower waist circumference. Our sub-analysis also suggested that higher greenness might support structural integrity in relevant brain regions.

Table 2 Spearman correlations between the main variables in the study

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. CERAD-NB	1	**0.35***	**0.12***	-0.08	-0.15	-0.16	**0.22***	**0.26***	0.13	0.05	**0.31***	**0.26***	**-0.42***	**-0.26***	-0.01	-0.18	0.07	0.05
2. MoCA		1	0.08	0.001	-0.01	0.03	0.13	0.06	0.13	-0.07	0.12	**0.22***	-0.15	-0.11	-0.05	0.11	0.06	0.06
3. $NDVI_{100\text{-}m}$			1	**0.63***	**0.41***	**0.19***	**-0.24***	-0.05	-0.15	-0.08	-0.04	-0.07	-0.14	-0.06	0.05	-0.001	0.03	0.13
4. $NDVI_{300\text{-}m}$				1	**0.87***	**0.63***	**-0.47***	-0.05	**-0.37***	0.06	-0.03	-0.10	-0.01	-0.15	-0.05	0.04	0.01	0.004
5. $NDVI_{500\text{-}m}$					1	**0.85***	**-0.57***	-0.11	**-0.48***	0.04	-0.05	-0.18*	0.07	-0.06	-0.06	0.15	0.05	-0.002
6. $NDVI_{1000\text{-}m}$						1	**-0.67***	**-0.22***	**-0.53***	0.09	-0.08	-0.18	0.14	0.02	-0.08	0.13	-0.03	-0.10
7. NO_2							1	0.12	**0.56***	-0.01	0.15	0.09	**-0.20***	-0.08	-0.03	-0.08	0.03	0.02
8. L_{den}								1	0.01	0.07	0.06	0.01	-0.18	-0.07	0.03	**-0.26***	-0.03	0.10
9. Population $_{500\text{-}m}$									1	-0.01	0.13	0.03	-0.05	0.05	0.08	0.06	0.15	0.09
10. Age										1	0.03	-0.15	-0.01	**0.28***	**0.24***	0.04	-0.08	-0.01
11. Education (ref. secondary)											1	0.04	**-0.27***	-0.10	0.03	0.01	-0.08	0.02
12. Sex (ref. male)												1	**-0.59***	**-0.37***	0.02	-0.13	-0.07	**-0.29***
13. Waist circumference													1	**0.42***	-0.09	0.15	0.06	-0.01
14. Systolic blood pressure														1	0.09	0.08	-0.05	-0.07
15. Cholesterol															1	0.09	-0.05	0.02
16. Glucose																1	0.12	<0.001
17. Smoking (pack-years)																	1	**0.34***
18. Alcohol drinking (ref. "no")																		1

CERAD-NB – Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery; MoCA – Montreal Cognitive Assessment; NDVI – normalised difference vegetation index; *Correlation is significant at the P<0.05 level (two-tailed)

Table 3 Associations between residential greenness and cognitive function (N=122)

Greenness	Model 1	Model 2	Model 3	Model 4	Model 5
	Outcome: Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB)				
$NDVI_{100\text{-}m}$	**2.12 (0.35, 3.89)***	**2.08 (0.33, 3.83)***	**1.83 (0.11, 3.54)***	**2.12 (0.39, 3.85)***	**2.64 (0.59, 4.68)***
$NDVI_{300\text{-}m}$	**1.48 (0.24, 2.72)***	**1.45 (0.23, 2.68)***	**1.27 (0.08, 2.48)***	1.18 (-0.07, 2.42)	**1.85 (0.42, 3.28)***
$NDVI_{500\text{-}m}$	**1.70 (0.28, 3.11)***	**1.66 (0.26, 3.06)***	**1.46 (0.09, 2.83)***	**1.51 (0.09, 2.94)***	**2.11 (0.47, 3.74)***
$NDVI_{1000\text{-}m}$	**1.91 (0.31, 3.50)***	**1.87 (0.30, 3.44)***	**1.64 (0.10, 3.19)***	**1.98 (0.40, 3.57)***	**2.37 (0.53, 4.21)***
	Outcome: Montreal Cognitive Assessment (MoCA)				
$NDVI_{100\text{-}m}$	**0.71 (0.07, 1.35)***	**0.67 (0.04, 1.31)***	**0.73 (0.09, 1.36)***	**0.71 (0.07, 1.34)***	**0.76 (0.14, 1.38)***
$NDVI_{300\text{-}m}$	**0.49 (0.05, 0.94)***	**0.47 (0.03, 0.91)***	**0.51 (0.07, 0.95)***	0.43 (-0.02, 0.89)	**0.53 (0.10, 0.96)***
$NDVI_{500\text{-}m}$	**0.57 (0.05, 1.08)***	**0.54 (0.03, 1.05)***	**0.58 (0.07, 1.09)***	0.51 (-0.01, 1.02)	**0.61 (0.11, 1.10)***
$NDVI_{1000\text{-}m}$	**0.64 (0.06, 1.21)***	**0.60 (0.03, 1.18)***	**0.65 (0.08, 1.22)***	**0.67 (0.10, 1.24)***	**0.68 (0.12, 1.24)***

