BMJ Open

Outdoor green space exposure and brain health measures related to Alzheimer's disease: a rapid review

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To cite: Besser L. Outdoor green space exposure and brain health measures related to Alzheimer's disease: a rapid review. *BMJ Open* 2021;**11**:e043456. doi:10.1136/bmjopen-2020-043456

► Prepublication history and supplemental material for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-043456).

Received 04 August 2020
Revised 17 March 2021
Accepted 09 April 2021

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ABSTRACT

Objectives Summarise studies of outdoor green space exposure and brain health measures related to Alzheimer's disease and related disorders (ADRD), and determine scientific gaps for future research.

Design Rapid review of primary research studies.

Methods and outcomes PubMed, Embase and Web of Science Core Collection were searched for articles meeting the criteria published on/before 13 February 2020. The review excluded papers not in English, focused on transient states (eg, mental fatigue) or not using individual-level measures of brain health (eg, average school test scores). Brain health measures of interest included cognitive function, clinical diagnosis of cognitive impairment/dementia/ADRD and brain biomarkers such as those from MRI, measures typically associated with ADRD risk and disease progression.

Results Twenty-two papers were published from 2012 to 2020, 36% on <18 years old, 32% on 18–64 years old and 59% on ≥65 years old. Sixty-four per cent defined green space based on the Normalised Difference Vegetation Index ('greenness'/healthy vegetation) and 68% focused on cognitive measures of brain health (eg, memory). Seventeen studies (77%) found green space-brain health associations (14 positive, 4 inverse). Greater greenness/green space was positively associated various cognitive domains in 10 studies and with MRI outcomes (regional brain volumes, cortical thickness, amygdala integrity) in three studies. Greater neighbourhood greenness was associated with lower odds/risk of cognitive impairment/ADRD in some studies but increased odds/risk in others (n=4 studies).

Conclusions Published studies suggest positive green space-brain health associations across the life course, but the methods and cohorts were limited and heterogeneous. Future research using racially/ethnically and geographically diverse cohorts, life course methods and more specific green space and brain health measures (eg, time spent in green spaces, ADRD biomarkers) will strengthen evidence for causal associations.

Strengths and limitations of this study

- ► Three major databases covering biomedical, psychological, environmental and social science topics and a range of keywords were searched to find pertinent studies regarding associations between green space exposure and Alzheimer's disease and related disorders brain health measures.
- ► Published literature reviews on green space and health and reference lists from the final sample of papers were reviewed to help ensure pertinent papers were included.
- ► This study was limited to a single reviewer and thus, the methods used to search, screen, select and chart the final sample of papers could not be duplicated/adjudicated by additional reviewers.
- ► As a rapid review, this study was not aimed at providing a quantitative evaluation of the evidence or risk of bias, and may have missed papers that would have been ascertained if additional reviewers were available.

INTRODUCTION

Nature contact involves time spent in green spaces (eg, gardens, parks, forests) and blue spaces (eg, lakes, rivers) where people live, work and play. Preliminary studies suggest associations between nature contact and health including reductions in depression, anxiety and cardiovascular risk factors; improved attention and mood; and increased physical activity.[1] Studies also suggest associations with brain health across the life course.[2–8] For instance, greater neighbourhood greenness (ie, healthy vegetation) has been associated with lower odds of Alzheimer's disease (AD) in older adults.[9]

AD and related disorders (ADRD) affect approximately 50 million people worldwide, and 15% of older adults have mild cognitive impairment, a frequent antecedent to dementia.[10 11] Older age, lower educational attainment and genetics (eg, apolipoprotein E (APOE) ε4 allele carriers) are some of the strongest predictors of AD risk and late-life cognitive decline.[12] Clinicians diagnose AD using biomarkers and/or cognitive assessments. Diagnostic biomarkers include cerebrospinal fluid (CSF) or positron emission (PET) scan biomarkers measuring brain amyloid beta and phosphorylated tau, the proteins responsible for AD neuropathology (ie, plaques and tangles).[13 14] Cognitive tests for AD typically evaluate memory of personal events (ie, episodic memory), the hallmark cognitive domain affected early in the disease course.[15] Episodic memory problems are correlated with atrophy of the hippocampus, and thus, MRI brain biomarkers such as hippocampal atrophy help support AD diagnosis and predict AD incidence and disease progression.[16] Other dementia disorders typically affect different cognitive domains/brain regions in the early stages of disease, and later stages of ADRD can affect additional cognitive domains and brain regions.[15]

The psychological and financial burden of ADRD on patients and families is substantial.[17 18] Healthcare systems are ill prepared to deal with the increase in ADRD prevalence accompanying the rapidly rising population of older adults,[19] and no effective treatments are currently available. Therefore, an accumulating body of research has focused on individual-level and community-level interventions that may be help prevent or delay ADRD. Provided there is supporting evidence, neighbourhood green space is one such community-level feature that may be promoted to improve lifelong brain health. Healthy brain development during childhood and maintenance of brain health throughout adulthood, assisted by living near health-enhancing green spaces, may help reduce ADRD risk.

Green space exposure may benefit brain health through a number of pathways.[1 20] They provide enriching, physical activity promoting and stress reducing environments that consequently may be associated with better brain health by affecting cerebral blood flow, angiogenesis, vascular integrity, cell proliferation/survival, vascular dysregulation and/or inflammation.[21–25] Green space exposure may reduce stress and mental fatigue and improve attention, consistent with the stress recovery theory and attention restoration theory.[26–28] Studies are available to support both theories. For instance, living within one mile of green spaces and visiting green spaces have been associated with experiencing less stress,[29] and gardening has been found to reduce levels of salivary cortisol, a stress hormone.[30] In adults, mood, restoration and sustained attention were improved after participating in a nature walk intervention in urban and rural locales.[28] These psychological benefits over the long term may additionally benefit mental health (eg, anxiety, depression), factors associated with brain health including ADRD risk.[31] Microbial and antigenic exposures from nature contact,[32] especially during childhood, may affect lifelong immune function and contribute to healthy microbiomes, which have been associated with mental health and AD.[33–35] Green spaces provide areas for recreational exercise. Exposure and access to natural places have been associated with greater physical activity in children through older adults,[36 37] and obtaining greater physical activity has been associated with reduced brain atrophy, cognitive decline and ADRD risk.[38 39] Natural areas provide spaces for social gathering and engagement.[40] Higher levels of social engagement have been associated with better cognitive function and reduced AD risk.[41 42] Lastly, natural areas and parks have been associated with lower levels of harmful air pollutants, including particular matter ≤10µm in size (PM_{10}) and nitrogen dioxide (NO_2)[43 44] that have been associated with worse cognition and greater ADRD risk.[45] The mechanisms by which air pollution affects the brain have been hypothesised to be direct and/or indirect (eg, systemic inflammation, adsorbed compounds).[46]

The budding and cross-disciplinary field of research on green spaces and ADRD/brain health will benefit from a review of pertinent studies spanning multiple disciplines. Literature used to inform primary research tends to be siloed to a researcher's area of expertise or based on limited or discipline-specific search terms. Given the nascent state of green space and ADRD-related brain health research and the lack of published literature reviews focused on the topic, this rapid review employed scoping aims. Rapid reviews are increasingly used in research to address the need for more readily available summaries of available evidence that cannot be achieved through the lengthy and resource-intensive process of systematic reviews.[47] Scoping reviews are useful in summarising new topics of research, findings for a broader set of health outcomes, or topics that may not have enough evidence amassed to assess the weight of evidence or risk of bias.[47–49]

The number of studies on green space and health has risen dramatically in the last decade,[50] but it remains unclear how many studied brain health outcomes. Therefore, consistent with the major goals of a scoping review,[48 49 51 52] this rapid review aimed: (1) to summarise the extant literature on green space-brain health associations across the life course, potentially providing impetus for future systematic reviews and (2) to identify knowledge gaps to inform future research. The primary intent was to identify and describe current evidence for benefits to cognition and brain structure/function due to green space exposure. These benefits may develop and persist in early- and mid-life to reduce ADRD risk in late life.

METHODS

Patient and public involvement

Patients and the public were not involved as this study focuses on a review of published papers with no analysis of participant data.

Identification and study selection

A single reviewer was available for this study. On 13 February 2020, PubMed, Web of Science Core Collection and Embase were queried for the following keywords: 'greenspace or green space or greenness or parks or park or park space or parkspace' and 'cognition or cognitive or memory or brain ageing or Alzheimer or Alzheimer's or dementia or cognitive impairment'. To help ensure the 13 February review did not miss pertinent papers, a second search of the three databases was performed on 18 July 2020, for the following keywords: 'neighbourhood environment or wilderness or greenery or natural space or natural environment or public garden or recreational resource or Normalised Difference Vegetation Index (NDVI) or built environment or open space or woodland' and 'brain volume or brain atrophy or neurodegenerative disease or Alzheimer biomarker or cognition or cognitive or memory or brain ageing or Alzheimer or Alzheimer's or dementia or cognitive impairment'. The keywords searched reflected the brain health measures of interest that are typically associated with ADRD risk/disease progression, including cognitive function, clinical diagnosis of cognitive impairment/dementia/ADRD and biomarkers such as those from brain imaging (eg, MRI).

The 18 July 2020 search was restricted to papers published on or before 13 February, 2020, to be consistent with the original search. A limitation of the 18 July 2020 search was the restriction to a search of titles in Web of Science. A full-text search led to 8574 papers that could not be feasibly reviewed based on available time and resources (ie, this is a rapid review). Of note, the final list of included papers from the February 13 search was ascertained either from the search of PubMed and Embase or the review of resulting titles from the search of full texts in Web of Science (ie, not from a full text review of papers in Web of Science). This suggests that the July search of titles in Web of Science was unlikely to have missed pertinent papers, but the possibility remains. A detailed description of the search strategy is provided in online supplemental figure 1.

