

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Outdoor green space exposure and brain health measures related to Alzheimer's disease: A rapid review
AUTHORS	Besser, Lilah

VERSION 1 – REVIEW

REVIEWER	Dzhambov, Angel Medical University of Plovdiv, Hygiene and Ecomedicine
REVIEW RETURNED	09-Sep-2020

GENERAL COMMENTS	<p>Thank you for the opportunity to review this manuscript. My overall impression is that this is an interesting submission, one that deals with a relatively poorly understood effects of greenspace on cognitive functioning and underlying neuroanatomical substrate. It is my belief that this topic will be of interest to environmental epidemiologists and psychologists alike. That said, I am of two minds about the systematic search strategy employed and reporting of what has been done.</p> <p>Major comments:</p> <ul style="list-style-type: none">• I see two major issues with this work. First, which I am not sure can be addressed at this point, is that there was a sole reviewer performing all steps of the review. true that this was a scoping review and as such the post-review assessment of included studies is more relaxed than in a systematic review (e.g., risk of bias in included studies is not a required element), but that does not negate the need for unbiased, transparent and reproducible searches. A second reviewer is a must-have. The ways out of this situation would be for a second reviewer to be included and asked to independently replicate the searches without any cues as to the results of those already performed, or for this review to forgo the tag of a scoping review. This label raises certain expectations that were not met in this case.• The other issue is one of reporting and presentation of this study. Although I find the scoping review guidelines to have largely been followed, the Methods and Results are all over the place and the reader gets lost. Restructuring those sections is needed, including the addition of subheadings in Methods and keeping the text more concise and dense.• Also, what I am missing is a summary table with study findings. Now you have tables showing the results of individual studies, but we need an overall summary table with the findings of this review. That is, how many studies
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	<p>looking at different combinations of exposure-outcome pairs across different age groups found positive, null or negative associations.</p> <ul style="list-style-type: none"> • I am not comfortable with the different set of search terms used in the updated searches in July. • “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” – This does not sound like a valid reason for excluding a portion of the findings. All retrieved records should be subject to the same review process. If you ended up with too many records after the electronic search, then your filters/keywords could have been not specific enough. <p>Other comments:</p> <ul style="list-style-type: none"> • The writing language style can use some polishing. • If you are going to talk about mediation results in the abstract, then list other mediators identified in the reviewed papers, e.g., WC in Dzhambov et al. Alternatively, kick the mediation piece out of the Abstract. • Don’t repeat as keywords terms that are already present in the title. • Make sure all statements in need of a reference get one. E.g., “Neighborhood greenspace is one such community....”, “The few studies incorporating self-reported....”, “Although studies have successfully....”, “As this was a scoping review....”, the paragraph starting with “Many of the studies of middle- and older...” • Where you talk about pathways linking greenspace to health, I am missing a reference to https://pubmed.ncbi.nlm.nih.gov/28672128/ • Where you go on to talk about the gut-brain axis and microbiome, you can cite: Nielsen CC, Gascon M, Osornio-Vargas AR, Shier C, Guttman DS, Becker AB, Azad MB, Sears MR, Lefebvre DL, Moraes TJ, Turvey SE, Subbarao P, Takaro TK, Brook JR, Scott JA, Mandhane PJ, Tun HM, Kozyrskyj AL. Natural environments in the urban context and gut microbiota in infants. <i>Environ Int.</i> 2020 Sep;142:105881. doi:10.1016/j.envint.2020.105881; Logan AC. Dysbiotic drift: mental health, environmental grey space, and microbiota. <i>J Physiol Anthropol</i> 2015; 34:23. • “...which have been associated with cognition and ADAD” – A few words on how, please. Oxidative stress, direct impact on the brain biochemistry, etc. • The Introduction is in need of a rationale for doing and needing this scoping review in the first place. How would it help advance the field? • There is also a need for a stronger rationale for choosing the scoping review organizing framework. E.g., the breadth of the research issue and heterogeneity in extant literature,
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	<p>etc.</p> <ul style="list-style-type: none"> • Consider whether you have truly followed the guidelines outlined in these seminal papers: Arksey, H., O'Malley, L., 2005. Scoping studies: towards a methodological framework. <i>Int. J. Soc. Res. Methodol.</i> 8 (1), 19–32. https://doi.org/10.1080/1364557032000119616.; Peters, M.D., Godfrey, C.M., Khalil, H., McInerney, P., Parker, D., Soares, C.B., 2015. Guidance for conducting systematic scoping reviews. <i>Int. J. Evid. Base. Healthc.</i> 13 (3), 141–146. https://doi.org/10.1097/XEB.0000000000000050 • “Articles published on/before February 13, 2020, were included in this review.” – How about the update of the search results? • I find Figure 1 somewhat overwhelming. It presents important details, but it too cramped. Why not provide a standard flow diagram and report the additional pieces of information (search string) in the supplementary file? • “focused on mental states (e.g., attention restoration, mental” – Restoration is more of a process than a mental state! • I would expect to see more strictly organized and well-defined subsections in Methods. Now, they feel mostly right but all over the place. • Data charting needs more figures on the prevalence of different study features/findings in addition to the tables • Did you consider how many studies employed multiple greenspace indicators? That is worth exploring. • When you indicate in the text the number of studies that had a specific characteristic, also report percentages and vice versa. • “Seventeen studies found associations (14 positive, four inverse) and five found no associations” – Finish the sentence. With what? • I’d like to see a table cross-checking findings by combinations of greenspace indicator and outcome • We need in the Intro some sort of brain map with regions of interest and corresponding cognitive domains relevant to ADAD diagnosis. Some readers may be confused by the different cognitive domains and brain structures you mention in the text. • Not all readers know what “modification” and “mediation” mean. Introduce those terms first. Relatedly, when you discuss mediation results, how about type of mediation modeling, which has been found to in part determine the study findings https://doi.org/10.1016/j.envres.2020.109613 • Elaborate on the ART and restorative environments theories. This is central to understanding and contextualizing the effect of greenspace on cogitation. • Explain in more detail how greenspace affects brain morphology - oxidative stress, enriched environment, etc. • The discussion feels like a partial repetition of the Results. Try to give it a more analytic perspective. • Discuss the strengths of fMRI versus structural MRI and its application in future studies • “Additional papers may have been obtained if different databases were searched,” – Does not sound compelling.
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	<ul style="list-style-type: none"> • “Many of the studies lacked consideration of early-life green space exposures and few examined actual time spent in green spaces, and thus, most were likely affected by misclassification/information bias” – Limitation of the primary studies, not of your work.
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REVIEWER	Paul, Lauren Public Health Ontario
REVIEW RETURNED	29-Sep-2020

