PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between retinal markers and cognition in older adults: a systematic review
AUTHORS	Jeevakumar, Varshanie; Sefton, Rebekah; Chan, Joyce; Gopinath, Bamini; Liew, Gerald; Shah, Tejal; Siette, Joyce

VERSION 1 – REVIEW

REVIEWER	Alber, Jessica University of Rhode Island, Biomedical and Pharmaceutical Sciences
REVIEW RETURNED	13-Jul-2021

GENERAL COMMENTS	Diagnostic utility of retinal scanning for assessing cognition in older adults: A systematic review The objective of this systematic review was to appraise the existing literature on the use of retinal scanning for assessing cognitive impairment in adults aged 65 years and over, analyse it's efficacy in comparison to standard cognitive screening tests, and provide directions for future research. The authors adhered to PRISMA guidelines and registered their systematic review with PROSPERO. They search technique used was thorough and the Tables are informative and help to structure the manuscript. The methods are presented clearly and replicable. The results are a narrative analysis. The conclusions are that retinal scanning could be a tool for the detection of cognitive impairment, with several caveats. The authors note that there is no other systematic review that incorporates so many studies, and includes both cross-sectional and longitudinal data, although the longitudinal data is minimal in this study. They also employ a robust search strategy and methodological rating system, and note most limitations of their work. These results are interesting and merit publication – I have the following minor comments: 1.) A major concern is that the studies use different devices (SPECTRALIS, Zeiss, Optovue, etc) to measure retinal neuronal thicknesses, and comparing across these manufacturers is fruitless, as all of the devices use proprietary software and post-processing algorithms for their images. This should be noted explicitly as a limitation. 2.) Another major concern is that the MMSE and MoCA are not sensitive measures to detect early changes in cognition in dementia, and this is well noted by the authors in the discussion section. However, it diminishes the impact of the findings, as the studies do not provide adequate evidence to endorse retinal imaging as a screening tool. Perhaps adding additional text about

	what is required to support the development of retinal screening as a biomarker for dementia risk would be helpful. 3.) Change objective in the abstract as a direct comparison between the efficacy of clinical tests and the efficacy of retinal imaging for the identification of cognitive impairment is not presented in this article. 4.) The introduction reviews retinal microvascular contributions to cognitive decline but then explores studies examining retinal neuronal damage and grey matter atrophy, ventricular enlargement, etc, which are neurodegenerative changes and may be reflected in retinal neuronal cells rather than the retinal vasculature or microvasculature. 5.) Inclusion of FTD, DLB, and PD studies are interesting but they are also examining different pathologies, different retinal biomarker changes, and different cognitive trajectories. Justify inclusion of these studies or include caveat indicating diversity of neurodegenerative diseases. 6.) Although general inclusion and exclusion criteria are stated, many disorders fall under the umbrellas listed, and at minimum a statement of who made the judgment to exclude should be listed. This limits replicability of search. 7.) In results, Rome and Italy are both listed as countries that studies were conducted in – Rome is in Italy and should be encompassed in this category? 8.) Some of the numbers do not add up – for example when looking at retinal scanning techniques – OCT was used for 44/47 studies but then the sub-types do not add up to 44 9.) Physical neuropsychological examination – clarify what is meant by this – a complete evaluation by a licensed neuropsychologist? 10.) Page 12 line 23 alludes to cognitive deterioration when examining cross-sectional data – deterioration implies longitudinal cognitive decline, which was not the case in these studies. Suggest re-wording this. 11.) Page 14 line 9, unclear what positive association refers to – is this implicating improved cognition with increasing retinal neuronal layer thickness? Clarify.

VERSION 1 – AUTHOR RESPONSE

Reviewer Comments	**Our response**	**Manuscript Page**
In the Introduction you cite two previous systematic reviews/meta-analyses from 2015 and explain how your paper adds to and updates on these. Please check to make sure there are no additional more recent systematic reviews on the topic – if there are, these should also be cited and discussed in the same way in the Introduction. Additionally, it would be useful to point out in the text that the previous reviews already cited	We thank the editor for making this suggestion. We have now clarified and pointed out in the introduction that the two reviews are from 2015 and have included a paragraph on more recent systematic review and/or meta-analysis articles.	6-7

are from 2015, as this would emphasise that your paper also provides an update, able to incorporate more recent studies.	The following paragraph has been included in the introduction along with relevant additional tracked changes: *"More recent systematic reviews and meta-analysis studies have reported similar ……..AD, MCI and/or preclinical AD population."*	
The results section of the abstract refers to reduced cognition and cognitive decline – as these are relative measures, rather than formal diagnoses of dementia, please consider rephrasing the article title to avoid referring to 'diagnostic utility', and ensure the text throughout (including abstract and main text) presents an accurate representation of your aims and inclusion criteria.	We thank the editor for making this suggestion. The article title has now been rephrased to "Association between retinal markers and cognition in older adults: a systematic review". Relevant tracked changes have been made throughout the text to reflect an accurate representation of the study aims and inclusion criteria.	Throughout
In the third bullet point in the 'Strengths and limitations' section, please change "These studies" to "The included studies".	We have made the requested change.	3
Please include, as a supplementary file, the precise, full search strategy (or strategies) for all databases, registers and websites, including any filters and limits used. Currently you only include this for MEDLINE, but this should include all search strategies for all databases. Please also update the main text to ensure the revised supplementary material is correctly cited.	The supplementary file now includes the full search strategy for all the databases. The manuscript has also been revised to cite the supplementary correctly.	Supplementary
Please also update the "Search strategy" section of the main text to include a summary list of search terms used across all databases.	This has been updated.	Supplementary
Please replace the PRISMA 2009 checklist with the more recent PRISMA 2020 checklist, indicating the pages where the required items are reported (updating the manuscript as needed to ensure all	This has now been replaced and is updated.	-