Titles were screened for topics definitely or possibly related to green space and ADRD-related brain health. Titles potentially related were included in the abstract review (eg, green space and child development, neighbourhood environment and AD, built environments and ageing, outdoors and mental health). After review, abstracts that moved on to full-text review had exposures/outcomes directly pertinent to this study, focused on associations between green space and other measures but mentioned brain health measures as covariates, or seemed possibly relevant by including closely related exposures or outcomes (eg, mental health, frailty, built environment, nature contact). Full texts included in the final sample reported associations between green space exposure and brain health outcomes in the main text or online supplemental file.

Articles were excluded if they: (1) were not in English; (2) were not primary research studies; (3) were focused on indoor green space/views; (4) used virtual reality to simulate green spaces; (5) were ecological studies (eg, average school test scores); (6) were focused on attention restoration or mental fatigue (transient states) or (7) centred on green space activities such as gardening without an adequate control/comparison group to sufficiently capture green space as the main exposure. Reference lists from the final sample and published green space-health reviews were reviewed to identify other studies meeting the eligibility criteria.[1–8]

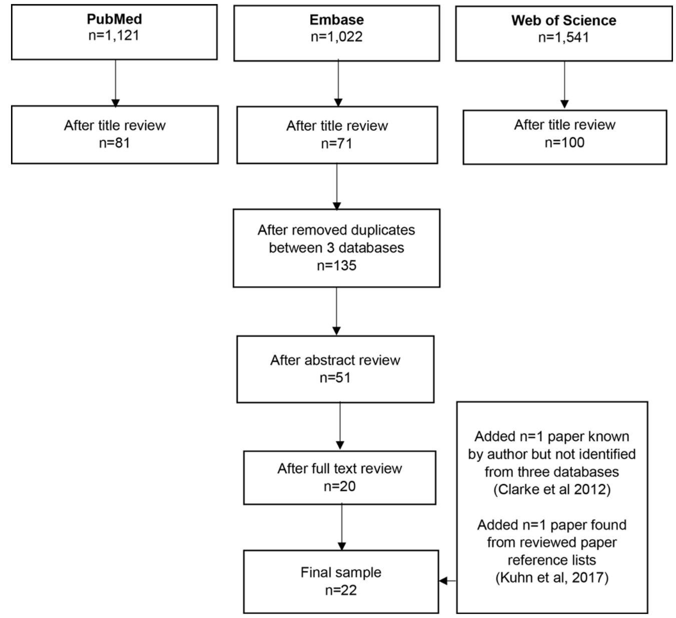

Figure 1 Sample size flow diagram (see online supplemental figure 1 for full details).

Charting and summarising the data

Papers were described by study design, location, age groups, green space and brain health measures and definitions, statistical methods and main findings (these data were charted into online supplemental tables 1–4). Key study elements were tabulated separately for three major age groups: children (0–17 years), adults (18–64 years) and older adults (≥65 years). Findings were stratified by age because while studies of children focus on the critical period of childhood development, studies of 18–64 years old focus on working adults and studies of ≥65 years old focus on retirement-age individuals. Green space exposures and brain health can differ substantially during these life stages. Results (positive, inverse, null associations) were summarised according to age groups, green space measures, brain health measures and examined green space-brain health associations to characterise the scope of the evidence to date.

RESULTS

Overall study characteristics

The final sample included 22 papers (figure 1).[9 53–73] Post hoc additions to the final sample, published on or before 13 February 2020, included one paper previously known by the author[53] and one paper identified from the final sample reference lists.[73] Tables 1–4 and online supplemental tables 1–4 summarise study characteristics and findings. Eight-two per cent (n=18)[9 54–58 60–64 66–69 71–73] of studies were published on/after 2017 (range: 2012–2020). Seven studies (32%) were in the UK, four (18%) in China, three in Spain (14%), two each (9%) in the USA and Canada and one each (4%) in Bulgaria, Germany, New Zealand and multiple regions (Spain, UK, the Netherlands) (figure 2). Eight studies (36%) focused on <18

Table 1 Summary of green space-brain health associations by age group

Citation*	Sample size	Population based/ random sample	Location	Children (<18 years)	Adults (18–64 years)	Older adults (≥65 years)
Brown[9]	249 405	Yes	USA			+
Cherrie[63]	281	Yes	UK	N	N	+
Cherrie[64]	281	Yes	UK			+N
Clarke[53]	949	Yes	USA		N	N
Dadvand[65]	2593	No	Spain	+N		
Dadvand[54]	987	Yes	Spain	+N		
Dadvand[66]	253	No	Spain	+N		
Dzhambov[72]	112	No	Bulgaria		+N	
de Keijzer[55]	6506	Yes	UK		+N	+N
Flouri[56]	4758	Yes	UK	+		
Hystad[57]	6658	Yes	Canada		- N	
Kuhn[73]	341	No	Germany			+N
Liao[67]	1312	No	China	+		
Reuben[68]	1658	Yes	UK	N		
Wang[69]	3544	No	China			N
Ward[70]	72	No	New Zealand	N		
Wu[59]	2424	Yes	UK			–
Wu[58]	7505	Yes	UK			- N
Yu[71]	3240	No	China			N
Yuchi[60]	678 000	Yes	Canada		+ -	+ -
Zhu[61]	6994	Yes	China			+
Zijlema[62]	1628	Yes	Spain, UK, Netherlands		+N	+N
Studies with positive associations				5	4	8
Studies with inverse associations				0	2	3
Studies with null associations				6	6	8
Total studies				8	7	13

*Full list of papers found in online supplemental text 1.
+, positive association; -, inverse association; N, null association.

years old (childhood),[54 56 63 65–68 70] seven (32%) focused on 18–64 years old (adulthood),[53 55 57 60 62 63 72] and 13 (59%) focused on ≥65 years old (older adulthood)[9 53 55 58–64 69 71 73] (figure 3). Fourteen studies (64%)[9 53–64 68] were based on population-based cohorts or random sampling strategies. Two studies (9%) examined life course associations, both investigating childhood and mid-life park space exposures and cognitive change in late life.[63 64]

Seventeen studies (77%) found associations (14 positive,[9 54–56 60–67 72 73] 4 inverse[57–60]) and 5 (23%) found no associations[53 68–71] between greenness/green space and brain health (tables 1–4, figure 4). Twelve studies (55%) reported a combination of positive, inverse and/or null associations.[54 55 57 58 60 62–66 72 73] All but one study[69] employed multivariable linear or logistic regression accounting for key confounders (ie, age, sex, socioeconomic status (SES)) and 12 (55%)[9 53–56 58 59 61 62 64 65 70] used regression methods accounting for data clustering/multilevel data.

Findings by age group

Children: Five[54 56 65–67] of the eight studies[54 56 63 65–68 70] found green space-brain health associations in children (five positive, zero inverse) (table 1). Greater neighbourhood greenness/green space was associated with working memory,[54 56] attention[54 65] and intellectual development[67] and with specific brain regions.[66] Null associations were found between greater greenness/green space and intelligence,[63] alerting,[65] orienting,[65] executive processing/function,[65 68] fluid ability,[68] crystallised ability,[68] working memory[68] and attention.[54 65 68] Time spent in green space measured via global positioning system (GPS) tracking was not associated with multiple cognitive domains (eg, visual and verbal memory, processing speed).[70]

Table 2 Summary of green space-brain health associations by green space measure

Citation*	Sample size	Population based/ random sample	Location	Longitudinal green space	Greenness (NDVI, EVI)	Percent/ area park space	Percent green space	Time spent in green space	Distance to natural outdoor environment	Other green space
Brown[9]	249 405	Yes	USA	No	+					
Cherrie[63]	281	Yes	UK	Yes		+N				
Cherrie[64]	281	Yes	UK	Yes		+N				
Clarke[53]	949	Yes	USA	No		N				
Dadvand[65]	2593	No	Spain	No	+N					
Dadvand[54]	987	Yes	Spain	Yes	+N					
Dadvand[66]	253	No	Spain	Yes	+N					
Dzhambov[72]	112	No	Bulgaria	No	+N					
De Keijzer[55]	6506	Yes	UK	Yes	+N					
Flouri[56]	4758	Yes	UK	No			+			
Hystad[57]	6658	Yes	Canada	Yes	- N					
Kuhn[73]	341	No	Germany	No			+N			
Liao[67]	1312	No	China	No	+					
Reuben[68]	1658	Yes	UK	Yes	N					
Wang[69]	3544	No	China	No	N					
Ward[70]	72	No	New Zealand	No				N		
Wu[59]	2424	Yes	UK	No			–			
Wu[58]	7505	Yes	UK	No			- N			
Yu[71]	3240	No	China	No	N					
Yuchi[60]	678 000	Yes	Canada	Yes	+ -					
Zhu[61]	6994	Yes	China	Yes	+					
Zijlema[62]	1628	Yes	Spain, UK, Netherlands	No	N			N	+	N
Studies with positive associations					9	2	2	0	1	0
Studies with inverse associations					2	0	2	0	0	0
Studies with null associations					10	3	2	2	0	1
Total studies					14	3	4	2	1	1

*Full list of papers found in online supplemental text 1.
-, inverse association; +, positive association; EVI, enhanced vegetation index; N, null association; NDVI, Normalised Difference Vegetation Index.