GENERAL COMMENTS	<p>This is an important review of the current evidence on the associations between green space and brain health outcomes. I have only a few suggestions for the author.</p> <p>1. I would recommend that the author update the review before publication. There have been a couple additional studies published this year that would be important for inclusion, and would help make the review more comprehensive. E.g.,</p> <ul style="list-style-type: none"> • Crous-Bou M et al. doi: 10.1016/j.envint.2020.105546; • Paul LA et al. doi: 10.1016/j.envres.2020.109520; • Wu YT et al. doi: 10.1186/s12889-020-09435-5 <p>There is also a thesis study that may be considered for inclusion (Slawsky 2019 https://digital.lib.washington.edu/researchworks/bitstream/handle/1773/44232/Slawsky_washington_02500_20009.pdf?sequence=1&isAllowed=y).</p> <p>2. There are some grammatical errors and run-on sentences throughout the manuscript; it could benefit from an additional proofread. E.g.,</p> <ul style="list-style-type: none"> • P.5 l.7 Remove comma after “people”. • P.6 l.37 Replace “has” with “have”. • P.6 l.54-56 This sentence should be broken up into two. • P.12 l.37-46 This sentence should be broken up. • P.21 l.3 Update to “risk of bias”. • P.21 l.25-33 This sentence should be broken up. • Please be consistent with use of the Oxford comma. <p>Some of the writing could also be streamlined/clarified. E.g.,</p> <ul style="list-style-type: none"> • P.6 l.10-14 Remove the list of pathways from the beginning of the paragraph as they are all subsequently listed and explained. • P.6 l.31 Please clarify the direction of association between air pollution and cognition. • P.17 l.20 Please further expand or provide references for the sentence “Compared to NDVI (greenness), percentage green space may better capture access to green spaces”. • P.18 l.9 Please further expand or provide references for the sentence “measures of time spent in green space provide the specificity of exposure needed to make informed decisions about green space-brain health associations.” • P.18. l.42-45 Please provide references for the sentence “These neurodevelopmental benefits may impart cognitive
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	<p>reserve and resilience through older ages, which protects against ADAD neuropathology and resists symptoms despite neuropathology.”</p> <p>3. To help readers, please add references for all subgroups of studies mentioned in the results. E.g.,</p> <ul style="list-style-type: none"> • P.9 I.20-31 References for the breakdown by country and age group. • P.9 I.45-56 References for the breakdown by green space measure. • P.10 I.16-31 References for the breakdown by study outcome. • P.10 I.35-43 References for the breakdown by association. • P.12 I.20-31 Please cite all studies mentioned. • P.12 I.31 It was mentioned that two studies found inverse results but only one was cited. • P.13 I.26-31 References for the breakdown by brain health measure. • P.13 I.52 – P.14 I.8 References for breakdown by effect modifiers. <p>4. Could the author add some discussion about the inverse associations between green space and Alzheimer’s/dementia diagnoses observed in some studies?</p> <p>5. I would recommend adding the sample size of each study to Tables 1-3.</p> <p>6. If Figure 1 and Supplementary Figure 1 are the same please remove one.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Thank you for the opportunity to review this manuscript. My overall impression is that this is an interesting submission, one that deals with a relatively poorly understood effects of greenspace on cognitive functioning and underlying neuroanatomical substrate. It is my belief that this topic will be of interest to environmental epidemiologists and psychologists alike. That said, I am of two minds about the systematic search strategy employed and reporting of what has been done.