required items are included).		
Please update the search past October 2020	This has now been completed, with the search extended until 17 March 2022.	-
We are not clear about the objective since studies of Parkinson's Disease are included. For example, which although has a cognitive element is primarily a degenerative motor disease with loss of movement control. Can you clarify?	These studies have now been excluded with a clearer focus on studies targeting Alzheimer Disease and mild cognitive impairment.	-
Reviewer 1		
These results are interesting and merit publication – I have the following minor comments: 1.) A major concern is that the studies use different devices (SPECTRALIS, Zeiss, Optovue, etc) to measure retinal neuronal thicknesses, and comparing across these manufacturers is fruitless, as all of the devices use proprietary software and post-processing algorithms for their images. This should be noted explicitly as a limitation.	We thank Reviewer 1 for noting a major study limitation. We have included this limitation under the revised 'STRENGTHS AND LIMITATIONS OF THIS STUDY' section as "*Majority of the included studies are cross-sectional and have used different retinal imaging devices and therefore it is not possible to compare across devices".* The below sentence is now included in the Discussion: *"Fifth, a major concern is that the studies use different company devices (such as Spectralis, Zeiss, Optovue) to measure retinal neuronal thickness, and comparing across these manufacturers is fruitless, as all the devices use proprietary software and respective post-processing algorithms for their images".*	3, 17
2.) Another major concern is that the MMSE and MoCA are not sensitive measures to detect early changes in cognition in dementia, and this is well noted by the authors in the discussion section. However, it diminishes the impact of the findings, as the studies do not provide adequate evidence to endorse retinal imaging as a screening tool. Perhaps	We thank Reviewer 1 for this suggestion. We have included the following information: *"As noted earlier, most studies have included MMSE and MoCA tests which are not sensitive measures to detect early changes in cognition in dementia, and therefore, diminishes the impact of our findings, as the studies do not*	16

adding additional text about what is required to support the development of retinal screening as a biomarker for dementia risk would be helpful.	*provide adequate evidence to endorse retinal imaging as a screening tool. Future retinal imaging studies should include a comprehensive neuropsychological battery to measure specific cognitive domains such as executive function, speed of processing, episodic memory, attention and global cognition as these domains are most impacted in dementia."*	
3.) Change objective in the abstract as a direct comparison between the efficacy of clinical tests and the efficacy of retinal imaging for the identification of cognitive impairment is not presented in this article.	We thank Reviewer 1 for making this suggestion. The below changes have been made to the objective in the abstract. *"To appraise the existing literature reporting an association between retinal markers and cognitive impairment in adults aged 65 years and over and to provide directions for future use of retinal scanning as a potential tool for dementia diagnosis".*	2
4.) The introduction reviews retinal microvascular contributions to cognitive decline but then explores studies examining retinal neuronal damage and grey matter atrophy, ventricular enlargement, etc, which are neurodegenerative changes and may be reflected in retinal neuronal cells rather than the retinal vasculature or microvasculature.	We have modified the introduction to clarify this point.	Introduction
5.) Inclusion of FTD, DLB, and PD studies are interesting but they are also examining different pathologies, different retinal biomarker changes, and different cognitive trajectories. Justify inclusion of these studies or include caveat indicating diversity of neurodegenerative diseases.	We agree with this statement and have now tightened the inclusion criteria to examine retinal biomarker changes for individuals with diagnosed AD or mild cognitive impairment only.	-
6.) Although general inclusion and exclusion criteria are stated, many disorders fall under the umbrellas listed, and at minimum a statement of who made the judgment to exclude should be listed. This limits replicability of search.	Please see above comment.	-

7.) In results, Rome and Italy are both listed as countries that studies were conducted in – Rome is in Italy and should be encompassed in this category?	This has now been removed and countries updated.	-
8.) Some of the numbers do not add up – for example when looking at retinal scanning techniques – OCT was used for 44/47 studies but then the sub-types do not add up to 44	Sub-types do not necessarily add up to 44 as OCT could be used to assess different parts. We have now updated the table and provided a summary for each of the sub-types for easier access.	Tables 1 and 3
9.) Physical neuropsychological examination – clarify what is meant by this – a complete evaluation by a licensed neuropsychologist?	We thank Reviewer 1 for their comment on this sentence. We have reworded the sentence as below for clarification: *"A comprehensive neuropsychological examination assessing cognitive performance was part of the initial work-up in 11 (23.4%) studies."*	11
10.) Page 12 line 23 alludes to cognitive deterioration when examining cross-sectional data – deterioration implies longitudinal cognitive decline, which was not the case in these studies. Suggest re-wording this.	We thank Reviewer 1 for their comment on this sentence. We have reworded cognitive deterioration to cognitive performance throughout the manuscript.	Throughout
11.) Page 14 line 9, unclear what positive association refers to – is this implicating improved cognition with increasing retinal neuronal layer thickness? Clarify.	This has now been clarified.	15