Adults (18–64 years): Five of the seven studies[53 55 57 60 63 72] found green space-brain health associations in adults (four positive,[55 60 62 72] two inverse[57 60] (table 1). Increased residential distance to natural outdoor environments was associated with longer cognitive test completion times,[62] and greater neighbourhood greenness was positively and inversely associated with dementia diagnoses (detailed in 'older adults' section below).[60] Greater neighbourhood greenness was cross-sectionally associated with better global cognition[72] and was associated with slower longitudinal decline on global cognition, reasoning and verbal fluency.[55] Additionally, greater neighbourhood green space was associated with greater cortical thickness in the prefrontal cortex, bilateral fusiform gyrus, left precuneus and insula, and right cuneus as measured via MRI.[72] Null associations were found between greater neighbourhood greenness/green space or 5-year change in greenness and measures of global cognition,[53 72] intelligence,[63] reaction time,[57] reasoning,[57] memory,[55 57 72] naming[72] and visual attention/executive processing.[62] No associations were found between self-reported visits or time spent in natural environments and visual attention/executive processing,[62] and no associations were observed between greater greenness and cortical thickness of other brain MRI regions (eg, right cuneus and insula).[72] Lastly, inverse associations were found between 5-year change in neighbourhood greenness and reasoning.[57]

Older adults (≥65 years). Ten of 13 studies[9 53 55 58–64 69 71 73] found green space-brain health associations in older adults (eight positive,[9 55 60–64 73] three inverse[58–60] (table 1).

Table 3 Summary of green space-brain health associations by brain health measure

Citation*	Sample size	Population based / random sample	Location	Longitudinal brain health measure	Cognition	MRI brain regions	Diagnosis of cognitive impairment/ dementia
Brown[9]	249 405	Yes	USA	No			+
Cherrie[63]	281	Yes	UK	Yes	+N		
Cherrie[64]	281	Yes	UK	Yes	+N		
Clarke[53]	949	Yes	USA	No	N		
Dadvand[65]	2593	No	Spain	Yes	+N		
Dadvand[54]	987	Yes	Spain	Yes	+N		
Dadvand[66]	253	No	Spain	No		+N	
Dzhambov[72]	112	No	Bulgaria	No	+	+N	
De Keijzer[55]	6506	Yes	UK	Yes	+N		
Flouri[56]	4758	Yes	UK	No	+		
Hystad[57]	6658	Yes	Canada	No	- N		
Kuhn[73]	341	No	Germany	No		+N	
Liao[67]	1312	No	China	No	+		
Reuben[68]	1658	Yes	UK	Yes	N		
Wang[69]	3544	No	China	No	N		
Ward[70]	72	No	New Zealand	No	N		
Wu[59]	2424	Yes	UK	No			–
Wu[58]	7505	Yes	UK	No			- N
Yu[71]	3240	No	China	No	N		
Yuchi[60]	678 000	Yes	Canada	Yes			+ -
Zhu[61]	6994	Yes	China	Yes			+
Zijlema[62]	1628	Yes	Spain, UK, Netherlands	No	+N		
Studies with positive associations					9	3	3
Studies with inverse associations					1	0	3
Studies with null associations					12	3	1
Total studies					15	3	5

*Full list of papers found in online supplemental text 1.
+, positive association; -, inverse association; N, null association.

Greater neighbourhood greenness was associated with lower risk of AD,[9] non-AD[60] and Parkinson's disease diagnoses[60] in some studies, but increased risk of cognitive impairment[58 59] and AD diagnoses[60] in others. Greater neighbourhood greenness/green space was positively associated with intelligence,[63 64] global cognition,[55] reasoning,[55] verbal fluency[55] and visual attention/executive processing.[55 62–64] In addition, greater green space (ie, forests) was associated with better amydala integrity measured via MRI.[73] Null associations were found between neighbourhood greenness/green space and intelligence,[63 64] global cognition,[53 69 71] short-term memory[55] and visual attention/executive processing.[62] Time spent in natural environments was not associated with visual attention/executive processing.[62] Lastly, urban green space was not associated with brain integrity measured via MRI.[73]

Findings by green space measure

Green space definitions included: (1) greenness measured using the NDVI or Enhanced Vegetation Index (EVI)[9 54 55 57 60–62 65–69 71 72]; (2) tree canopy/cover measured using vegetation continuous fields (VCF)[54]; (3) neighbourhood percentage green/park space or park area[53 56 58 59 63 64 73]; (4) time spent in green space (objective or self-reported)[62 70]; (5) self-reported amount of natural environment near residence[62] and (6) distance from residence to natural outdoor environment[62] (table 2). Three studies examined more than one green space measure: (1) NDVI and VCF[54]; (2) NDVI and EVI[55]; and (3) NDVI, distance to natural outdoor environment,

Table 4 Findings by green space-brain health association investigated and author name

Green space measure*	Cognition			MRI			Diagnosis of cognitive impairment/dementia		
	+	–	N	+	–	N	+	–	N
Greenness/ NDVI	Dadvand[a] Dadvand[b] Liao De Keijzer Zhu Dzhambov	Hystad	Dadvand[a] Dadvand[b] Reuben De Keijzer Hystad Zijlema Wang Yu	Dadvand[c] Dzhambov		Dadvand[c] Dzhambov	Yuchi Brown	Yuchi	
Percent green/ park space	Cherrie[d] Cherrie[e] Flouri		Cherrie[d] Cherrie[e] Clarke	Kuhn		Kuhn		Wu[f] Wu[g]	Wu[g]
Time spent in green space			Ward Zijlema						
Other	Zijlema		Zijlema						

Year of publication: [a]2015; [b]2017; [c]2018; [d]2018; [e]2019; [f]2015; [g]2017.
*Full list of papers found in online supplemental text 1.
-, inverse association; +, positive association; N, null association; NDVI, Normalised Difference Vegetation Index.

and self-reported green space measures.[62] Most studies measured green space in the residential neighbourhood, although a few additionally measured green space surrounding schools and school routes.[64 65] No studies examined work area green spaces. NDVI was the most commonly used measure. The boundaries used to define green space exposures varied greatly (eg, 100–1500 m radial buffers around residences, 1000 m buffers around postcode centroids, US Census tracts, 50 m buffers around school route).

NDVI: Ten of 14 studies[9 54 55 57 60–62 65–69 71 72] using NDVI found associations (nine positive,[9 54 55 60 61 65–67 72] two inverse[57 60] (table 2). Of the studies with positive findings, one examined MRI brain measures[66] and three examined risk/odds of cognitive impairment/dementia.[9 60 61] The remaining studies with positive findings focused on various cognitive domains. In studies with inverse associations, 5-year NDVI increase was associated with worse reasoning in 40–69 years old[57] and greater greenness was associated with lower risk of non-AD dementia and Parkinson's disease among 45–84 years old.[60]

Park space: Two[63 64] of three studies on percent/amount of residential park space found positive associations with cognitive change in late life (table 2). These positive associations were restricted to childhood and mid-life park space exposures and cognitive changes from ages 70 to 76. No associations were observed between early-life and mid-life exposures and cognitive changes from ages 11 to 76 or between late-life park space exposure and cognitive changes at any age (11–76 years). The third study found no associations between neighbourhood park area and cognition.[53]

Other measures: Measures of time spent in green space based on objective GPS tracking[70] or self-report[62]

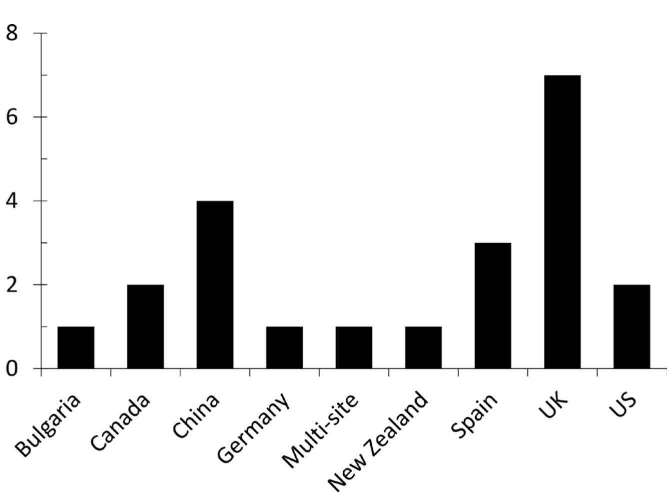

Figure 2 Number of studies by country.

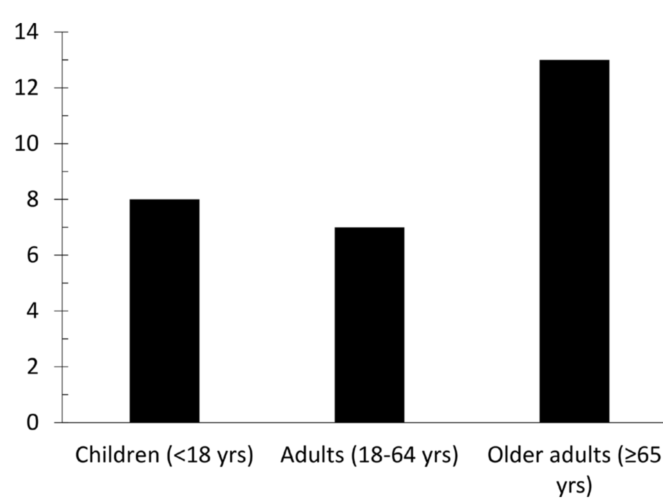

Figure 3 Number of studies by age group.