NDVI – normalised difference vegetation index; Model 1 (main model): adjusted for sex, age, education, city, and population in the 500-m radius; Model 2: Model 1 covariates + smoking and alcohol; Model 3: Model 1 covariates + waist circumference, systolic blood pressure, total cholesterol, and blood glucose; Model 4: Model 1 covariates + nitrogen dioxide; Model 5: Model 1 covariates + day-evening-nigh noise level. The sample size for Model 5 was 83; Non-standardised linear regression coefficients with their 95 % CI are presented; *Association is significant at the P<0.05 level (two-tailed)

Table 4 Single mediation models linking residential greenness and cognitive function (N=122)

Greenness	Indirect effects on CERAD-NB total score through specific mediators				
	Waist circumference	**Systolic blood pressure**	**Total cholesterol**	**Glucose**	**Air pollution (NO_2)**
$NDVI_{100\text{-}m}$	**0.35 (0.02, 1.04)***	0.17 (-0.17, 0.80)	-0.04 (-0.59, 0.14)	-0.01 (-0.52, 0.49)	-0.39 (-1.25, 0.004)
$NDVI_{300\text{-}m}$	**0.25 (0.01, 0.70)***	0.12 (-0.13, 0.53)	-0.02 (-0.47, 0.09)	-0.01 (-0.35, 0.35)	-0.27 (-0.88, 0.02)
$NDVI_{500\text{-}m}$	**0.28 (0.02, 0.82)***	0.14 (-0.12, 0.63)	-0.03 (-0.46, 0.11)	-0.01 (-0.41, 0.40)	-0.31 (-0.96, 0.02)
$NDVI_{1000\text{-}m}$	**0.32 (0.02, 0.92)***	0.15 (-0.15, 0.70)	-0.03 (-0.60, 0.12)	-0.01 (-0.47, 0.47)	-0.35 (-1.14, 0.01)

CERAD-NB – Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery; NDVI – normalised difference vegetation index; NO_2 – nitrogen dioxide; Mediation models are adjusted for sex, age, education, city, and population in the 500-m radius. Each mediator is tested independently of the others; Non-standardised linear regression coefficients with their 95 % CI are presented; *Association is significant at the P<0.05 level (two-tailed)

Greenness is a feature of the living environment that has been receiving growing attention as potentially beneficial influence on cognitive function in children and adults. Our findings support earlier epidemiological research showing protective effect on several cognitive domains (19, 34, 35, 50, 51). For example, Dadvand et al. (50) observed enhanced working memory and lower inattentiveness in children exposed to greenness, both at school and neighbourhood. This beneficial effect on attention was corroborated by another study that looked at lifelong exposure to residential greenness during preschool and early primary school years (34). Cognitive decline over a 10-year follow-up was slower in middle-aged British civil servants living in greener neighbourhoods (35), and another study showed that proximity to nature benefited cognitive function (51). Interestingly, when we looked into specific subtests, greenness was positively associated only with verbal fluency, which measures semantic memory and executive functions (cognitive flexibility) (23). However, at this point, we can offer no clear explanation of these findings. Other authors (22) have also reported significant association between exposure to traffic noise and some CERAD subtests.

Mechanisms believed to mediate these benefits are complex and manifold (6). For example, vegetation biomass can mitigate concentrations of some air pollutants and disrupt propagation of sound waves, which, in turn, have been linked to impaired neurocognitive function (7). We observed counterintuitive bivariate associations between NO_2 and L_{den} with CERAD-NB, even though literature reports detrimental effects on neurodevelopment. For instance, Tzivian et al. (52) reported positive associations between long-term air pollution and traffic noise exposures and mild cognitive impairment, with some evidence of synergistic effects (53). Another recent study (22) observed inverse relationships between noise levels and total cognition as well as constructional praxis in elderly women tested with CERAD. To our knowledge, only two studies have tested mediation by air pollution/noise; one (51) did not find any such evidence in adults, but the other (34) showed partial mediation by traffic-related air pollution in children. Clearly, further research on these potential mediators is needed.