RESPONSE: Thank you for your careful, thoughtful review. I think it has led to a significant improvement in the paper.

Major comments:

I see two major issues with this work. First, which I am not sure can be addressed at this point, is that there was a sole reviewer performing all steps of the review. true that this was a scoping review and as such the post-review assessment of included studies is more relaxed than in a systematic review (e.g., risk of bias in included studies is not a required element), but that does not negate the need for unbiased, transparent and reproducible searches. A second reviewer is a must-have. The ways out of this situation would be for a second reviewer to be included and asked to independently replicate the searches without any cues as to the results of those already performed, or for this review to forgo the tag of a scoping review. This label raises certain expectations that were not met in this case.

RESPONSE: I agree that a second reviewer is generally needed for a systematic/scoping review, but was not possible, and thus I had originally titled it as a “rapid scoping review” to try to clarify the nature of the review. I have revised the title, descriptions and justification/references to describe the paper as a rapid review using methods similar to but not fully meeting the criteria of a scoping review (i.e., scoping aims). I hope this helps address your concerns but I am open to a more appropriate way to title/label this review.

I have added a few of references regarding purpose and drawbacks of rapid reviews to the final paragraph in the introduction: 1) Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info Libr J* 2009;26(2):91-108; 2) Tricco AC, Antony J, Zarin W, et al. A scoping review of rapid review methods. *BMC Med* 2015;13:224.

