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Neighbourhood walkability in relation to cognitive functioning in patients with disorders along the heart-brain axis

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ABSTRACT

This study examined associations of neighbourhood walkability with cognitive functioning (i.e., global cognition, memory, language, attention-psychomotor speed, and executive functioning) in participants without or with either heart failure, carotid occlusive disease, or vascular cognitive impairment. Neighbourhood walkability at baseline was positively associated with global cognition and attention-psychomotor speed. These associations were stronger in patients with vascular cognitive impairment. Individuals who live in residential areas with higher walkability levels were less likely to have impairments in language and executive functioning at two-year follow-up. These findings highlight the importance of the built environment for cognitive functioning in healthy and vulnerable groups.

1. Introduction

Cognitive impairment is a deficiency in one or multiple domains of cognitive functioning, and can, for instance, be manifested by deficits in memory, language, attention-psychomotor speed, and executive functioning (Centers for Disease Control and Prevention, 2022; International Statistical Classification of Diseases, 2010). Cognitive impairment in older adults has substantial personal, societal and economic burden (GBD 2016 Dementia Collaborators, 2019; Pais et al., 2020; Winblad et al., 2016). The prevalence of cognitive impairment among older adults (i.e., aged ≥65 years) is substantial (Pais et al., 2020; Besser et al., 2017; Timmermans et al., 2019). With the rapid aging of the population, the prevalence and burden of cognitive impairment is expected to rise dramatically in the next few decades (Pais et al., 2020; Winblad et al., 2016; Besser et al., 2017). Therefore, identifying modifiable determinants of cognitive impairment in older adults to inform interventions that aim to prevent or reduce cognitive impairment in this group is considered an important public health priority (Besser et al., 2018; World Health Organization, 2012).

Cognitive impairment prevention or risk reduction strategies have mainly focused on individual-level factors, such as lifestyle and socioeconomic position (Wu et al., 2016, 2017). It has recently been argued that characteristics of the residential neighbourhood built environment may affect cognitive functioning in older adults, and several mechanisms have been proposed regarding how this environment may affect cognitive functioning in this group (Besser et al., 2017; Wu et al., 2015a, 2017; Cassarino and Setti, 2015; Russ et al., 2012; Cerin, 2019). Firstly, neighbourhood built environmental characteristics, such as population density, retail and service destination density, land use mix, street connectivity, and green space density may directly provide cognitive stimulation (e.g., through interactions, perceptions, attention restoration, and decision-making) (Besser et al., 2017, 2021; Wu et al., 2017; Cassarino and Setti, 2015; Clarke et al., 2012). Secondly, neighbourhood built environmental characteristics may influence health behaviours that have been associated with multiple biological mechanisms, and ultimately with cognitive functioning (Besser et al., 2017; Wu et al.,

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2017; Cerin, 2019; Groot et al., 2016; Barnett et al., 2017; Cerin et al., 2017; Van Cauwenberg et al., 2018; De la Torre, 2012; Leeuwis et al., 2017; De Leeuw et al., 2002; Guiney et al., 2015; Knight et al., 2021; Torres et al., 2015). For instance, neighbourhood walkability reflects the degree to which the neighbourhood built environment is conducive to walking (Lam et al., 2022; Timmermans et al., 2021), and has been positively associated with physical activity in older adults (Barnett et al., 2017; Cerin et al., 2017; Van Cauwenberg et al., 2018). In turn, higher levels of physical activity have been associated with less cardiovascular risk factors, less white matter hyperintensities, and increased cerebral blood flow, which may lead to better cognitive functioning (Cerin, 2019; De la Torre, 2012; Leeuwis et al., 2017; De Leeuw et al., 2002; Guiney et al., 2015; Knight et al., 2021; Torres et al., 2015). Thirdly, residential environments with more social and mental engagement opportunities (e.g., higher levels of retail and service destination density and green space density) may improve mental health, and consequently cognition (Besser et al., 2017, 2021; Wu et al., 2017; Aggarwal et al., 2014; Generaal et al., 2018, 2019).

Several studies have examined associations of built environmental characteristics with cognitive functioning in older adults (Besser et al., 2017; Wu et al., 2017; Gan et al., 2022), and show that higher levels of neighbourhood walkability components are associated with higher level of cognitive functioning in this group, including population density (Wu et al., 2015b, 2017), retail and service destination density (Besser et al., 2017, 2018, 2021; Clarke et al., 2012, 2015), land use mix (Wu et al., 2015b, 2017), street connectivity (Watts et al., 2015), green space density (Wu et al., 2017), and sidewalk density (Clarke et al., 2015). Existing studies mainly examined cross-sectional associations of residential built environmental characteristics with cognitive functioning, and studies assessing longitudinal associations are lacking (Besser et al., 2017; Wu et al., 2017). Furthermore, existing studies mainly examined associations of single built environmental characteristics with older adults' cognitive functioning and do not take into account that individuals are exposed to multiple environmental characteristics at the same time, that these characteristics are likely to interact with each other, and individually might have little influence (Besser et al., 2017; Wu et al., 2017; Gan et al., 2022). It has therefore been argued that environmental exposures should be studied in combination rather than with a traditional single exposure approach (Jia et al., 2019). Finally, previous studies focused on environment-cognition associations in older adults from the general population. To our knowledge, studies including clinical patient groups who may be more dependent on their immediate residential environment and who are at increased risk of cognitive impairments are lacking (Besser et al., 2017).

It has been suggested that patients with disorders along the heart-brain axis, including patients with heart failure (HF), carotid occlusive disease (COD) and cognitive vascular impairment (VCI), are at increased risk of cognitive impairments due to hemodynamic disorders, brought on by impaired pump function (HF), low blood supply to the brain (COD), and vascular brain damage (VCI) (Leeuwis et al., 2020). Due to their physical and cognitive vulnerability, they may be more dependent on their local living environment, and are more susceptible to residential built environmental factors (Lawton, 1986; Lawton et al., 1973; Aneshensel et al., 2016). Neighbourhood walkability may have a beneficial impact on hemodynamic dysfunction and abnormalities in the circulatory system, ultimately resulting in better cerebral blood flow (Cerin, 2019; De la Torre, 2012; Leeuwis et al., 2017; Guiney et al., 2015). This impact might be more pronounced in patients with disorders along the heart-brain axis than in relatively healthy people, resulting in stronger positive associations between neighbourhood walkability and cognitive functioning in these patient groups. Associations of cerebral blood flow and cognitive functioning are suggested to be stronger in patients with VCI, and therefore the associations of walkability with cognitive functioning are expected to be most prominent in this patient group (Leeuwis et al., 2020).