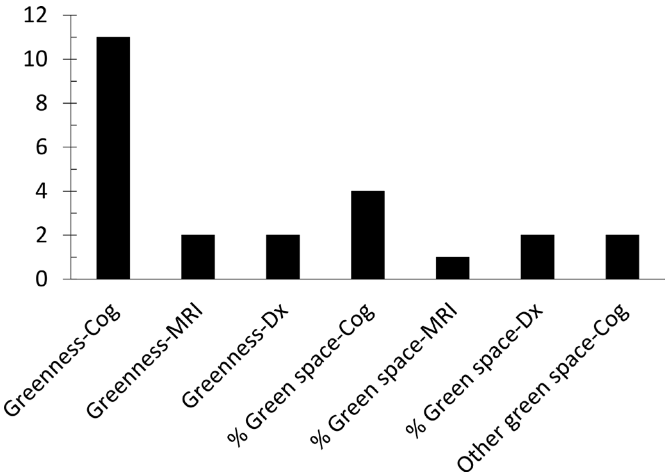

Figure 4 Number of studies by green space-brain health association. Cog, cognition; Dx, diagnosis of cognitive impairment/dementia; Greenness, measure of greenness such as Normalised Difference Vegetation Index, % green space, per cent or amount of neighbourhood composed of green space/park space; other green space, time spent in green space, distance to nearest green/park space and/or self-reported measures.

were not associated with cognition. Positive associations were observed between percentage residential green space derived from land use data and spatial working memory,[56] and between distance to the nearest natural outdoor environment and visual attention/executive processing.[62] Greater amounts of forest surrounding the residence were associated with greater amygdala integrity, whereas amount of neighbourhood urban green space was not associated with MRI measures of brain integrity.[73] Percentage green space and private gardens based on land use data was inversely associated with odds of cognitive impairment/dementia.[58 59] Tree canopy/cover (VCF) was not associated with attention in children.[54] Lastly, self-reported amount of residential natural environment was not associated with visual attention/executive processing.[62]

Findings by brain health measure

Fifteen studies (68%) examined cognitive function.[53–57 62–65 67–72] A range of cognitive domains were assessed, including but not limited to global cognition, working memory, attention, reasoning, verbal fluency and executive function. Five studies (23%)[58 59 61 69 71] used the Mini Mental State Exam, a global cognition screening test, while the remaining used a variety of other instruments. Five studies (23%)[9 58–61] examined diagnosis of cognitive impairment or dementia (including AD and Parkinson disease) and three focused on brain MRI.[66 72 73] Eight studies (36%)[54 55 60 61 63–65 68] used longitudinal data on brain health, but only five (23%)[55 60 63–65] actually examined longitudinal changes in brain health (ie, cognitive decline or dementia risk).

Ten studies (45%) found associations between green space and cognition (nine positive,[54–56 62–65 67 72] one inverse[57]) (table 3). Greater greenness/green space was associated with global cognition, working memory, spatial working memory attention, visual attention, reasoning, fluency and measures of intelligence and childhood intellectual development, as delineated in the sections further above. The three studies using brain MRI found positive associations between greenness/green space and certain brain regions,[66] cortical thickness[72] and amygdala integrity.[73] Two studies found positive associations between greenness/green space and AD,[9] non-Alzheimer's dementia[60] and Parkinson's disease[60] diagnoses, whereas three found inverse associations with AD[60] or cognitive impairment/dementia diagnoses.[58 59]

Effect modification

Effect modification is variation in the association between an exposure and outcome depending on the value of another factor. Seven[55 57 58 61 63 64 67] of 11 studies[9 54–58 61 63–65 67] found effect modification (online supplemental table 4). Green space-brain health associations were stronger in/limited to women[55 57 63]; APOE ε4 non-carriers[61 63] and those with lower occupational class,[63] higher education levels,[55] lower body mass index[67] and younger age[61] (in study of older adults). Associations also were stronger among residents of conurbations[58] (urbanised area comprised of multiple cities/towns), areas with lower traffic accident densities[64] and areas of higher deprivation.[55] Other studies found no effect modification by neighbourhood SES,[9 56 65] sex,[64] maternal education,[65] residential stability/years in residence,[56] race,[57] marital status,[57] city[57] or household income.[57]

Mediation

Three[65 71 72] of seven studies[53 55 62 65 67 71 72] suggested mediation, which is the presence of an intermediary variable associated with both the exposure and outcome that potentially explains the causal mechanism linking the two variables (online supplemental table 4). Traffic-related air pollution (elemental carbon in residence) mediated associations between school greenness and working memory and attentiveness in children[65] and self-reported physical activity mediated associations between greater residential greenness and global cognition in older adults.[71] Associations between greater neighbourhood greenness and better global cognition among middle-aged adults were mediated by lower waist circumference but not by systolic blood pressure, total cholesterol, glucose, air pollution (NO_2) or traffic-related noise.[72] The other four studies found no mediation of green space-brain health associations by physical activity,[53 55 62] social measures (eg, interaction, loneliness),[53] perceived mental health,[62] traffic noise annoyance,[62] worry about air pollution[62] or air pollution levels (ie, $PM_{2.5}$).[55]

DISCUSSION

Evidence was found for associations between green space exposure measured at various life stages and brain health. Seventy-one per cent of NDVI studies (greenness) found positive associations. Greater neighbourhood greenness/green space was positively associated with multiple cognitive domains, brain regions and lower odds/risk of AD and non-AD dementia. However, some studies found inverse or null associations, few studies were conducted within each major age group, and the studies employed limited and heterogeneous methods and definitions. The remainder of this section focuses on the second aim of the scoping review, which is to identify scientific gaps for future research.

Brain health measures

The diversity of employed brain health measures limits study comparisons. Measures of attention were associated with green space in more than one study,[54 62 65] but additional research is needed to confirm these associations. Studies more frequently assessed executive function, attention, and working memory, and fewer examined short-term or long-term memory, language/fluency, processing speed or visuospatial function. The focus on the former cognitive domains may be due to data availability, but also potential hypothesised underlying mechanisms relating green space and brain health, in which green space exposure restores attention and reduces mental fatigue/stress.[26–28] Nonetheless, green space exposures may be associated with other cognitive measures reflecting brain regions susceptible to green space-related behaviours/exposures. New studies are needed to assess green space associations with cognitive domains commonly affected in typical and atypical AD presentations, including episodic memory,[15] visuospatial processing[74] and language.[75] These cognitive domains have been associated with physical activity, social engagement and air pollution exposure[76–78] and are important to investigate in future studies given the plausible mechanisms relating green spaces and these health behaviours/exposures (as detailed in introduction).

Greater greenness/green space displayed mixed associations (positive/inverse) with diagnoses of cognitive impairment or dementia. The mixed findings may be explained by the employed study methods, as three of the four studies were cross-sectional and none examined or controlled for early-life and mid-life factors beyond educational attainment. With the onset of health problems or cognitive symptoms, individuals may be more likely to move to greener rural and suburban areas where there are assisted living and nursing care residences. Thus, the associations between greater late-life neighbourhood greenness/green space and increased odds/risk of cognitive impairment may be explained by reverse causality/self-selection into greener neighbourhoods in later life. Reverse causality will need to be ruled out in future studies by using more sophisticated study designs and methods (eg, life course, instrumental variables).

Clinical diagnoses may be biased by cultural or education factors that may increase or decrease the chance of receiving a diagnosis irrespective of disease presence. For instance, minorities may be more likely to receive dementia diagnoses if educational and cultural differences are unaccounted for in cognitive testing or if a higher prevalence of comorbidities increases ADRD risk.[79] Nevertheless, diagnoses are clinically significant measures of brain health, particularly when made by specialists with expertise in discerning the presence and aetiology of dementia, and thus are useful measures for future green space-brain health research in older adults.

To date, three studies investigated associations between green space and MRI biomarkers, specifically regional brain volumes,[66] measures of structural integrity[73] and measures of cortical thickness[72] obtained from structural MRI. The study of associated brain regions[66] used an intensive method of analysis (examining associations for each three-dimensional pixel (voxel) of brain image) that significantly limited the number of confounders included in the multivariable analyses. An alternative to the voxel-wise analysis, which would allow controlling for multiple important confounders, would be to measure brain health/atrophy using regional brain volumes (mm^3) and cortical thickness determined through standardised segmentation techniques.[80] The findings for associations between greater greenness/green space and greater amygdala integrity and cortical thickness will need to be replicated. Lastly, measures of global brain atrophy from MRI, such as total grey matter volume or ventricular volume, may be a useful addition for future studies under the presumption that green space exposures affect overall brain development and ageing.

Green space measures

This review suggests that NDVI is a valuable measure for future studies of green space and brain health. However, NDVI does not assess tree canopy/cover or other qualities of green spaces (eg, park amenities).[20] Future work will need to consistently incorporate quality measures including tree canopy/cover, availability of park amenities (eg, walking trails), and safe walking routes/sidewalks, which will help identify types of green space environments[20] most effective at promoting brain health.

Studies measuring percentage of the neighbourhood composed of green space (ie, parks) found positive,[56 63 64 73] inverse[58 59] and null associations,[53 58 63 64 73] warranting additional studies. Compared with NDVI (greenness), percentage green space may better capture access to green spaces. For instance, associations with NDVI measures can be affected by the chosen cut points to define healthy vegetation (eg, NDVI >0.40 or NDVI >0.60), the satellite image used to derive NDVI (affected by season and cloud cover), or green space fragmentation (pockets) that can skew mean NDVI values.[20] Green space access may be a stronger predictor of healthy behaviours such as physical activity, particularly among socioeconomically disadvantaged individuals with limited resources and opportunities for exercise.[81] Other measures of green space access to should be investigated (eg, number of neighbourhood parks) to determine the strongest predictors of both healthy behaviours and better brain health.

The single study incorporating self-reported measures of green space exposure found no associations.[62] Objective green space measures are necessary to suggest target amounts and qualities of green space for interventions, plans and policies. However, self-reported and perceived measures may be useful in tandem with objective measures. Valid and reliable green space questionnaires would minimise burden and data security concerns in attempting to derive objective measures from residential addresses across the life span.