Table 5 Comparison of characteristics between participants with MRI (brain region of interest data) and those without MRI

Characteristics	No MRI data (n=87)	With MRI data (n=25)	P-value
Sociodemographic factors			
Age, years (mean, SD)	50.06 (3.39)	49.73 (3.20)	0.682
Men (n, %)	35 (38.9)	6 (27.3)	0.459
Higher education (n, %)	66 (73.3)	16 (72.7)	1.000
Greenness			
$NDVI_{100\text{-}m}$ (mean, SD)	0.39 (0.08)	0.40 (0.09)	0.684
$NDVI_{300\text{-}m}$ (mean, SD)	0.40 (0.06)	0.41 (0.06)	0.263
$NDVI_{500\text{-}m}$ (mean, SD)	0.41 (0.06)	0.43 (0.07)	0.111
$NDVI_{1000\text{-}m}$ (mean, SD)	0.42 (0.07)	0.44 (0.08)	0.361
Cognitive function			
CERAD-NB (mean, SD)	82.44 (7.99)	82.77 (3.90)	0.858
MoCA (mean, SD)	26.08 (2.84)	25.73 (1.98)	0.585
Other covariates			
Pack-years of smoking (median, IQR)	**2.25 (15.00)**	**13.75 (23.50)**	**0.001**
Alcohol consumption (n, %)	62 (68.9)	14 (63.6)	0.621
Waist circumference, cm (mean, SD)	93.31 (14.69)	97.14 (16.45)	0.287
Systolic blood pressure, mmHg (mean, SD)	119.11 (12.47)	122.05 (13.15)	0.330
Total cholesterol, mmol/L (mean, SD)	5.96 (1.17)	5.50 (0.91)	0.087
Glucose, mmol/L (mean, IQR)	**5.36 (0.99)**	**5.92 (1.60)**	**0.040**
NO_2, $\mu g/m^3$ (mean, SD)	19.01 (4.00)	17.52 (4.12)	0.122
L_{den}>65 dB(A) (n, %)[a]	37 (56.1)	9 (52.9)	1.000
Residence in Plovdiv city (n, %)	66 (73.3)	17 (77.3)	0.792
$Population_{500\text{-}m}$ (median, IQR)	8930.64 (6334.30)	6587.49 (7331.20)	0.433

CERAD-NB – Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery; IQR – interquartile range; L_{den} – day-evening-nigh noise level; NDVI – normalised difference vegetation index; MoCA – Montreal Cognitive Assessment; MRI – magnetic resonance imaging; NO_2 – nitrogen dioxide; SD – standard deviation; [a] L_{den} was only available for participants residing in the city of Plovdiv (n=83)

We also tested several cardiovascular risk factors (abdominal adiposity, high blood pressure, high cholesterol, and glucose) as potential mediators and found that only waist circumference mediated the effect of greenness. This is in line with findings that proximity to green spaces and overall residential greenness may be conducive to physical health (54) and protect against obesity (16), and that, in turn, abdominal obesity is predictive of cognitive impairment (55). We speculate that it would take a long-term prospective study (as opposed to our cross-sectional one) to establish the real effect of the other potential mediators analysed in our study.

Only a handful of studies have looked into the associations between residential greenness and brain structure. Our exploratory MRI of 25 participants suggests that greenness within the 100-m radius of the residence may preserve the average cortical thickness across brain regions whose thinning is otherwise associated with cognitive impairment and Alzheimer's disease (31, 32). Despite the low statistical power of our analysis, the direction of associations was consistent with previous neuroimaging findings of positive association between lifelong exposure to greenness and grey matter volume in the prefrontal and premotor cortex of children (19). Kühn et al. (18) reported forest within 1 km radius of home benefits amygdalar integrity. One possible explanation is that neighbourhood features like parks and street vegetation along commuting lines provide diverse sensory experience and thus elicit processes behind brain plasticity (18, 56, 57).