The present study expands the current literature by examining cross-sectional and longitudinal associations of neighbourhood walkability with global cognitive functioning as well as with functioning in specific cognitive domains (i.e., memory, language, attention-psychomotor speed, and executive functioning) in reference participants and patients with disorders along the heart-brain axis in the Netherlands. Additionally, this study assesses whether these associations differ across groups. It is hypothesized that individuals living in neighbourhoods with higher levels of neighbourhood walkability at baseline are less likely to have cognitive impairments at baseline as well as at two-year follow-up. It is also hypothesized that higher levels of neighbourhood walkability at baseline are associated with an increase in cognitive functioning over time. Furthermore, it is expected that the cross-sectional and longitudinal associations of neighbourhood walkability with cognitive functioning are stronger in the more vulnerable patient groups, particularly in those with VCI, than in the relatively healthy reference group.

2. Materials and methods

2.1. Study design and study sample

Data from the Heart-Brain Study were used in this study (version 3, 1-1-2020). The Heart-Brain Study investigates the relationships between (cardio)vascular factors, the hemodynamic status of the heart and the brain, and cognitive functioning using data from reference participants and patients with disorders along the heart-brain axis (i.e., heart failure (HF), carotid occlusive disease (COD), and possible vascular cognitive impairment (VCI)) from cardiology, memory, and neurology outpatient clinics from four sites in the Netherlands: Amsterdam UMC, location VU University medical center (AUMC-VUmc) in Amsterdam, Leiden University Medical Center (LUMC) in Leiden, Maastricht University Medical Center (MUMC) in Maastricht, and University Medical Center Utrecht (UMCU) in Utrecht (Hooghiemstra et al., 2017). The baseline data collection took place from 2014 to 2017. The two-year follow-up measurement was conducted from 2016 to 2019. Ethical approval was obtained from the Review Board of LUMC (P.14.002). All participants have provided informed consent.

The study protocol with detailed inclusion and exclusion criteria per participant group has been described previously (Hooghiemstra et al., 2017). Most important inclusion criteria for all patient groups were a diagnosis of HF, COD or VCI according to current guidelines, age $\geq$50 years, ability to undergo Magnetic Resonance Imaging (MRI) and cognitive testing, and independence in daily life. Patients with HF were included irrespective of left ventricular ejection fraction and coronary artery disease according to the European Cardiology Society guidelines with a stable clinical situation. Patients with COD had a significant stenosis (i.e., >80%) or occlusion of the internal carotid artery as assessed with Magnetic Resonance Angiography. For possible VCI, patients were included with cognitive complaints (regardless of the severity of cognitive impairment (i.e., subjective cognitive decline to dementia)), combined with moderate to severe vascular brain injury on MRI, or mild vascular brain injury with presence of vascular risk factors, with a Mini-Mental State Examination score of $\geq$20 (Folstein et al., 1975). Most important exclusion criteria for all patient groups were clinical evidence of a brain disease other than Alzheimer Disease and VCI, a psychiatric diagnosis that affects cognitive functioning, and atrial fibrillation at the moment of inclusion. Healthy reference participants were recruited via advertisements and among spouses of patients. The proportion of persons with cardiovascular risk factors (e.g., hypertension, hypercholesterolemia, diabetes mellitus, obesity, and currently smoking) was lower in the healthy reference group than in the patient groups.

Baseline data were used in all cross-sectional analyses. The baseline sample included 566 participants (129 reference participants, 162 HF, 109 COD, and 166 VCI). Information on six-digit postal codes at baseline were lacking for all 155 participants who were included at the MUMC in Maastricht, and therefore these participants were excluded from the cross-sectional analyses. From the remaining group (n = 411), participants with lacking baseline data on cognitive functioning outcome measures (n = 3) and residential environmental characteristics (n = 5) were excluded from the cross-sectional analyses. The analytical sample for the cross-sectional baseline analyses consisted of 403 participants (100 reference participants, 98 HF, 100 COD, and 105 VCI) with full baseline data.

Baseline and two-year follow-up data were used in all longitudinal analyses. The follow-up sample included 385 participants (98 reference participants, 96 HF, 77 COD, and 114 VCI). Information on six-digit postal codes at baseline were lacking for all 88 follow-up participants who were included at the MUMC in Maastricht, and consequently these individuals were excluded from the longitudinal analyses. From the remaining group (n = 297), participants with lacking data on cognitive functioning outcome measures at follow-up (n = 1) and residential environmental characteristics at baseline (n = 4) were excluded from the longitudinal analyses. Additionally, eight participants were excluded from these analyses because they have moved between baseline and two-year follow-up. The analytical sample for the longitudinal analyses consisted of 284 participants (83 reference participants, 63 HF, 71 COD, and 67 VCI) with full baseline and follow-up data. Participants who were included in the cross-sectional analyses, but not in the longitudinal analyses, were older, had more often a disorder along the heart-brain axis and had lower levels of global cognition, memory, language, and attention-psychomotor speed. No significant differences were observed in terms of sex, educational level, area-level socioeconomic status, and neighbourhood walkability levels. There was no significant difference in the proportion of dropouts across the three patient groups. The VCI patients who were included in the cross-sectional analyses, but not in the longitudinal analyses, had lower levels of cognitive functioning, and were more often highly educated, than their counterparts with HF and COD. No differences were observed in other individual- and area-level characteristics across the patient groups that dropped out between baseline and two-year follow-up.

2.2. Dependent variable

2.2.1. Cognitive functioning

Cognitive functioning was examined using an extensive and standardized neuropsychological test battery that has been developed in the context of the Dutch Parelsnoer Initiative (Aalten et al., 2014). The various tests cover global cognitive functioning and four major cognitive domains, including: memory, language, attention-psychomotor speed, and executive functioning. For each separate cognitive domain, the various tests have been described in Supplementary File 1.