This paper does not promise more than the methods can achieve, carefully delineates the search methods, and acknowledges the limitations of the review throughout the text. Despite the caveats, it provides a unique contribution and point of reference for this growing field of study. I have made note of the limitations in the methods and discussion. For example: “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 methods and 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^{46 48 50 51}, it was never intended to systematically evaluate the evidence for risk of bias, which will be reserved for future systematic reviews.” (Discussion)

The other issue is one of reporting and presentation of this study. Although I find the scoping review guidelines to have largely been followed, the Methods and Results are all over the place and the reader gets lost. Restructuring those sections is needed, including the addition of subheadings in Methods and keeping the text more concise and dense.

RESPONSE: I have revised the methods and results to hopefully streamline and clarify as suggested. For instance, subheadings were added to the methods and the descriptions of the types of green space measures have been moved to the section on ‘Findings by green space measure’ to group all related information in one place.

Also, what I am missing is a summary table with study findings. Now you have tables showing the results of individual studies, but we need an overall summary table with the findings of this review. That is, how many studies looking at different combinations of exposure-outcome pairs across different age groups found positive, null or negative associations.

RESPONSE: Thanks for this suggestion. I originally summarized at the bottom of Tables 1-3 for each column (ex: “Significant studies: 5 of 8”). However, to address your suggestion, I added the number of positive, null, and negative associations at the bottom of Tables 1-4. As mentioned in the scoping methods paper you referenced below, I would prefer not to provide additional summaries because “unlike a systematic review the scoping study does not seek to ‘synthesize’ evidence or to aggregate findings from different studies. Whilst a scoping study will need some analytic framework or thematic construction in order to present a narrative account of existing literature, there is no attempt made to present a view regarding the ‘weight’ of evidence in relation to particular interventions or policies. (Arksey et al).”

I am not comfortable with the different set of search terms used in the updated searches in July. “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” – This does not sound like a valid reason for excluding a portion of the findings. All retrieved records should be subject to the same review process. If you ended up with too many records after the electronic search, then your filters/keywords could have been not specific enough.

RESPONSE: I unfortunately did not have the time/resources to review those 8574 papers as a single reviewer and author. Instead, I chose to describe the methods in detail so that others could fully understand my methods or build upon them for a systematic review. It is hoped that relabeling it as a rapid review and further discussing the review's limitations will help address your concerns. For instance, these edits/additions have been made:

"A full text search led to 8,574 papers that could not be feasibly reviewed based on available time and resources (i.e., 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 (i.e., 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 Supplemental Figure 1." (Methods)

"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 methods and 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^{46 48 50 51}, it was never intended to systematically evaluate the evidence for risk of bias, which will be reserved for future systematic reviews." (Discussion)

Using the same keywords for all three databases, a "reasonable" number of papers were returned from the full text search of PubMed and Embase (around 500 papers), but not Web of Science (over 8000) and so this is not related to the keyword combination used in July but instead the broader scope of papers in Web of Science that are not typically pertinent to this topic of interest (but that used some of the keywords in the paper).

Other comments:

The writing language style can use some polishing.

RESPONSE: I have reviewed the paper thoroughly and polished the style and grammar.

If you are going to talk about mediation results in the abstract, then list other mediators identified in the reviewed papers, e.g., WC in Dzhambov et al. Alternatively, kick the mediation piece out of the Abstract.

RESPONSE: For simplicity and space saving reasons, I removed discussion of mediation from the abstract.

Don't repeat as keywords terms that are already present in the title.

RESPONSE: The keywords have been updated accordingly.

Make sure all statements in need of a reference get one. E.g., "Neighborhood greenspace is one such community....", "The few studies incorporating self-reported....", "Although studies have successfully....", "As this was a scoping review....", the paragraph starting with "Many of the studies of middle- and older..."

RESPONSE: References have been added to these statements.

Where you talk about pathways linking greenspace to health, I am missing a reference to <https://pubmed.ncbi.nlm.nih.gov/28672128/>

RESPONSE: This reference has been added to this sentence: "Green space exposure may benefit brain health through a number of pathways."