The majority of studies did not measure actual exposure to green spaces (ie, time spent in green spaces).[62 70] Travel diaries could be used to assess time spent in green spaces, although compliance in diary completion and misreporting may be an issue.[82] Although studies have successfully incorporated GPS to investigate neighbourhood environmental exposures and outcomes including physical activity,[83–85] costs, difficulty in recruiting, participant time required and non-compliance can be a hurdle.[86] Despite these limitations, GPS and travel diary measures of time spent in green space provide increased specificity of exposure needed to make informed decisions about green space-brain health associations. If individuals live in neighbourhoods with greater access to green space but they do not regularly spend time in those spaces, then associations with brain health observed in prior research have been spurious or biased by residual confounding.

Places for estimating green space exposures may depend on the age group under study, but only two studies measured non-residential exposures.[64 65] Green space exposure may occur most frequently in residential and school environments among children; residential, working and recreational environments among working adults; and residential and recreational environments among older adults.[64 84] Future studies will benefit from a more comprehensive assessement of places for green space exposures, and longitudinal studies following individuals progressing through these life stages should keep age-based differences in activity spaces in mind.

Life course exposures

Many of the studies of middle-aged and older-aged adults were cross-sectional[9 53 57–59 61 62 69 71–73] and lacked consideration of earlier life green space exposures.[9 53 55 57–62 69 71–73] Childhood exposures may be most critical for determining late-life brain health by influencing healthy brain development. These neurodevelopmental benefits may impart cognitive reserve and resilience through older ages, which protects against ADRD neuropathology and resists symptoms despite neuropathology.[87] Green space exposure patterns during childhood may also establish healthy habits including physical activity that continue through adulthood to boost and maintain brain health. The importance of including childhood measures in future studies also applies to confounders such as early-life personal and neighbourhood SES, which have been found to be associated with late-life cognitive health.[88]

Some evidence suggests that mid-life behaviours may be stronger predictors of late-life cognitive decline and dementia risk than late-life behaviours.[89 90] In a similar fashion, green space exposures in mid-life versus late-life may be more strongly associated with late-life brain health. Mid-life exposures are of particular interest because the neuropathology associated with ADRD often starts decades prior to symptom development (ie, in mid-life).[91] During mid-life, green space-related behaviours/exposures such as physical activity may help resist the development of ADRD neuropathology or decrease the neuropathological burden.[92] Yet, even late-life green space exposures may help maintain brain health in older age by providing accessible places that encourage exercise, relaxation, and socialising. Life course studies are needed to determine the critical periods of green space exposure related to late-life brain health and ADRD risk.

Causal mechanisms

Traffic-related air pollution and self-reported physical activity were found to be mediators, providing preliminary evidence for these two causal mechanisms. Future evaluation of mediation by physical activity should use rigorous, objective measures such as those obtained from accelerometers. Social engagement and related measures were not found to be mediators, and mental health (eg, anxiety, depression) and immune function were not examined in any study. Altogether, few studies examined mediation, additional work is need to determine causal pathways for green space-brain health associations and future studies will need to employ rigorous methods to evaluate mediation.[93]

Future research directions

New studies will need to incorporate longitudinal measures of green space (accumulation of exposures and changes over time) and brain health. GPS-based measures of green activity spaces and time spent in green spaces will improve the quantification and quality assessment of green space exposures. Use of brain biomarkers such as structural and functional MRI, PET scans and CSF biomarkers to detect brain neurodegeneration/ADRD may provide biological evidence for associations. Green space exposures should temporally precede the brain health measures, and the validity and reliability of green space measures need to be established. Causal mechanisms need to be delineated through rigorous investigation of potential mediators. In addition, the evidence base will be strengthened by capitalising on natural experiments (eg, planned green space additions) to study green space associations with brain health.

Future studies will need to incorporate relevant factors insufficiently examined to date, including the potential impact of residential moves, seasonality of exposure/regional climate, bias due to self-selection into greener neighbourhoods (ie, reverse causality) and neighborhood-level confounders (eg, crime, population density). Research is needed on the pertinent places (eg, neighbourhood, work, recreational) and boundaries (eg, 1000 m buffer) for green space exposures. Studies need to determine if associations are present irrespective of or instead depend on race/ethnicity and culture, by demonstrating associations in multiple international contexts and in various regions of diverse countries such as the USA.

LIMITATIONS

Limitations of the reviewed studies include lack of consideration of early-life green space exposures and examination of actual time spent in green spaces. Thus, the studies were likely affected by misclassification/information bias. Selection bias was also likely for many of the studies that restricted to samples with non-missing data on exposures and outcomes.

This review may be limited by positive publication bias. In addition, papers may have been missed due to the nature of this rapid review, which was based on three databases, a restricted review of the Web of Science search results (detailed in the methods section and online supplemental figure 1), and a single reviewer. However, the review of reference lists and related reviews helped reduce the possibility. As this was a rapid review with scoping aims,[47 49 51 52] it was never intended to systematically evaluate the evidence for risk of bias, which will be reserved for future systematic reviews.

CONCLUSION

This rapid review identified twenty-two studies of green space and brain health. The majority of studies were cross-sectional and the green space and brain health measures were heterogeneous. Despite the limitations, multiple studies investigating neighbourhood greenness found positive associations with brain health outcomes at various life stages. Thus, the evidence is suggestive that green space is associated with brain health and future systematic reviews are warranted. The observed positive associations need to be replicated in longitudinal and life course studies of diverse cohorts and in studies using more rigorous measurements and statistical methods. These improvements are needed to build a case for community-level green space interventions to impart brain resilience, maintain/improve cognition and reduce ADRD risk in late life.

Contributors LB is the sole author of this paper and as such completed all of the work, including data acquisition and interpretation, drafting and revising the paper for intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work.

Funding LB is supported by National Institutes of Health/National Institute on Aging award K01AG063895.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. Deidentified data (ie, search results from the databases) are available on request of LB (lbesser@fau.edu). Any reuse or sharing of these data require LB's approval.

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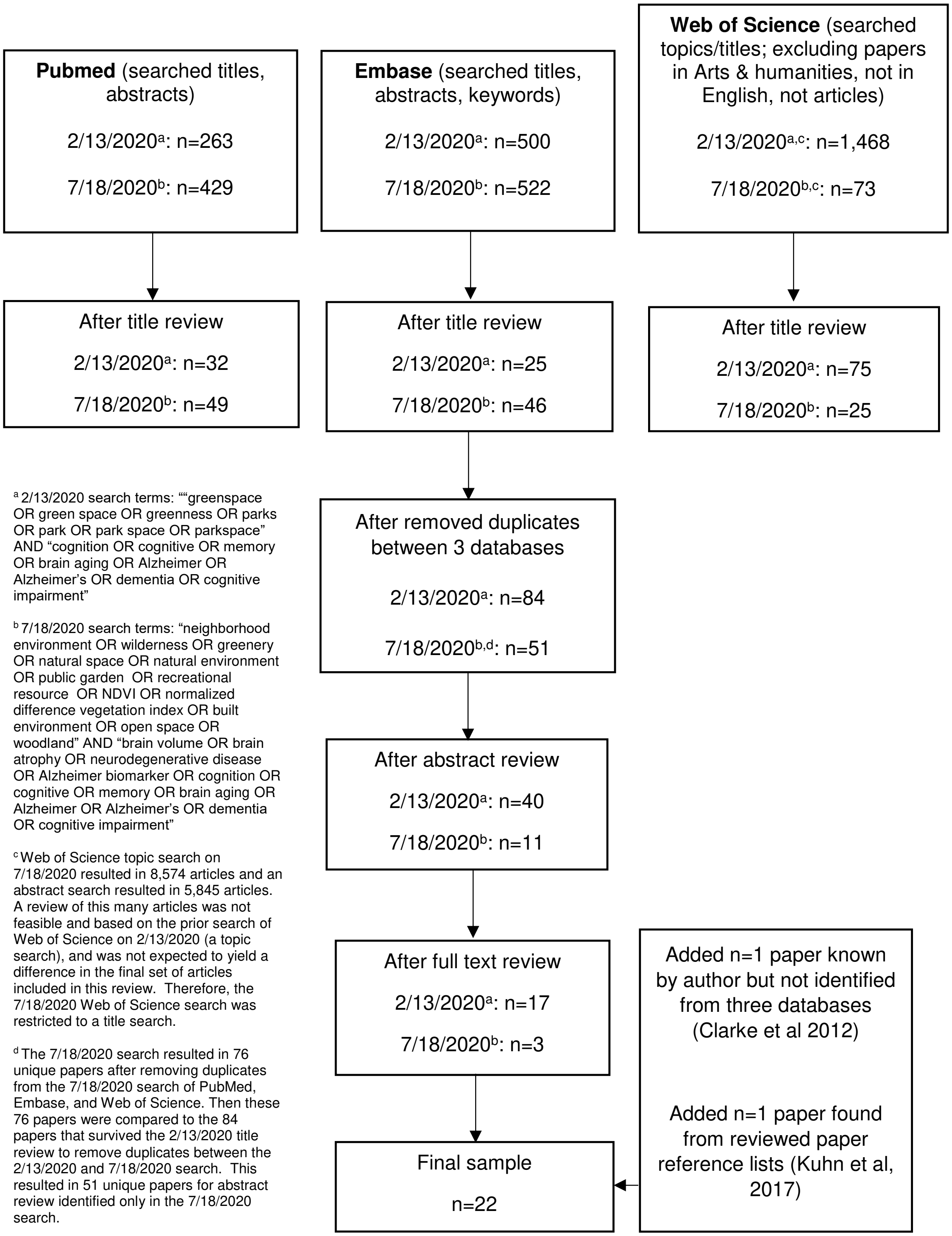
Supplemental Figure 1. Detailed diagram of literature search strategy



[a] 2/13/2020 search terms: ""greenspace OR green space OR greenness OR parks OR park OR park space OR parkspace" AND "cognition OR cognitive OR memory OR brain aging OR Alzheimer OR Alzheimer's OR dementia OR cognitive impairment"

[b] 7/18/2020 search terms: "neighborhood environment OR wilderness OR greenery OR natural space OR natural environment OR public garden OR recreational resource OR NDVI OR normalized difference vegetation index OR built environment OR open space OR woodland" AND "brain volume OR brain atrophy OR neurodegenerative disease OR Alzheimer biomarker OR cognition OR cognitive OR memory OR brain aging OR Alzheimer OR Alzheimer's OR dementia OR cognitive impairment"

[c] Web of Science topic search on 7/18/2020 resulted in 8,574 articles and an abstract search resulted in 5,845 articles. A review of this many articles was not feasible and based on the prior search of Web of Science on 2/13/2020 (a topic search), and was not expected to yield a difference in the final set of articles included in this review. Therefore, the 7/18/2020 Web of Science search was restricted to a title search.