Contact with natural landscapes may promote perceived restorative quality and reduce exposure to traffic noise and air pollution, thus stimulating outdoor social interaction and physical activity (6, 44). In turn, these processes have been related to positive alterations in brain structures implicated in mental well-being and cognition. For example, perceived restorative quality has been linked to lower activation of the bilateral cuneus, precuneus, and the right cingulate gyrus (58); the amygdala has been implicated in modulating neural networks involved in social cognition (59); and physical activity has been reported to positively correlate with brain matter volume in hippocampal gyrus and white matter volume in precuneus and posterior cingulate gyrus (60). Collectively, these findings encourage further investigation of the effects of neighbourhood greenness on the brain and the underlying mechanisms of these effects. It is important to understand to what extent psycho-social and ecological mediators that mediate the effects of greenness (6) contribute to changes in the brain structures that shape neurocognitive functions.

Strengths and limitations

Our exploratory study has several limitations. First, its cross-sectional design precludes establishing causality. Although the participants resided in their current home for the last five years, we had no information on their residential history, which would be needed to estimate lifelong exposure to greenness (cf. 19). However, we consider it unlikely that changes in the brain structure or cognitive function would influence participants' choice of residence. Despite this conservative scenario, the surprisingly consistent protective associations of greenness with CERAD-NB and MoCA support our working hypothesis. However, all significant correlations with cortical thickness disappeared after false discovery rate correction. Furthermore, we had a modest convenience sample that precludes any generalisation.

Informed by earlier literature (34, 35), we used summertime satellite images to calculate NDVI as a proxy for surrounding greenness (cf. 35). Although satellite image-based measures capture overall amount of green vegetation, they do not account for actual interaction with it, such as visual exposure and spending time in green spaces (61). Current recommendations in the filed advocate considering daily mobility patterns (62), greenness visible from the eye-level (61), and operationalising interaction with greenness in a life-course perspective (63, 64). However, because this was a secondary analysis of an already existing clinical dataset, we did not have access to information that would allow for moving beyond static environmental exposure assessment. Even so, seasonal changes in vegetation cover were previously found to have little impact on the association between NDVI and mental health in Plovdiv (44).

Our analyses focused on greenness because high-resolution data were not available for air pollution and noise. The NO_2 map had a resolution of 100x100 m and was generated using a global land use regression model that may not be optimal for capturing exposure contrasts at a fine spatial scale over a small territory such as the city of Plovdiv (40). L_{den} was taken from an EU noise map, but exposure data were only available in 5-dB isophones, limiting the number of distinct values in this variable and the power to detect small effects. Furthermore, we observed positive bivariate associations between these air/noise pollution and cognition. These counterintuitive findings may be due to the fact that NO_2 and L_{den} are higher in downtown Plovdiv, where the socioeconomic standard is also higher and residents have better access to healthcare. However, this explanation is speculative, as we did not have neighbourhood-level data of either. Finally, blue spaces, which may also be beneficial for cognitive function, were not considered in this study, because they highly coincided with traffic sources in the study area (cf. 44).

Notwithstanding these limitations, this study has a number of strengths. To our knowledge, it is one of the few studies on residential greenness and cognitive function and the third one to attempt linking residential greenness to structural brain imaging data. We employed two clinically validated measures of cognitive function (CERAD and MoCA), as opposed to some larger epidemiological studies that used more crude tools (51). We also had information

Table 6 Associations between residential greenness and cortical thickness (N=25)

Region of interest	Pearson correlation with $NDVI_{100\text{-}m}$	Uncorrected P-value	Benjamini-Hochberg P-value[a]
Left paracentral gyrus	+0.558	**0.007**	0.089
Left lateral orbitofrontal gyrus	+0.529	**0.011**	0.089
Right fusiform gyrus	+0.526	**0.012**	0.089
Left precuneus	+0.514	**0.014**	0.089
Right cortical thickness	+0.503	**0.017**	0.089
Right cuneus	+0.500	**0.018**	0.089
Left cortical thickness	+0.494	**0.019**	0.089
Right lateral orbitofrontal gyrus	+0.491	**0.020**	0.089
Left fusiform gyrus	+0.480	**0.024**	0.089
Left caudal middle frontal gyrus	+0.474	**0.026**	0.089
Right medial orbitofrontal gyrus	+0.474	**0.026**	0.089
Right caudal middle frontal gyrus	+0.463	**0.030**	0.090
Left insula	+0.461	**0.031**	0.090
Left medial orbitofrontal gyrus	+0.446	**0.037**	0.101
Left pars triangularis	+0.440	**0.040**	0.102
Left superior frontal gyrus	+0.420	0.051	0.122
Right rostral middle frontal gyrus	+0.415	0.055	0.122
Left pars orbitalis	+0.404	0.062	0.132
Right precuneus	+0.389	0.074	0.148
Left rostral middle frontal gyrus	+0.358	0.102	0.186
Right superior frontal gyrus	+0.355	0.105	0.186
Right pars orbitalis	+0.352	0.108	0.186
Right pars triangularis	+0.330	0.133	0.211
Left pars opercularis	+0.328	0.137	0.211
Left entorhinal area	+0.326	0.139	0.211
Left cuneus	+0.299	0.176	0.254
Right entorhinal area	+0.296	0.181	0.254
Right parahippocampal gyrus	+0.288	0.194	0.263
Left hippocampus	-0.278	0.211	0.276
Right paracentral gyrus	+0.240	0.282	0.357
Right amygdala	+0.232	0.300	0.367
Right pars opercularis	+0.182	0.418	0.497
Left precentral gyrus	+0.152	0.501	0.577
Right hippocampus	-0.134	0.551	0.616
Right insula	+0.129	0.568	0.617
Right precentral gyrus	+0.079	0.726	0.766
Left amygdala	+0.056	0.806	0.827
Left parahippocampal gyrus	+0.022	0.921	0.921