All test scores were standardized into z-scores, using reference participants as reference group (Leeuwis et al., 2020; Hooghiemstra et al., 2017). Higher z-scores implied better performance. Subsequently, the test z-scores were averaged to create four cognitive domain scores. The domain scores were based on available tests and were calculated when at least one test was available for that domain (Hooghiemstra et al., 2017). A score for global cognitive functioning was constructed by calculating the mean of the four domain scores (Leeuwis et al., 2020; Hooghiemstra et al., 2017). Changes in global cognitive functioning as well as in cognitive domains were examined by subtracting the scores at baseline from those at two-year follow-up. In addition to these continuous measures of cognitive functioning, dichotomous measures were assessed. A cognitive domain was considered to be impaired (0 = no, 1 = yes) when the domain score was below −1.5 (Hooghiemstra et al., 2017). Based on the number of impaired cognitive domains, a categorical measure of cognitive functioning was determined: no cognitive impairment (i.e., 0 impaired domains; reference category), minor cognitive impairment (i.e., 1 impaired domain), and major cognitive impairment (i.e., ≥2 impaired domains) (Hooghiemstra et al., 2017).

2.3. Independent variable

2.3.1. Neighbourhood walkability

Neighbourhood walkability within 500-m Euclidean buffer zones around the centroid of each participant's residential six-digit postal code area was objectively measured using the Dutch neighbourhood walkability index (range: 0 (low)-100 (high)). The walkability index has been developed in the Geoscience and Health Cohort Consortium, and is a composite measure combining six key spatial components that particularly facilitate walking, and potentially also stimulate cognitive functioning (Besser et al., 2017, 2018, 2021; Wu et al., 2015b, 2017; Clarke et al., 2012, 2015; Generaal et al., 2018, 2019; Gan et al., 2022; Watts et al., 2015; Lakerveld et al., 2020; Timmermans et al., 2018a). These six components entail: population density, retail and service destination density, land use mix, street connectivity, green space density, and sidewalk density. Detailed information about the construction of the neighbourhood walkability index, and its components, is available in Supplementary File 2.

2.4. Covariates

The cross-sectional analyses were adjusted for the following covariates at baseline: age in years, sex (man (reference category) versus woman), educational level, and area-level socioeconomic status. The longitudinal analyses were additionally adjusted for the relevant cognitive functioning measure at baseline.

Educational level was categorized into: low (Verhage categories 1–4; reference category), intermediate (Verhage category 5), and high (Verhage categories 6–7) (Verhage, 1964; Rijnen et al., 2020).

Objectively measured area-level socioeconomic status scores were obtained from the Netherlands Institute for Social Research (Netherlands Institute for Social Research, 2019). These scores are based on the average income, the percentage of residents with a low income, the percentage of residents with a low level of education, and the percentage of unemployed residents in the neighbourhood. Higher scores indicate a higher area-level socioeconomic status (Netherlands Institute for Social Research, 2019).

2.5. Statistical analyses

Characteristics of the study samples and the area-level exposure measures are presented using descriptive statistics for the full samples as well as for each participant group, separately. One-way Analyses of Variance (including post-hoc Bonferroni corrections) and Pearson Chi-square tests were conducted to compare groups when appropriate.

Multilevel linear regression analyses, multilevel logistic regression analyses and multilevel multinomial logistic regression analyses with center as a second level were performed to examine the cross-sectional associations of neighbourhood walkability with the continuous, dichotomous, and categorical measures of cognitive functioning at baseline, respectively. Similar analyses were conducted to assess the longitudinal associations of neighbourhood walkability at baseline with cognitive functioning at two-year follow-up, and with change in cognitive functioning over the two-year follow-up period. By conducting multilevel analyses, the clustering of observations (level-1 unit) within the same University Medical Center (level-2 unit) has been taken into account. The cross-sectional analyses were adjusted for age, sex, educational level, and area-level socioeconomic status at baseline. The longitudinal analyses were additionally adjusted for the relevant cognitive functioning measure at baseline. These analyses were also conducted for each separate neighbourhood walkability component.

To study possible effect modification by participant group (i.e., reference participants (reference group), HF, COD, and VCI), an interaction term between neighbourhood walkability and participant group was created. Each interaction term, together with its two main terms, were statistically tested in a fully adjusted model.

There is no consensus on which buffer size best captures the neighbourhood built environment relevant for cognitive functioning. In order to examine the robustness of our findings, the cross-sectional and longitudinal associations of neighbourhood walkability with cognitive functioning outcome measures were assessed in sensitivity analyses in which the neighbourhood walkability index was derived from 250-, 1000-, and 2000-m Euclidean buffer zones.

Information on whether the included participants at AUMC-VUmc moved between baseline and two-year follow-up was missing. A very small proportion of participants at LUMC (5.1%) and UMCU (1.9%) did relocate between baseline and two-year follow-up. Therefore, it was assumed that all participants at AUMC-VUmc (n = 111) did not move during this time frame, and these participants were included in the main longitudinal analyses. In order to examine whether this has affected our results, the main longitudinal analyses were repeated in sensitivity analyses in which these participants were excluded.

In all statistical analyses, a p-value below 0.05 was considered as statistically significant. All statistical analyses were performed in IBM SPSS Statistics (Version 26.0) (IBM Corp, 2019).

3. Results

Characteristics of the study samples for the cross-sectional as well as longitudinal analyses and all relevant area-level exposure measures are presented in Table 1.

3.1. Cross-sectional associations at baseline

Higher levels of neighbourhood walkability were significantly associated with better global cognitive functioning ($\beta = 0.007$, 95% CI = 0.002–0.012) and attention-psychomotor speed ($\beta = 0.011$, 95% CI = 0.004–0.018). Accordingly, a 10-point increase in neighbourhood walkability corresponds with a 0.070 increase in global cognitive functioning, which is 14.0% of the average global cognitive outcome score in the full sample. Non-significant positive associations of neighbourhood walkability with memory, language, and executive functioning were found (Table 2).