[d] The 7/18/2020 search resulted in 76 unique papers after removing duplicates from the 7/18/2020 search of PubMed, Embase, and Web of Science. Then these 76 papers were compared to the 84 papers that survived the 2/13/2020 title review to remove duplicates between the 2/13/2020 and 7/18/2020 search. This resulted in 51 unique papers for abstract review identified only in the 7/18/2020 search.

Supplemental Text 1. List of 22 papers included in systematic review

Brown SC et al. (2018) Health Disparities in the Relationship of Neighborhood Greenness to Mental Health Outcomes in 249,405 U.S. Medicare Beneficiaries Int J Environ Res Public Health 15 doi:10.3390/ijerph15030430

Cherrie MPC et al. (2018) Green space and cognitive ageing: A retrospective life course analysis in the Lothian Birth Cohort 1936 Soc Sci Med 196:56-65 doi:10.1016/j.socscimed.2017.10.038

Cherrie MPC, Shortt NK, Ward Thompson C, Deary IJ, Pearce JR (2019) Association Between the Activity Space Exposure to Parks in Childhood and Adolescence and Cognitive Aging in Later Life Int J Environ Res Public Health 16 doi:10.3390/ijerph16040632

Clarke PJ, Ailshire JA, House JS, Morenoff JD, King K, Melendez R, Langa KM (2012) Cognitive function in the community setting: the neighbourhood as a source of 'cognitive reserve'? J Epidemiol Community Health 66:730-736 doi:10.1136/jech.2010.128116

Dadvand P et al. (2015) Green spaces and cognitive development in primary schoolchildren Proc Natl Acad Sci U S A 112:7937-7942 doi:10.1073/pnas.1503402112

Dadvand P et al. (2018) The Association between Lifelong Greenspace Exposure and 3-Dimensional Brain Magnetic Resonance Imaging in Barcelona Schoolchildren Environ Health Perspect 126:027012 doi:10.1289/EHP1876

Dadvand P et al. (2017) Lifelong Residential Exposure to Green Space and Attention: A Population-based Prospective Study Environ Health Perspect 125:097016 doi:10.1289/EHP694

Dzhambov AM, Bahchevanov KM, Chompalov KA, Atanassova PA (2019) A feasibility study on the association between residential greenness and neurocognitive function in middle-aged Bulgarians Arh Hig Rada Toksiko 70:173-185 doi:10.2478/aiht-2019-70-3326

de Keijzer C et al. (2018) Residential Surrounding Greenness and Cognitive Decline: A 10-Year Follow-up of the Whitehall II Cohort Environ Health Perspect 126:077003 doi:10.1289/EHP2875

Flouri E, Papachristou E, Midouhas E (2019) The role of neighbourhood greenspace in children's spatial working memory The British journal of educational psychology 89:359-373 doi:10.1111/bjep.12243

Hystad P PY, Noisel N, Boileau C (2019) Green space associations with mental health and cognitive function: Results from the Quebec CARTaGENE cohort Environmental Epidemiology 3:e040

Kuhn S et al. (2017) In search of features that constitute an "enriched environment" in humans: Associations between geographical properties and brain structure Scientific reports 7 doi:ARTN 11920

Liao J et al. (2019) Residential exposure to green space and early childhood neurodevelopment Environment international 128:70-76 doi:10.1016/j.envint.2019.03.070

Reuben A et al. (2019) Residential neighborhood greenery and children's cognitive development Social science & medicine (1982) 230:271-279 doi:10.1016/j.socscimed.2019.04.029

Wang D, Lau KK, Yu R, Wong SYS, Kwok TTY, Woo J (2017) Neighbouring green space and mortality in community-dwelling elderly Hong Kong Chinese: a cohort study BMJ open 7:e015794 doi:10.1136/bmjopen-2016-015794

Ward JS, Duncan JS, Jarden A, Stewart T (2016) The impact of children's exposure to greenspace on physical activity, cognitive development, emotional wellbeing, and ability to appraise risk Health Place 40:44-50 doi:10.1016/j.healthplace.2016.04.015

Wu YT, Prina AM, Jones A, Matthews FE, Brayne C, Collaboration MRCCF, Study A (2017) The Built Environment and Cognitive Disorders: Results From the Cognitive Function and Ageing Study II Am J Prev Med doi:10.1016/j.amepre.2016.11.020

Wu YT et al. (2015) Community environment, cognitive impairment and dementia in later life: results from the Cognitive Function and Ageing Study Age Ageing 44:1005-1011 doi:10.1093/ageing/afv137

Yu R, Wang D, Leung J, Lau K, Kwok T, Woo J (2018) Is Neighborhood Green Space Associated With Less Frailty? Evidence From the Mr. and Ms. Os (Hong Kong) Study Journal of the American Medical Directors Association 19:528-534 doi:10.1016/j.jamda.2017.12.015

Yuchi W, Sbihi H, Davies H, Tamburic L, Brauer M (2020) Road proximity, air pollution, noise, green space and neurologic disease incidence: a population-based cohort study Environmental health : a global access science source 19:8 doi:10.1186/s12940-020-0565-4

Zhu A, Yan L, Shu C, Zeng Y, Ji JS (2020) APOE epsilon4 Modifies Effect of Residential Greenness on Cognitive Function among Older Adults: A Longitudinal Analysis in China Scientific reports 10:82 doi:10.1038/s41598-019-57082-7

Zijlema WL et al. (2017) The relationship between natural outdoor environments and cognitive functioning and its mediators Environ Res 155:268-275 doi:10.1016/j.envres.2017.02.017

Supplemental Table 1. Green space and brain health studies including children and adolescents (<18 year olds)

Citation[a], sample size, location	Sample source	Age, sex, race/ethnicity	Green space measure	Brain health measure	Statistical Method (covariates)	Associations (positive, inverse, null)
Cherrie (2018) n=281 Edinburgh, Scotland	Lothian Birth Cohort (P)	11-78 years 48% female Race/ethnicity not specified	Park space (L): % park space (Location: residential; Boundary: 500m, 1000m, 1500m buffer) Time period: childhood, adulthood, older adulthood	Cognition (L): Moray House Test No 12 (domain: intelligence) Time period: childhood, adulthood, older adulthood	Multivariable linear regression (sex, father's occupation, number per room in childhood household, childhood smoking status, adulthood occupation, alcohol consumption, adulthood smoking status)	Positive: Greater neighborhood % park space in childhood and adulthood associated with less cognitive change from 70 to 76 years. Null: Greater neighborhood % park space in childhood, adulthood, and older adulthood not associated with cognitive change from age 11 to 70. No association between % park space in late-life and cognitive change from 70 to 76 years.
Dadvand (2015) n=2,593 Barcelona, Spain	36 primary schools in Barcelona	7-10 years (mean=8.5) 50% female 16% not Spanish, 84% Spanish	Greenness (CS): NDVI (Location: residential, school, school commute; Boundary: residential-250m buffer, school and commute route-50m buffer) Time period: childhood	Cognition (L): Computerized n-back test (domain: working memory); Computerized attentional network test (domain: attention, alerting, orienting, executive processing) Time period: childhood	Multivariable linear mixed effects regression (age, sex, maternal education, residential neighborhood SES)	Positive: Greater school greenness and total greenness (school, home, commute) associated with 12-month enhancement in working memory and attention. Greater commute route greenness associated with 12-month enhancement in working memory. Null: No association between residential greenness and cognition, commute greenness and attention, or any greenness measure and alerting, orienting, executive processing.