NDVI – normalised difference vegetation index; [a]Correction for false discovery rate

on potential confounding/mediating lifestyle, biomedical, and environmental factors, which have not been considered as a set elsewhere. Another strength is that we sampled middle-aged individuals, who are an understudied group in the field, as opposed to other studies, which focused on either children (19, 34, 50) or elderly populations (35, 52). Overall, we believe that these novel features justify the present feasibility work.

CONCLUSIONS

Living in a greener neighbourhood might be associated with better cognitive function in middle-aged Bulgarians. This effect is partly mediated by lower central adiposity. Tentative evidence suggests that greenness might also contribute to the structural integrity of the brain regions responsible for cognitive functions. Future research should build upon our findings and investigate larger, more representative population groups.

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Conflict of interest

None to declare.

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Istraživanje povezanosti stambenog zelenila s neurokognitivnom funkcijom u sredovječnih Bugara

Najnovija istraživanja upućuju na to da izloženost vegetaciji u mjestu stanovanja ("zelenilu") može usporiti pad kognitivne funkcije te očuvati cjelovitost s njom povezanih moždanih struktura. Međutim, malo se zna o takvom djelovanju zelenila, osobito u siromašnijim zemljama i populacijama srednje životne dobi. Stoga je u ovom istraživanju analizirana povezanost između zelenila i neurokognitivne funkcije na prigodnom uzorku od 122 sredovječna bugarska stanovnika koji su bili podvrgnuti dvama kognitivnim testovima: jednom za utvrđivanje znakova Alzheimerove bolesti (Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery, krat. CERAD-NB) te drugom za ocjenu kognitivne funkcije (Montreal Cognitive Assessment, krat. MoCA). Osim toga, dostupni su nam bili podaci dobiveni magnetnom rezonancijom moždanih struktura 25 sudionika. Njihove kućne adrese povezane su normaliziranim indeksom razlike u vegetaciji (engl. Normalised Difference Vegetation Index, krat. NDVI) kojim se mjeri razina zelenila u četvrti (u polumjeru od 100 do 1000 m). Rezultati pokazuju da je viši NDVI bez iznimke povezan s višim ocjenama testova CERAD-NB i MoCA kroz sve polumjere i statističke modele prilagođene po različitim kovarijatima. Na tu povezanost zelenila i testova posredno je utjecao opseg struka. NDVI u polumjeru od 100 metara od adrese stanovanja bio je povezan sa srednjom debljinom korteksa u objema moždanim polutkama, ali se ta povezanost pokazala marginalno značajnom ($P<0,1$) nakon korekcije zbog ocjene lažnoga otkrivanja uslijed višestrukih statističkih usporedbi. Zaključak je da život u zelenijoj četvrti može biti povezan s boljom kognitivnom funkcijom u sredovječnih Bugara te da na nju utječe i manji opseg struka. Naši rezultati također donekle upućuju na to da zelenilo pridonosi strukturnoj cjelovitosti moždanih područja koja upravljaju kognitivnim funkcijama. Buduća bi istraživanja trebala proširiti te rezultate obuhvativši veće i reprezentativnije populacijske skupine.

KLJUČNE RIJEČI: kognitivna funkcija; neurološki razvoj; NMR; prirodni okoliš; zelene površine