Individuals who live in residential areas with higher walkability levels were significantly less likely to have major cognitive impairment ($OR_{major\_impairment} = 0.97$, 95% CI = 0.95–0.99) than no cognitive impairment. In addition, individuals who live in residential areas with higher walkability levels were significantly less likely to have impairments in memory (OR = 0.97, 95% CI = 0.95–0.99) and attention-psychomotor speed (OR = 0.97, 95% CI = 0.95–0.99). No significant associations were observed between neighbourhood walkability and impairment in language and executive function (Table 2).

A similar pattern of findings was found for three of the six neighbourhood walkability components, including population density, street connectivity, and sidewalk density (Supplementary File 3, Tables S1.1-S1.6).

Significant neighbourhood walkability by participant group interaction terms indicated that the cross-sectional associations of neighbourhood walkability with the continuous measures of global cognition, memory, language and attention-psychomotor speed were stronger in patients with VCI (Table 2 and Supplementary File 4).

3.2. Longitudinal associations

In the full sample, the associations of neighbourhood walkability at baseline with the continuous cognitive functioning outcome measures at two-year follow-up were non-significantly positive (Table 3). Individuals who live in residential areas with higher walkability levels at baseline were significantly less likely to have impairments in language (OR = 0.95, 95% 0.90–0.99) and executive functioning (OR = 0.95, 95% CI = 0.91–0.99) at two-year follow-up. A similar pattern of findings was found for population density, street connectivity, and sidewalk density (Supplementary File 3, Tables S2.1-S2.6). A significant neighbourhood walkability by participant group interaction term indicated that the association of neighbourhood walkability at baseline with the continuous measure of executive functioning at two-year follow-up was stronger in patients with VCI (Table 3 and Supplementary File 4).

Higher levels of neighbourhood walkability at baseline were non-significantly associated with an increase in cognitive functioning over the two-year follow-up period (Table 4). None of the six neighbourhood walkability components were significantly associated with change in cognitive functioning over time in the full sample (Supplementary File 3, Tables S3.1-S3.6). Non-significant neighbourhood walkability by participant group interaction terms indicated that the associations of neighbourhood walkability at baseline with changes in cognitive functioning over time did not differ by participant groups (Table 4 and Supplementary File 4).

3.3. Sensitivity analyses

The results of the cross-sectional sensitivity analyses, including neighbourhood walkability indices that were derived from 250-, 1000-, and 2000-m Euclidean buffer zones, were largely in line with the results of the main analyses in which the included neighbourhood walkability index was derived from a 500-m Euclidean buffer zone (Supplementary File 3, Tables S4.1-S4.3).

The sensitivity analyses, including the neighbourhood walkability index that was derived from a 250-m Euclidean buffer zone, indicated significant positive associations of neighbourhood walkability at baseline with global cognitive functioning ($\beta_{250m} = 0.006$, 95% CI = 0.001–0.011) and language ($\beta_{250m} = 0.012$, 95% CI = 0.002–0.021) at two-year follow-up. Similar to the main analyses, these sensitivity analyses revealed that individuals who live in residential areas with higher walkability levels were significantly less likely to have impairments in language ($OR_{250m} = 0.94$, 95% CI = 0.90–0.99) and executive functioning ($OR_{250m} = 0.96$, 95% CI = 0.92–0.99) (Supplementary File 3, Table S5.1). Neighbourhood walkability, derived from a 1000-m and 2000-m Euclidean buffer zone, was not significantly associated with cognitive functioning at two-year follow-up in the full sample (one exception: $OR_{2000m\_language} = 0.95$, 95% CI = 0.91–0.99) (Supplementary File 3, Tables S5.2-S5.3).

Sensitivity analyses (using 250-m Euclidean buffer zones) did indicate that higher neighbourhood walkability levels at baseline were significantly associated with an improvement in global cognitive functioning ($\beta_{250m} = 0.006$, 95% CI = 0.001–0.011) and language ($\beta_{250m} = 0.011$, 95% CI = 0.002–0.020) over the two-year follow-up period (Supplementary File 3, Table S6.1). The findings of the sensitivity analyses (using 1000- and 2000-m Euclidean buffer zones) were largely in line with those of the main analyses (Supplementary File 3, Tables S6.2-S6.3).

The sensitivity analyses, in which participants from AUMC-VUmc were excluded due to missing data on relocation between baseline and two-year follow-up, generally indicated similar findings as the main analyses (Supplementary File 3, Table S7.1 and Table S8.1).

4. Discussion

This study examined cross-sectional and longitudinal associations of neighbourhood walkability with global cognitive functioning, memory, language, attention-psychomotor speed, and executive functioning in reference participants and patients with HF, COD, or VCI, and assessed whether these associations differ across groups. The cross-sectional findings indicate that higher levels of neighbourhood walkability were associated with higher levels of global cognitive functioning and attention-psychomotor speed. These associations were stronger in patients with VCI. Additionally, it was found that individuals who lived in residential areas with higher walkability levels were less likely to have major cognitive impairment or to have impairments in memory and

Table 1
Baseline characteristics of the study samples and area-level exposure measures. [a]