Dadvand (2017) n=888 at 4-5 year follow-up; n=987 at 7-year follow-up Sabadell and Valencia, Spain	Infancia y Medio Ambiente (INMA) cohort (P)	4-7 years 49% female Race/ethnicity not specified	Greenness (L): NDVI and Vegetation Continuous Fields (% woody vegetation >5 m high) (Location: residential; Boundary: 100m, 300m, 500m buffer) Time period: childhood	Cognition (L): Conners' Kiddie Continuous Performance Test (4-5 year olds) (domain: attention); Attentional Network Task (7 year olds) (domain: attention) Time period: childhood	Multivariable linear mixed effects regression (age, sex, preterm birth, maternal cognitive performance, maternal smoking during pregnancy, exposure to environmental tobacco smoke, maternal education, neighborhood SES)	Positive: Greater neighborhood greenness (birth to 4-5 years old) associated with attention at 4-5 years and greater greenness (birth to 7 years old) associated with attention at 7 years old. Null: % neighborhood woody vegetation >5m not associated with attention.
Dadvand (2018) n=253 Barcelona, Spain	Brain Development and Air Pollution Ultrafine Particles in School Children (BREATHE)	Mean: 8.4 years 49% female Race/ethnicity not specified	Greenness (L): NDVI (Location: residential; Boundary: 100m, 500m buffer) Time period: childhood	Magnetic Resonance Imaging (CS) of gray and white matter in regional clusters Time period: childhood	Adjusted voxel-wise regression using statistical parametric maps (maternal education, neighborhood SES- included one or the other in the analysis)	Positive: Greater neighborhood greenness exposure since birth associated with left and right prefrontal cortex, left premotor cortex, and white matter. Null: No associations between greenness and other brain regions.
Flouri (2019) n=4,758 UK	UK Millenium Cohort Study (MCS) (P)	Mean: 10.6 years 49% female 74% white 26% non-white	Green space (CS): % green space (Location: residential; Boundary: ward) Time period: childhood	Cognition (CS): Cambridge Neuropsychological Test Automated Battery SWM Test (domain: spatial working memory) Time period: childhood	Multivariable, multilevel linear regression (age in months, gender, family socioeconomic status, ethnicity, sports participation, computer gaming, residential mobility since infancy, neighborhood deprivation)	Positive: Greater % neighborhood green space associated with better spatial working memory.

Liao (2019) n=1,312 Wuhan, China	Women and Children Medical and Healthcare Center of Wuhan	Mean: 39 weeks 46% female Race/ethnicity not specified	Greenness (CS): NDVI (Location: residential; Boundary: 300m buffer) Time period: childhood	Cognition (CS): Bayley Scales of Infant Development – Mental Development Index (Domain: perceptual acuities, memory, learning and problem solving, abstract thinking) Time period: childhood	Multivariable, multiple linear regression (household income, maternal age, maternal education, maternal pre-pregnancy BMI, maternal passive smoking during pregnancy, gestational age, birth weight, residence areas)	Positive: Greater neighborhood greenness at birth associated with better Mental Development Index scores.
Reuben (2019) n=1,658 UK	Environmental Risk (E-Risk) Longitudinal Study (same sex twin study) (P)	Age 5, 12, and 18 52% female Race/ethnicity not specified	Greenness (L): NDVI (Location: residential; Boundary: 1-mile buffer) Time period: childhood	Cognition (L): Wechsler Preschool and Primary Scale of Intelligence-Revised, Wechsler Intelligence Scale for Children-IV, Wechsler Adult Intelligence Scale-IV (domain: crystalized and fluid cognitive ability); Spatial Span test (domain: executive function); Spatial Working Memory test (domain: working memory); Rapid Visual Information Processing test (domain: attention)	Multivariable analysis of covariance model for longitudinal model (sex, polygenic score for educational attainment, family socioeconomic status, neighborhood socioeconomic status) Multivariable information maximum likelihood (FIML) estimated regression, accounting for missing data (same covariates as longitudinal models)	Null: Neighborhood greenness not associated with fluid ability, crystallized ability, executive function, attention, or working memory measured any age.
Ward (2016) n=72 Auckland, New Zealand	Three intermediate schools	11-14 years (mean=12.7) 59% female Race/ethnicity not specified	Time spent in green space from GPS (CS) Time period: childhood	Cognition (CS): CNS Vital Signs (domain: visual memory, verbal memory, processing speed, psychomotor speed, reaction time, cognitive flexibility, executive function) Time period: childhood	Multivariable generalized linear mixed regression (sex, age, school)	Null: % time spent in greenspace not associated with any cognitive domain.

Abbreviations: CS = cross-sectional; L= longitudinal; UK = United Kingdom; P = population-based/random sampling
[a] Full list of papers found in Supplemental Text 1

Supplemental Table 2. Green space and brain health studies including adults aged 18-64 years

Citation[a], sample size, location	Sample source	Age, sex, race/ethnicity	Green space measure	Brain health measure	Statistical Method (covariates)	Associations (positive, inverse, null)
Cherrie (2018)	See Table 1					
Clarke (2012) n = 949 Chicago, US	Chicago Community Adult Health Study (P)	≥50 years 56% female 37% black, 18% Hispanic, 43% white, 3% other race/ethnicity	Park space (CS): Park area in square miles (Location: residential; Boundary: US Census tract) Time period: adulthood, older adulthood	Cognition (CS): Modified Telephone Instrument for Cognitive Status (domain: global cognition) Time period: adulthood, older adulthood	Multivariable, multilevel linear regression (age, gender, marital status, race/ethnicity, employment status, socioeconomic position, index of comorbid conditions, physical activity, social interaction)	Null: neighborhood park area not associated with global cognition.
De Keijzer (2018) n=6,506 UK	The Whitehall II study (P)	45-68 years 29% female 91% white 9% non-white	Greenness (L): NDVI and EVI (Location: residential; Boundary: 500m, 1000m buffer around postcode centroid) Time period: adulthood, older adulthood	Cognition (L): Alice Heim 4 test of intelligence (domain: reasoning); S words, Animal names (domain: phonemic and semantic verbal fluency); Free recall test (domain: short-term memory); Global cognition z-score derived from 4 tests Time period: adulthood, older adulthood	Multivariable linear mixed effects regression (gender, ethnicity, education, time varying: age, marital status, employment grade, neighborhood SSES, diet, alcohol consumption, smoking status)	Positive: Greater neighborhood greenness associated with slower decline in global cognition, reasoning, and fluency. Null: Neighborhood greenness not associated with short-term memory.

Dzhambov (2019) n=112 Plovdiv, Bulgaria	Convenience sample of volunteers	45-55 years (mean: 50) 59% female Race/ethnicity not specified	Greenness (CS): NDVI (Location: residential; Boundary: 100m, 100m, 750m, 1000m buffer around residence) Time period: adulthood	Cognition (CS): Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB), including Verbal Fluency test (domain: fluency), modified Boston Naming Test (domain: naming), Word List Memory (domain: memory), Word List Recall (domain: memory), Word List Recognition; Montreal Cognitive Assessment (MoCA) (domain: global cognition); Magnetic Resonance Imaging (CS) of cortical thickness of multiple brain regions of interest Time period: adulthood	Multivariable linear regression (age, sex, education, city, neighborhood population, smoking, alcohol consumption, waist circumference, blood pressure, cholesterol, blood glucose, nitrogen dioxide [NO_2], road traffic noise)	Positive: Greater greenness associated with better global cognition and verbal fluency. Greater greenness associated with greater cortical thickness in both hemispheres in the prefrontal cortex, bilateral fusiform gyrus, left precuneus and insula, and right cuneus. Null: Greater greenness was not associated with scores on the subtests of the CERAD-NB except the Verbal Fluency Test. Greater greenness was not associated with cortical thickness in regions of the brain other than those listed above.
Hystad (2019) n=6,658 Quebec, Canada	CARTaGENE Cohort (P)	40-69 years (mean: 55) 55% female 81% white 19% non-white	Greenness (L): NDVI (Location: residential; Boundary: 100m, 300m, 500m, 1000m buffer around postal codes) Time period: adulthood	Cognition (CS): Reaction time test (domain: reaction time); Paired associates learning (domain: working memory); verbal and numeric reasoning (domain: executive function) Time period: adulthood	Multivariable linear regression (age, sex, household income, race, marital status, city, population density)	Inverse: Five-year change in greenness associated with worse reasoning. Null: Five-year average neighborhood greenness not associated with reaction time, reasoning, or working memory. Five-year change in greenness not associated with reaction time or working memory.

Yuchi (2020) n=678,000 Vancouver, British Columbia, Canada	Medical Services Plan Physician Visit and Hospital Discharge data (P)	45-84 years Sex not provided for entire sample Race/ethnicity not specified	Greenness (L): NDVI (Location: residential; Boundary: 100m buffer) Time period: adulthood, older adulthood	Diagnosis (L): Alzheimer's disease, non-Alzheimer's disease; and Parkinson's disease (source: hospital records, physician visits, prescription history) Time period: adulthood, older adulthood	Multivariable Cox proportion hazards model for non-Alzheimer's disease and Parkinson's disease (age, sex, comorbidities, neighborhood household income, neighborhood education, neighborhood ethnicity); Multivariable conditional logistic regression for Alzheimer's disease (comorbidities, neighborhood household income, neighborhood education, neighborhood ethnicity)	Positive: Greater neighborhood greenness associated with lower hazard ratio for non-Alzheimer's disease and Parkinson's disease. Inverse: Greater neighborhood greenness associated with increased odds of Alzheimer's disease.
Zijlema (2017) n=1,628 Barcelona, Spain Doetinchem, Netherlands Stoke-on-Trent, UK	Positive Health Effects of the Natural Outdoor Environment in Typical Populations in Different Regions in Europe (PHENOTYPE) (P)	Mean: 48 years 54% female Race/ethnicity not specified	Greenness (CS): NDVI (Location: residential; Boundary: 100m, 300m, 500m buffer); Other green space measures (CS): Residential distance to natural outdoor environment, self-reported amount of natural outdoor environment; self-reported visits to natural outdoor environment; self-reported time visiting natural outdoor environment Time period: adulthood, later-adulthood	Cognition (CS): Color Trails Test completion time and errors (domain: visual attention/effortful executive processing) Time period: adulthood, older adulthood	Multivariable, multilevel linear and logistic regression (age, sex, education, neighborhood socioeconomic status, time spent away from home, Color Trails Test quality)	Positive: Greater residential distance to natural outdoor environments associated with greater cognitive test completion time. Null: Residential greenness, percentage residential natural environment, self-reported natural environment visits, and self-reported time spent visiting natural environment not associated with cognition.