Where you go on to talk about the gut-brain axis and microbiome, you can cite: Nielsen CC, Gascon M, Osornio-Vargas AR, Shier C, Guttman DS, Becker AB, Azad MB, Sears MR, Lefebvre DL, Moraes TJ, Turvey SE, Subbarao P, Takaro TK, Brook JR, Scott JA, Mandhane PJ, Tun HM, Kozyrskyj AL. Natural environments in the urban context and gut microbiota in infants. *Environ Int.* 2020 Sep;142:105881. doi:10.1016/j.envint.2020.105881; Logan AC. Dysbiotic drift: mental health, environmental grey space, and microbiota. *J Physiol Anthropol* 2015; 34:23.

RESPONSE: These references have been added to the sentence on microbiomes.

“...which have been associated with cognition and ADAD” – A few words on how, please. Oxidative stress, direct impact on the brain biochemistry, etc.

RESPONSE: The sentence has been revised and reference added: “The mechanisms by which air pollution affects the brain have been hypothesized to be direct and/or indirect (e.g., systemic inflammation, adsorbed compounds).”

The Introduction is in need of a rationale for doing and needing this scoping review in the first place. How would it help advance the field? There is also a need for a stronger rationale for choosing the scoping review organizing framework. E.g., the breadth of the research issue and heterogeneity in extant literature, etc.

RESPONSE: The introduction has been updated to address your suggestions: “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. Scoping reviews are useful in summarizing 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. The number of studies on green space and health has risen dramatically in the last decade, but it remains unclear how many studied brain health outcomes....”

Consider whether you have truly followed the guidelines outlined in these seminal papers: Arksey, H., O'Malley, L., 2005. Scoping studies: towards a methodological framework. *Int. J. Soc. Res. Methodol.* 8 (1), 19–32. <https://doi.org/10.1080/1364557032000119616>; Peters, M.D., Godfrey, C.M., Khalil, H., McInerney, P., Parker, D., Soares, C.B., 2015. Guidance for conducting systematic scoping reviews. *Int. J. Evid. Base. Healthc.* 13 (3), 141–146. <https://doi.org/10.1097/XEB.0000000000000050>

RESPONSE: I've incorporated these references into the introduction paragraph. The methods in this paper appear to follow these guideline papers.

“Articles published on/before February 13, 2020, were included in this review.” – How about the update of the search results?

RESPONSE: The methods have been updated to clarify: “The July 18, 2020 search was restricted to papers published on or before February 13, 2020, to be consistent with the original search.”

I find Figure 1 somewhat overwhelming. It presents important details, but it too cramped. Why not provide a standard flow diagram and report the additional pieces of information (search string) in the supplementary file?

RESPONSE: I have collapsed the information in that table and left the details to be reported in the supplementary figure 1.

“focused on mental states (e.g., attention restoration, mental” – Restoration is more of a process than a mental state!

RESPONSE: The sentence has been revised to: "...studies (e.g., average school test scores); 6) were focused on attention restoration or mental fatigue (transient states);..."

I would expect to see more strictly organized and well-defined subsections in Methods. Now, they feel mostly right but all over the place.

RESPONSE: Headers have been added to the methods to be consistent with scoping reviews: "Identification and study selection" and "Charting and summarizing the data".

Data charting needs more figures on the prevalence of different study features/findings in addition to the tables

RESPONSE: Figures 2-4 have been added to provide prevalence of study features: country, age group, and greenspace-brain health association examined.

Did you consider how many studies employed multiple greenspace indicators? That is worth exploring.

RESPONSE: This has been added briefly to the results section: "Three studies examined more than one green space measure: 1) NDVI and VCF; 2) NDVI and EVI; and 3) NDVI, distance to natural outdoor environment, and self-reported green space measures."

When you indicate in the text the number of studies that had a specific characteristic, also report percentages and vice versa.

RESPONSE: This has been updated throughout the results section.

"Seventeen studies found associations (14 positive, four inverse) and five found no associations" – Finish the sentence. With what?

RESPONSE: The sentence has been updated: "Seventeen studies (77%) found associations (14 positive, four inverse) and five (23%) found no associations between greenness/green space and brain health."