Variables	Study sample included in cross-sectional analyses					Study sample included in longitudinal analyses				
	Total (n = 403)	Reference participants (n = 100)	HF (n = 98)	COD (n = 100)	VCI (n = 105)	Total (n = 284)	Reference participants (n = 83)	HF (n = 63)	COD (n = 71)	VCI (n = 67)
Dependent variables										
Cognitive functioning										
Global cognitive functioning (Mean ± SD) [b]	−0.5 ± 0.9	Ref	−0.3 ± 0.6	−0.5 ± 0.7 [g]	−1.1 ± 1.2 [g, h, i]	−0.4 ± 1.0	Ref	−0.2 ± 0.5	−0.6 ± 0.9 [d]	−1.1 ± 1.3 [f, g, h]
Memory (Mean ± SD) [b]	−0.7 ± 1.8	Ref	−0.2 ± 1.1	−0.6 ± 1.3	−1.9 ± 2.8 [g, h, i]	−0.5 ± 1.9	Ref	0.1 ± 0.9	−0.6 ± 2.0 [d]	−1.8 ± 2.6 [g, h, i]
Language (Mean ± SD) [b]	−0.3 ± 0.7	Ref	−0.2 ± 0.5	−0.4 ± 0.5 [d]	−0.8 ± 1.0 [g, h, i]	−0.4 ± 1.2	Ref	−0.2 ± 0.6	−0.3 ± 0.5	−1.1 ± 1.9 [f, g, h]
Attention-psychomotor speed (Mean ± SD) [b]	−0.6 ± 1.1	Ref	−0.4 ± 0.8	−0.9 ± 1.0 [e, g]	−1.1 ± 1.2 [g, h]	−0.6 ± 1.2	Ref	−0.4 ± 0.7	−1.1 ± 1.6 [e, g]	−1.0 ± 1.3 [e, g, i]
Executive function (Mean ± SD) [b]	−0.3 ± 0.9	Ref	−0.2 ± 0.5	−0.4 ± 0.8 [d]	−0.8 ± 0.9 [f, g, h]	−0.3 ± 0.8	Ref	−0.3 ± 0.8	−0.2 ± 0.7	−0.6 ± 1.0 [g]
Cognitive impairment (%) [b]				[e, g]	[f, g, h]				[d, e]	[f, g, h]
No cognitive impairment	72.0	93.0	86.7	64.0	45.7	76.4	94.0	88.9	71.8	47.8
Minor cognitive impairment	16.1	6.0	8.2	26.0	23.8	14.8	6.0	7.9	19.7	26.9
Major cognitive impairment	11.9	1.0	5.1	10.0	30.5	8.8	0.0	3.2	8.5	25.4
Impairment in memory (%) [b]										
Yes	18.1	3.0	7.1	17.0 [d, e]	43.8 [g, h, i]	13.4	1.2	6.3	8.5 [d]	40.3 [g, h, i]
Impairment in language (%) [b]										
Yes	5.5	0.0	2.0	4.0 [d]	15.2 [e, f, g]	5.6	2.4	1.6	1.4	17.9 [d, e, f]
Impairment in attention-psychomotor speed (%) [b]										
Yes	15.1	2.0	6.1	23.0 [g]	28.6 [g, h]	12.3	1.2	3.2	25.4 [g, h]	20.9 [e, g]
Impairment in executive function (%) [b]										
Yes	7.2	3.0	4.1	3.0	18.1 [e, g, i]	6.0	1.2	4.8	2.8	16.4 [d, e, f]
Change in cognitive functioning over two-year follow-up										
Global cognitive functioning (Mean ± SD)	–	–	–	–	–	−0.1 ± 0.6	Ref	0.1 ± 0.3	−0.1 ± 0.5	−0.2 ± 0.9
Memory (Mean ± SD)	–	–	–	–	–	0.1 ± 1.1	Ref	0.1 ± 0.8	0.1 ± 0.9	−0.2 ± 1.7
Language (Mean ± SD)	–	–	–	–	–	−0.1 ± 1.0	Ref	0.1 ± 0.4	−0.1 ± 0.4	−0.4 ± 1.6
Attention-psychomotor speed (Mean ± SD)	–	–	–	–	–	0.1 ± 0.8	Ref	−0.1 ± 0.4	−0.3 ± 1.0	−0.3 ± 1.1
Executive function (Mean ± SD)	–	–	–	–	–	0.1 ± 0.7	Ref	−0.1 ± 0.7	0.2 ± 0.6	0.1 ± 1.0
Independent variables										
Neighbourhood walkability (components) [c]										
Neighbourhood walkability index (Mean ± SD)	32.0 ± 14.8	31.8 ± 14.0	36.0 ± 13.8	28.2 ± 14.5 [e]	32.1 ± 15.7	31.8 ± 14.5	31.7 ± 14.0	36.3 ± 13.6	27.0 ± 13.7 [e]	32.6 ± 15.4
Population density [z-score] (Mean ± SD)	5.4 ± 3.9	5.5 ± 3.4	6.6 ± 4.0	4.3 ± 3.7 [e]	5.3 ± 4.3	5.3 ± 3.8	5.4 ± 3.2	6.7 ± 4.2	3.9 ± 2.6 [e]	5.5 ± 4.5
Retail and service destination density [z-score] (Mean ± SD)	1.7 ± 2.3	1.7 ± 2.4	1.9 ± 2.2	1.5 ± 2.4	1.7 ± 2.2	1.7 ± 2.3	1.7 ± 2.6	1.8 ± 2.1	1.6 ± 2.5	1.6 ± 1.8
Land use mix [z-score] (Mean ± SD)	2.6 ± 1.3	2.4 ± 1.2	2.8 ± 1.3	2.4 ± 1.3	2.7 ± 1.3	2.5 ± 1.3	2.4 ± 1.2	2.7 ± 1.2	2.3 ± 1.4	2.7 ± 1.2
Street connectivity [z-score] (Mean ± SD)	4.1 ± 1.8	4.3 ± 1.6	4.3 ± 1.6	3.7 ± 1.8	4.0 ± 1.9	4.0 ± 1.7	4.2 ± 1.6	4.4 ± 1.7	3.6 ± 1.9 [e]	4.0 ± 1.8

(*continued on next page*)

Table 1 (*continued*)