Abbreviations: CS = cross-sectional; L = Longitudinal; P = population-based/random sampling; EVI = Enhanced Vegetation Index; UK = United Kingdom
[a] Full list of papers found in Supplemental Text 1

Supplemental Table 3. Green space and brain health studies including older adults aged ≥65 years

Citation[a], sample size, location	Sample source	Age, sex, race/ethnicity	Green space measure	Brain health measure	Statistical Method (covariates)	Associations (positive, inverse, null)
Brown (2018) n=249,405 Florida, US	US Medicare Beneficiaries from Miami-Dade County, Florida (P)	Age: 65-111 years (mean: 76) 58% female 77% non-white 23% white	Greenness (CS): NDVI (Location: residential; Boundary: US Census block) Time period: older adulthood	Diagnosis (CS): Alzheimer's disease (source: US Centers for Medicare and Medicaid Services) Time period: older adulthood	Multivariable, multilevel logistic regression (age, sex, race/ethnicity, neighborhood income)	Positive: Greater neighborhood greenness associated with lower odds of Alzheimer's disease.
Cherrie (2018)	See Table 1					
Cherrie (2019) n=281 Edinburgh, UK	Lothian Birth Cohort (P)	Age: 70-76 years Female: 48% Race/ethnicity not specified	Park space (L): % park space (Location: residential, school, school route; Boundary: 1000m buffer around home, school, school route) Time period: childhood	Cognition (L): Moray House Test No 12 (domain: intelligence) Time period: older adulthood (sex, father's occupation, number per room in childhood household, childhood smoking status, adulthood occupation, alcohol consumption, adulthood smoking status)	Multivariable, multilevel linear regression	Positive: % park space at ages 11-18 near home, school, and school route associated with less cognitive change from 70 to 76 years. Null: No association between % park space measures at ages 4-11 and cognitive change from 70 to 76 years.
Clarke (2012)	See Table 2					
De Keijzer (2018)	See Table 2					
Kuhn (2017) n=341 Berlin, Germany	Berlin Aging Study II	61-82 years (mean: 70) 38% female Race/ethnicity not specified	Green space (CS): Amount of forest and urban green (Location: residential; Boundary: 1km surrounding residence) Time period: older adulthood	Magnetic Resonance Imaging (CS) of integrity of amygdala, pregunual anterior cingulate cortex (pACC), and dorsolateral prefrontal cortext (DLPFC) determined from	Structural Equation Modeling (SEM) (age, sex, years of education)	Positive: Greater amount of forest in neighborhood associated with greater amydala integrity. Null: No association between amount of forest and pACC or DLPFC integrity, or between amount

				indicators of brain structural integrity (grey matter volume, magnetization transfer ratio, mean diffusivity) Time period: Older adulthood		of urban green and any brain measure.
Wang (2017) n=3,544 Hong Kong, China	Community based-cohort	≥65 years (median: 72) 50% female Race/ethnicity not specified	Greenness (CS): NDVI (Location: residential; boundary: 300m buffer) Time period: older adulthood	Cognition (CS): Mini Mental State Exam (domain: global cognition) Time period: older adulthood	Spearman's correlation coefficients (unadjusted analysis)	Null: no correlation between neighborhood greenness and global cognition.
Wu (2015) n=2,424 UK	Medical Research Council Cognitive Function and Ageing Study (P)	Age ≥74 years (Mean: 82) 60.7% female Race/ethnicity not specified	Green space (CS): % green space/private gardens (Location: residential; Boundary: Lower – Layer Super Output Area for postcode) Time period: older adulthood	Cognitive status (CS): Cognitive impairment (source: Mini Mental State Exam ≤25) Diagnosis (CS): dementia (source: Geriatric Mental Status and Automatic Geriatric Examination for Computer Assisting Taxonomy) Time period: older adulthood	Multivariable, multilevel logistic regression (age, gender, education, social class, number chronic illnesses, area deprivation)	Inverse: Individuals living with highest quartile of neighborhood green space (versus lowest) had increased odds of cognitive impairment and dementia.
Wu (2017) n=7,505 UK	Medical Research Council Cognitive Function and Ageing Study II (P)	Median: 74 years 54% female Race/ethnicity not specified	Green space (CS): % green space/private gardens (Location: residential; Boundary: Lower – Layer Super Output Area for postcode) Time period: older adulthood	Cognitive status (CS): Cognitive impairment (source: Mini Mental State Exam ≤25) Diagnosis (CS): dementia (source: Geriatric Mental Status and Automatic Geriatric Examination for Computer Assisting Taxonomy) Time period: older adulthood	Multivariable, multilevel logistic regression (age gender, education, number chronic illnesses, area deprivation)	Inverse: Individuals living with highest quintile of neighborhood green space/private gardens (versus lowest) had increased odds of cognitive impairment. Null: No associations between neighborhood green space and odds of dementia.

Yu (2018) n=3,240 Hong Kong, China	Mr. and Ms. Os (Hong Kong) study	Mean: 72 years 49% female Race/ethnicity not specified	Greenness (CS): NDVI (Location: residential; Boundary: 300m buffer) Time period: older adulthood	Cognition (CS): Mini Mental State Exam (domain: global cognition) Time period: older adulthood	Multivariable regression path analysis (age, sex, marital status, socioeconomic status, alcohol intake, diet quality, baseline frailty status)	Null: Greater neighborhood greenness not directly associated with cognition.
Yuchi (2020)	See Table 2					
Zhu (2020) n=6,994 China	Chinese Longitudinal Healthy Longevity Survey (CLHLS) (P)	Mean: 80 years 51% female Race/ethnicity not specified	Greenness (L): NDVI (Longitudinal: no; Location: residential; Boundary: 500m buffer) Time period: older adulthood	Cognitive status (L): Cognitive impairment (source: Mini Mental State Exam <24) Time period: older adulthood	Multivariable logistic regression using generalized estimating equations (age, gender, marital status, urban/rural residence, education, occupation, financial support, social and leisure activity, smoking status, alcohol consumption, and physical activity)	Positive: Individuals living in highest quartile of neighborhood greenness had lower odds of cognitive impairment.
Zijlema (2017)	See Table 2					

Abbreviations: CS = cross-sectional; L = longitudinal; P = population-based/random sampling; UK = United Kingdom
[a] Full list of papers found in Supplemental Text 1

Supplemental Table 4. Studies examining effect modification and mediation

Citation[a]	Effect modifier examined	Effect modification findings	Mediator examined	Mediation findings
Brown (2018)	Neighborhood income level	No effect modification	None	N/A
Cherrie (2018)	Sex APOE ε4 allele Adult occupational class Adulthood park availability	Association between greater childhood park availability and slower cognitive decline from 70-76 years strongest in those with greater adulthood park availability, and these associations were stronger for women, APOE ε4 non-carriers, and individuals who had skilled/unskilled jobs (versus professional).	None	N/A
Cherrie (2019)	Sex Traffic Accident Density	No effect modification by sex. Association between childhood park activity space was not associated with cognitive aging differentially by traffic accident density; however, association between greater adolescent park activity space and better cognitive aging was restricted to those with lower traffic accident density (versus higher).	None	N/A
Clarke (2012)	None	N/A	Physical activity Social interaction	No mediation
Dadvand (2015)	Maternal education Neighborhood SES	Not effect modification	Traffic Related Air Pollution (elemental carbon, residential indoors)	Elemental carbon explained 20-65% of associations between school greenness and cognitive changes and resulted in changed (no longer significant) associations between school greenness and working memory and attentiveness.
Dadvand (2017)	Cohort location (Sabadell versus Valencia)	No effect modification	None	N/A

De Keijzer (2018)	Sex Education Area level deprivation	Association between greater greenness and slower decline in global cognition found for women but not men, stronger in those with higher education (versus lower), and stronger among those with higher area deprivation (versus lower).	Physical activity Air pollution Social support	No mediation
Dzhambov (2019)	None	N/A	Waist circumference Systolic blood pressure Total cholesterol Glucose Air pollution (NO_2)	Lower waist circumference mediated association between greater greenness and higher CERAD-NB score (global cognition).
Flouri (2019)	Neighborhood deprivation Residential stability	No effect modification	None	N/A
Hystad (2019)	Education Sex Age Household income Race Marital status Years in current residence City	Adjusted models were stratified but no statistical tests for differences between strata (i.e., no interaction terms used). Associations appeared to vary by sex, age, and education.	None	N/A
Liao (2019)	Household income Pre-pregnancy body mass index Infant sex	Greater greenness associated with better cognition among children of mothers with pre-pregnancy BMI<24 $kg/m^{2.}$	Traffic related air pollution (PM2.5) Physical outdoor activities	No mediation
Wu (2017)	Urbanicity	Among those living conurbation areas with higher % green space, lower odds of cognitive impairment. Among those living in rural areas, those with higher % green space associated with greater odds of cognitive impairment.	None	N/A
Yu (2018)	None	N/A	Physical activity Depression	Physical activity mediated association between greater greenness and global cognition.

Zhu (2020)	Age (65-79 years; 80+ years) APOE genotype (ε4 carriers vs. non-carriers)	Greater greenspace associated with lower odds of cognitive impairment among 65-79 year olds but not 80+ year olds, and among APOE ε4 non-carriers but not ε4 carriers. These are stratified results, no interaction terms had p<0.05.	None	N/A
Zijlema (2017)	None	N/A	Physical activity Social interaction Loneliness Neighborhood social cohesion Perceived mental health Traffic noise annoyance Worry about air pollution	No mediation

Abbreviations: APOE = apolipoprotein E; BMI = body mass index; PM = particulate matter
[a] Full list of papers found in Supplemental Text 1