I'd like to see a table cross-checking findings by combinations of greenspace indicator and outcome

RESPONSE: I was not 100% sure what you were suggesting, but I believe you suggested a count of total number of positive, negative, and null associations for each combination of greenspace and brain health outcome. This has been added, see the new Table 4 and Figure 4.

We need in the Intro some sort of brain map with regions of interest and corresponding cognitive domains relevant to ADAD diagnosis. Some readers may be confused by the different cognitive domains and brain structures you mention in the text.

RESPONSE: The following has been added to the introduction: "Cognitive tests for AD typically evaluate memory of personal events (i.e., 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, magnetic resonance imaging (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."

Not all readers know what "modification" and "mediation" mean. Introduce those terms first. Relatedly, when you discuss mediation results, how about type of mediation modeling, which has been found to in part determine the study findings. <https://doi.org/10.1016/j.envres.2020.109613>

RESPONSE: Mediation and modification have been defined in the results: “Three of seven studies 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”, and “Effect modification is variation in the association between an exposure and outcome depending on the value of another factor”. The provided reference has been added to the discussion paragraph on mediation: “...and future studies will need to employ rigorous methods to evaluate mediation”.

Elaborate on the ART and restorative environments theories. This is central to understanding and contextualizing the effect of greenspace on cognition.

RESPONSE: More/references have been added to the introduction to support those theories: “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, and gardening has been found to reduce levels of salivary cortisol, a stress hormone. In adults, mood, restoration, and sustained attention were improved after participating in a nature walk intervention in urban and rural locales.”

Explain in more detail how greenspace affects brain morphology - oxidative stress, enriched environment, etc.

RESPONSE: A brief description and references have been provided in the introduction: “Green spaces 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.”

The discussion feels like a partial repetition of the Results. Try to give it a more analytic perspective.

RESPONSE: The second aim of the review (identify gaps in literature) is the primary focus of the discussion. Some rewording/revising has been done throughout the discussion to try to be less descriptive/repetitive with the results.

Discuss the strengths of fMRI versus structural MRI and its application in future studies

RESPONSE: Thank you for the suggestion but I chose only to edit the text to differentiate “structural and function MRI” because a discussion of the strengths and uses of these MRI biomarkers would be out of place without describing the other biomarkers (CSF, PET, etc.). I think that may be too detailed for the average reader.

“Additional papers may have been obtained if different databases were searched,” – Does not sound compelling.

RESPONSE: This has been revised to acknowledge the limitations of the rapid review: “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 methods and Supplemental Figure 1), and a single reviewer.”

“Many of the studies lacked consideration of early-life green space exposures and few examined actual time spent in green spaces, and thus, most were likely affected by misclassification/information bias” – Limitation of the primary studies, not of your work.

RESPONSE: Based on your comment, I have create two paragraphs, one focused on limitations of the reviewed studies and one on limitations of the review.

Reviewer: 2

This is an important review of the current evidence on the associations between green space and brain health outcomes. I have only a few suggestions for the author.

I would recommend that the author update the review before publication. There have been a couple additional studies published this year that would be important for inclusion, and would help make the review more comprehensive. E.g.,

- Crous-Bou M et al. doi: 10.1016/j.envint.2020.105546;
- Paul LA et al. doi: 10.1016/j.envres.2020.109520;
- Wu YT et al. doi: 10.1186/s12889-020-09435-5

There is also a thesis study that may be considered for inclusion

(Slawsky 2019 https://digital.lib.washington.edu/researchworks/bitstream/handle/1773/44232/Slawsky_washington_0250O_20009.pdf?sequence=1&isAllowed=y).

RESPONSE: Thank you for these suggestions but I decided not to add these papers because they are published after Feb 13, 2020, and are therefore outside of the delineated cut point date for study inclusion. If the editor and/or reviewers strongly prefer that I add these papers, I can do this, although I think it will be out of place with the overall search/inclusion strategy. However, I will not have the time/resources to update the review of the 3 databases to include all references from February 14, 2020, to present.