Variables	Study sample included in cross-sectional analyses					Study sample included in longitudinal analyses				
	Total (n = 403)	Reference participants (n = 100)	HF (n = 98)	COD (n = 100)	VCI (n = 105)	Total (n = 284)	Reference participants (n = 83)	HF (n = 63)	COD (n = 71)	VCI (n = 67)
Green space density [z-score] (Mean ± SD)	0.1 ± 0.5	−0.1 ± 0.3	−0.1 ± 0.4	0.1 ± 0.8	0.1 ± 0.5 [d]	−0.1 ± 0.5	−0.1 ± 0.3	−0.1 ± 0.4	0.1 ± 0.8	0.1 ± 0.5
Sidewalk density [z-score] (Mean ± SD)	4.9 ± 2.9	4.8 ± 2.7	5.7 ± 2.6	4.1 ± 2.8 [h]	4.9 ± 3.2	4.8 ± 2.9	4.8 ± 2.7	5.8 ± 2.7	3.9 ± 2.7 [e]	5.0 ± 3.3
Covariates										
Age in years (Mean ± SD)	68.2 ± 8.6	65.9 ± 7.6	70.1 ± 9.8 [d]	66.0 ± 8.0 [e]	70.1 ± 7.8 [g, i]	67.2 ± 8.0	66.0 ± 7.2	69.0 ± 9.5	65.2 ± 7.6 [e]	69.4 ± 7.1 [f]
Sex (%)										
Women	33.7	46.0	33.7	22.0 [g]	33.3	35.6	44.6	34.9	23.9	37.3
Educational level (%)				[d]	[f]				[d]	[f]
Low	23.8	19.0	29.6	27.0	20.0	24.3	16.9	28.6	26.8	26.9
Intermediate	32.3	29.0	30.6	44.0	25.7	34.5	32.5	33.3	46.5	25.4
High	43.9	52.0	39.8	29.0	54.3	41.2	50.6	38.1	26.7	47.8
Area-level socioeconomic status score (Mean ± SD)	0.4 ± 0.9	0.4 ± 0.8	0.5 ± 0.9	0.1 ± 1.0 [d, e]	0.5 ± 1.0 [f]	0.4 ± 0.9	0.5 ± 0.7	0.5 ± 0.9	0.1 ± 1.0 [d]	0.5 ± 0.9 [f]
Other variables										
Center (%)			[g]	[g, h]	[g, h, i]			[g]	[g, h]	[g, h, i]
AUMC-VUmc	40.0	22.0	60.2	0.0	64.8	39.1	24.1	61.9	0.0	77.6
LUMC	37.0	46.0	39.8	8.0	0.0	25.0	48.2	38.1	9.9	0.0
UMCU	23.0	32.0	0.0	92.0	35.2	35.9	27.7	0.0	90.1	22.4

[a] Abbreviations: AUMC-VUmc = Amsterdam UMC, location VU University medical center, COD = patients with carotid occlusive disease; HF = patients with heart failure; LUMC = Leiden University Medical Center; Ref = reference group; SD = standard deviation; UMCU = University Medical Center Utrecht; VCI = patients with possible vascular cognitive impairment.

[b] For the study sample included in the longitudinal analyses, the presented cognitive functioning outcome measure has been measured at two-year follow-up.

[c] The neighbourhood walkability index (index range: 0–100) and the standardized components were derived from 500-m Euclidean buffer zones around the centroid of the six-digit postal code areas where participants were living.

[d] p-value <0.05 compared to reference participants.

[e] p-value <0.05 compared to patients with heart failure.

[f] p-value <0.05 compared to patients with carotid occlusive disease.

[g] p-value <0.001 compared to reference participants.

[h] p-value <0.001 compared to patients with heart failure.

[i] p-value <0.001 compared to patients with carotid occlusive disease.

Table 2
Cross-sectional associations of neighbourhood walkability with cognitive functioning at baseline. [a-c].

Variables	Neighbourhood walkability: Neighbourhood walkability index (500-m Euclidean buffer zone) [d]				
	Total (n = 403)	Reference participants (n = 100)	HF (n = 98)	COD (n = 100)	VCI (n = 105)
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Cognitive functioning outcome measure					
Global cognitive functioning	**0.007 (0.002–0.012)**	0.001 (−0.005–0.007)	−0.004 (−0.011–0.003)	0.002 (−0.006–0.010)	**0.023 (0.009–0.038)**
Memory	0.010 (−0.002–0.022)	−0.005 (−0.016–0.005)	−0.004 (−0.019–0.011)	−0.001 (−0.018–0.015)	**0.037 (0.002–0.072)**
Language	0.003 (−0.001–0.008)	−0.001 (−0.007–0.006)	−0.002 (−0.009–0.005)	−0.003 (−0.011–0.005)	**0.015 (0.002–0.027)**
Attention-psychomotor speed	**0.011 (0.004–0.018)**	0.001 (−0.008–0.010)	−0.002 (−0.012–0.010)	0.011 (−0.002–0.024)	**0.024 (0.007–0.041)**
Executive function	0.006 (−0.001–0.012)	0.009 (−0.001–0.017)	−0.009 (−0.019–0.001)	0.001 (−0.009–0.012)	**0.018 (0.004–0.033)**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Cognitive impairment					
No cognitive impairment	1.00	1.00	1.00	1.00	1.00
Minor cognitive impairment	0.99 (0.97–1.01)	1.01 (0.95–1.08)	1.05 (0.99–1.12)	0.98 (0.95–1.02)	0.97 (0.94–1.02)
Major cognitive impairment	**0.97 (0.95–0.99)**	1.01 (0.91–1.11)	1.02 (0.95–1.10)	1.00 (0.95–1.05)	**0.93 (0.90–0.97)**
Impairment in memory					
No	1.00	1.00	1.00	1.00	1.00
Yes	**0.97 (0.95–0.99)**	1.02 (0.95–1.10)	0.99 (0.94–1.05)	0.99 (0.95–1.03)	**0.95 (0.91–0.98)**
Impairment in language					
No	1.00	1.00	1.00	1.00	1.00
Yes	0.98 (0.94–1.01)	–	1.04 (0.97–1.12)	1.01 (0.94–1.07)	**0.95 (0.91–0.99)**
Impairment in attention-psychomotor speed					
No	1.00	1.00	1.00	1.00	1.00
Yes	**0.97 (0.95–0.99)**	0.99 (0.92–1.06)	1.03 (0.96–1.09)	0.98 (0.94–1.01)	**0.95 (0.92–0.99)**
Impairment in executive function					
No	1.00	1.00	1.00	1.00	1.00
Yes	1.01 (0.99–1.04)	1.01 (0.94–1.08)	1.05 (0.98–1.12)	1.03 (0.97–1.10)	0.99 (0.95–1.02)

[a] Abbreviations: CI = confidence interval; COD = patients with carotid occlusive disease; HF = patients with heart failure; n = number; OR = odds ratio; VCI = patients with possible vascular cognitive impairment.
[b] The associations are adjusted for age, sex, educational level, and area-level socioeconomic status at baseline.
[c] In bold: p-value<0.05.
[d] The neighbourhood walkability index was derived from 500-m Euclidean buffer zones around the centroid of the six-digit postal code areas where participants were living.

Table 3
Associations of neighbourhood walkability at baseline with cognitive functioning at two-year follow-up. [a-c].

Variables	Neighbourhood walkability: Neighbourhood walkability index (500-m Euclidean buffer zone) [d]				
	Total (n = 284)	Reference participants (n = 83)	HF (n = 63)	COD (n = 71)	VCI (n = 67)
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Cognitive functioning outcome measure					
Global cognitive functioning	0.004 (−0.001–0.008)	0.002 (−0.004–0.008)	−0.002 (−0.008–0.005)	0.006 (−0.004–0.016)	0.008 (−0.007–0.025)
Memory	0.005 (−0.005–0.015)	−0.001 (−0.009–0.008)	0.004 (−0.011–0.019)	0.009 (−0.014–0.033)	0.010 (−0.019–0.039)
Language	0.008 (−0.001–0.017)	0.006 (−0.011–0.024)	−0.006 (−0.013–0.001)	0.002 (−0.005–0.009)	0.018 (−0.011–0.047)
Attention-psychomotor speed	0.001 (−0.007–0.007)	0.002 (−0.003–0.008)	−0.005 (−0.012–0.002)	−0.003 (−0.022–0.016)	0.001 (−0.021–0.022)
Executive function	0.005 (−0.001–0.010)	0.002 (−0.005–0.010)	−0.012 (−0.025–0.002)	0.005 (−0.004–0.014)	**0.019 (0.006–0.032)**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Cognitive impairment					
No cognitive impairment	1.00	1.00	1.00	1.00	1.00
Minor cognitive impairment	0.98 (0.95–1.01)	1.00 (0.94–1.08)	0.97 (0.89–1.05)	1.00 (0.94–1.07)	0.94 (0.88–1.01)
Major cognitive impairment	0.98 (0.93–1.02)	–	1.00 (0.88–1.14)	0.88 (0.73–1.05)	0.99 (0.91–1.07)
Impairment in memory					
No	1.00	1.00	1.00	1.00	1.00
Yes	0.99 (0.95–1.03)	1.02 (0.94–1.11)	0.98 (0.90–1.06)	0.98 (0.91–1.05)	1.01 (0.96–1.07)
Impairment in language					
No	1.00	1.00	1.00	1.00	1.00
Yes	**0.95 (0.90–0.99)**	0.99 (0.91–1.08)	–	0.98 (0.89–1.08)	0.97 (0.92–1.03)
Impairment in attention-psychomotor speed					
No	1.00	1.00	1.00	1.00	1.00
Yes	1.01 (0.97–1.05)	1.01 (0.96–1.06)	1.02 (0.91–1.13)	1.02 (0.97–1.08)	1.00 (0.94–1.05)
Impairment in executive function					
No	1.00	1.00	1.00	1.00	1.00
Yes	**0.95 (0.91–0.99)**	1.01 (0.92–1.10)	1.06 (0.97–1.17)	0.98 (0.89–1.07)	**0.92 (0.86–0.98)**

[a] Abbreviations: CI = confidence interval; COD = patients with carotid occlusive disease; HF = patients with heart failure; n = number; OR = odds ratio; VCI = patients with possible vascular cognitive impairment.
[b] The associations are adjusted for age, sex, educational level, area-level socioeconomic status, and the relevant cognitive functioning outcome measure at baseline.
[c] In bold: p-value<0.05.
[d] The neighbourhood walkability index was derived from 500-m Euclidean buffer zones around the centroid of the six-digit postal code areas where participants were living.

Table 4
Associations of neighbourhood walkability at baseline with change in cognitive functioning over the two-year follow-up period. [a-c].

Variables	Neighbourhood walkability: Neighbourhood walkability index (500-m Euclidean buffer zone) [d]				
	Total (n = 284)	Reference participants (n = 83)	HF (n = 63)	COD (n = 71)	VCI (n = 67)
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Change in cognitive functioning outcome measure					
Global cognitive functioning	0.001 (−0.001–0.008)	0.002 (−0.004–0.007)	−0.002 (−0.009–0.005)	0.006 (−0.002–0.014)	0.008 (−0.009–0.025)
Memory	0.006 (−0.003–0.014)	−0.001 (−0.009–0.008)	0.004 (−0.011–0.019)	0.009 (−0.007–0.025)	0.010 (−0.019–0.039)
Language	0.008 (−0.001–0.017)	0.006 (−0.012–0.023)	−0.006 (−0.013–0.001)	0.002 (−0.004–0.009)	0.018 (−0.011–0.047)
Attention-psychomotor speed	0.001 (−0.006–0.007)	0.002 (−0.002–0.008)	−0.005 (−0.012–0.002)	−0.003 (−0.021–0.015)	−0.001 (−0.020–0.020)
Executive function	0.004 (−0.002–0.009)	0.002 (−0.006–0.010)	−0.011 (−0.025–0.002)	0.005 (−0.004–0.014)	0.015 (−0.001–0.030)

[a] Abbreviations: CI = confidence interval; COD = patients with carotid occlusive disease; HF = patients with heart failure; n = number; VCI = patients with possible vascular cognitive impairment.
[b] The associations are adjusted for age, sex, educational level, area-level socioeconomic status, and the relevant cognitive functioning outcome measure at baseline.
[c] In bold: p-value<0.05.
[d] This neighbourhood walkability component was derived from 500-m Euclidean buffer zones around the centroid of the six-digit postal code areas where participants were living.

attention-psychomotor speed. The longitudinal analyses showed that individuals who live in residential areas with higher walkability levels were less likely to have impairments in language and executive functioning at two-year follow-up. Although, the main analyses (using 500-m buffer zones) did not show that neighbourhood walkability was associated with change in cognitive functioning over the two-year follow-up period, sensitivity analyses (using 250-m buffer zones) did show that exposure to higher levels of neighbourhood walkability at baseline were significantly associated with an improvement in global cognitive functioning and language over time.