There are some grammatical errors and run-on sentences throughout the manuscript; it could benefit from an additional proofread. E.g.,

- P.5 I.7 Remove comma after “people”.
- P.6 I.37 Replace “has” with “have”.
- P.6 I.54-56 This sentence should be broken up into two.
- P.12 I.37-46 This sentence should be broken up.
- P.21 I.3 Update to “risk of bias”.
- P.21 I.25-33 This sentence should be broken up.
- Please be consistent with use of the Oxford comma.

RESPONSE: Your suggested changes were made unless the sentence was removed/revised to address other reviewer comments.

Some of the writing could also be streamlined/clarified. E.g.,

P.6 I.10-14 Remove the list of pathways from the beginning of the paragraph as they are all subsequently listed and explained.

RESPONSE: This has been edited to: “Green space exposure may benefit brain health through a number of pathways.”

P.6 I.31 Please clarify the direction of association between air pollution and cognition.

RESPONSE: This has been edited to: “...including PM₁₀ and NO₂ that have been associated with worse cognition and greater ADRD risk.”

P.17 I.20 Please further expand or provide references for the sentence “Compared to NDVI (greenness), percentage green space may better capture access to green spaces”.

RESPONSE: This has been added: “For instance, associations with NDVI measures can be affected by the chosen cut points to define healthy vegetation (e.g., 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.”

P.18 I.9 Please further expand or provide references for the sentence “measures of time spent in green space provide the specificity of exposure needed to make informed decisions about green space-brain health associations.”

RESPONSE: This has been added: “If individuals live in neighborhoods 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.”

P.18. I.42-45 Please provide references for the sentence “These neurodevelopmental benefits may impart cognitive reserve and resilience through older ages, which protects against ADAD neuropathology and resists symptoms despite neuropathology.”

RESPONSE: A reference has been added.

To help readers, please add references for all subgroups of studies mentioned in the results. eg.

- P.9 I.20-31 References for the breakdown by country and age group.
- P.9 I.45-56 References for the breakdown by green space measure.
- P.10 I.16-31 References for the breakdown by study outcome.
- P.10 I.35-43 References for the breakdown by association.
- P.12 I.20-31 Please cite all studies mentioned.
- P.12 I.31 It was mentioned that two studies found inverse results but only one was cited.
- P.13 I.26-31 References for the breakdown by brain health measure.
- P.13 I.52 – P.14 I.8 References for breakdown by effect modifiers.

RESPONSE: Citations have been added for all of the mentioned studies.

Could the author add some discussion about the inverse associations between green space and Alzheimer’s/dementia diagnoses observed in some studies?

RESPONSE: This has been added: “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 neighborhood greenness/green space and increased odds/risk of cognitive impairment may be explained by reverse causality/self-selection into greener neighborhoods in later life.”

I would recommend adding the sample size of each study to Tables 1-3.

RESPONSE: Sample size has been added to these tables.

If Figure 1 and Supplementary Figure 1 are the same please remove one.

RESPONSE: Supplemental Figure 1 has more information and per the suggestion of another reviewer, now provides even more details than Figure 1. Figure 1 has been simplified to reduce clutter/potential confusion.

VERSION 2 – REVIEW

REVIEWER	Dzhambov, Angel Medical University of Plovdiv, Hygiene and Ecomedicine
REVIEW RETURNED	17-Nov-2020
GENERAL COMMENTS	<p>Thank you for considering my suggestions. As a result, I think this revised version is more balanced and tempered.</p> <p>Still, I suggest that you add references for most of the sentences in the subsection "Green space measures" on page 20. Reference 20 on your list (Markevych et al.) discusses different greenspace measures and their applicability, so it seems fitting.</p>

VERSION 2 – AUTHOR RESPONSE

Thank you for reviewing the revised manuscript. To address your suggestion, a number of references have been added throughout the “Green space Measures” section on pages 20-21, including references to the Markevych paper.