By examining cross-sectional as well as longitudinal associations of objectively measured neighbourhood walkability with cognitive functioning in reference participants as well as in a clinical sample of patients with disorders along the heart-brain axis, this study is an innovative effort to improve our understanding of environmental determinants of cognitive functioning in healthy and vulnerable individuals (Besser et al., 2017; Wu et al., 2017; Cerin et al., 2020; Wey et al., 2021). A particular strength of this study is the use of a composite exposure measure of neighbourhood walkability that combines objectively measured high-resolution Geographic Information System data on six components of the built residential environment that have been associated with cognitive functioning in previous studies, separately (Besser et al., 2017, 2018, 2021; Wu et al., 2015b, 2017; Clarke et al., 2012, 2015; Gan et al., 2022; Watts et al., 2015). This composite measure takes into account that individuals are exposed to multiple environmental characteristics at the same time, that these characteristics are likely to interact with each other, and individually might have relatively little influence (Jia et al., 2019).

This study has several limitations to consider. Firstly, the sample sizes in the current study were fairly small, which resulted in less precision around the estimates, and thereby in a lower ability to find statistically significant results. Secondly, due to the relative short follow-up period and the lack of (substantial) changes in neighbourhood walkability over time, we were unable to appropriately examine whether changes in this environmental exposure measure were associated with changes in cognitive functioning, and consequently, we were unable to make stronger assumptions about the causal relation between neighbourhood walkability and cognition. Thirdly, this study examines the association of cognitive functioning with neighbourhood walkability in the residential six-digit postal code area of participants, which is a commonly used detailed spatial level for residential environmental exposure assessment (Lakerveld et al., 2020; Timmermans et al., 2018a, 2018b). However, this study does not consider exposure to this environmental factor in other places where people spend substantial amounts of time (e.g., places for work, shopping, and recreation). Assumed that people with better cognitive functioning spent more time at these places, this may have led to an underestimation of the associations. Fourthly, there was a maximum temporal mismatch of two years between the collection of individual-level data and some of the linked walkability components for some participants in this study. However, it is not likely that these mismatches have substantially biased our findings, because neighbourhood walkability components have shown to be relatively stable over such time window (Timmermans et al., 2021; Noordzij et al., 2021). Finally, although we adjusted for relevant covariates in our analyses, there still might be residual confounding factors that we did not take into account, such as the number of years that participants live in their neighbourhood and their occupational status and household income.

Neighbourhoods that are characterized by higher walkability levels may positively affect (domains of) cognitive functioning by providing a "brain training" setting that directly stimulate cognition (Besser et al., 2017, 2021; Wu et al., 2017; Cassarino and Setti, 2015; Clarke et al., 2012), or by supporting healthy lifestyles, mental health and social engagement (Besser et al., 2017, 2021; Wu et al., 2017; Barnett et al., 2017; Cerin et al., 2017; Van Cauwenberg et al., 2018; Aggarwal et al., 2014; Generaal et al., 2018, 2019). This may have a positive impact on the hemodynamic dysfunction and abnormalities in the circulatory system, ultimately leading to better cerebral blood flow (Cerin, 2019; De la Torre, 2012; Leeuwis et al., 2017; Guiney et al., 2015). Patients with VCI, who are characterized by vascular brain injuries, may particularly benefit more from this, which may explain the stronger positive associations of neighbourhood walkability with cognitive functioning in this patient group (Leeuwis et al., 2020). This study further showed that neighbourhood walkability at baseline (using 500-, 1000-, and 2000-m buffer zones) was not associated with change in cognitive functioning over the two-year follow-up period. This might be due to a lack of statistical power in these analyses. However, sensitivity analyses (using 250-m buffer zones) did indicate that exposure to higher levels of neighbourhood walkability are associated with an improvement in global cognitive functioning and language over time. This suggests that especially built environmental aspects of the direct residential environment might be relevant for improving cognitive functioning over time.

Before informing policies about the positive, and potentially clinically relevant, impact of improving neighbourhood walkability levels for residents' cognitive functioning, the present results need to be confirmed in future research. Future research could replicate our approach with data from a larger number of participants and over a longer follow-up period. Such approach would enable to appropriately assess whether changes in built environmental characteristics are associated with changes in cognitive functioning over time, and would be informative to the causal relationship between these environmental characteristics and cognition. Furthermore, future research could incorporate other potentially relevant factors or by-products from the built as well as social environment for cognition (e.g., area-level air pollution, blue space, and social cohesion) (Cerin, 2019; Cerin et al., 2020; Power et al., 2011; Zhang et al., 2019), and could also examine the role of potentially relevant mediating factors (e.g., physical activity, mental health, cerebral blood flow, white matter hyperintensities, and neuro-inflammation) (Cerin, 2019; Besser et al., 2021; Brockmeyer and D'Angiulli, 2016; Wellenius et al., 2013). In addition, future studies could not only take environmental exposures in the residential environment into account, but could also use time-activity-weighted exposure measures, that consider exposures at other significant places where individuals spent their time (Park and Kwan, 2017). This may improve the assessment of environmental factors that an individual is exposed to, and may reduce bias of estimated environment-cognition associations.

5. Conclusions

The main analyses in this study (using 500-m buffer zones) provide supportive evidence for positive cross-sectional associations of neighbourhood walkability with cognitive functioning in reference participants and patients with disorders along the heart-brain axis; particularly in those with VCI. The main analyses also indicate that higher levels of walkability at baseline lower the odds of impaired language and executive functioning at two-year follow-up. Sensitivity analyses (using 250-m buffer zones) provide evidence that exposure to higher levels of neighbourhood walkability are associated with an improvement in global cognitive functioning and language over the two-year follow-up period. Together, these findings highlight the importance of the built environment for cognitive functioning in healthy and vulnerable groups.

Authors' contributions

EJT, MLB and IV conceptualized the study. EJT conducted all analyses, interpreted the data, and drafted the manuscript, and is responsible for the overall content of the manuscript. AEL, MLB, JLvA, GJB, HPBLR, JLK, ACvR, MJPvO and IV provided critical feedback on the manuscript. All authors approved the manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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Supplementary data

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