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Diagnostic utility of retinal scanning for assessing cognition in older adults: a systematic review

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ABSTRACT

Objectives To appraise the existing literature on the use of retinal scanning for assessing cognitive impairment in adults aged 65 years and over, analyse its efficacy in comparison to standard cognitive screening tests and provide directions for future research.

Design Systematic review of peer-reviewed empirical articles investigating the diagnostic utility of retinal scanning in assessing cognitive impairment.

Data sources Three electronic databases, Medline, PsychINFO, and EMBASE were searched from inception until October 2020.

Eligibility criteria All empirical articles in the English language investigating diagnostic utility of retinal scanning in humans aged ≥ 65 years using various methodologies including Optical Coherence Tomography (OCT), in assessing diagnosed cases of dementia were included. Studies with no explicit association between retinal scanning findings and cognition were excluded. Risk of bias was assessed using the QUADAS Tool.

Data extraction and synthesis Data extraction was conducted by one author and reviewed by another. Results were synthesised and described narratively.

Results Forty-seven eligible studies examining 4,119 older adults were included. Majority of studies were cross-sectional (n=44) and were clinic- or hospital-based. OCT was the most commonly used retinal methodology to measure thickness of four retinal layers (nerve fibre layer, ganglion cell complex, choroid, and macula). Cross-sectional studies identified a positive correlation between retinal measures and cognition with 51.1% of studies using OCT detecting a significant positive relationship between the thinning of at least one retinal area and poorer cognition. Longitudinal studies (n=3) using OCT also identified significant reductions in nerve fibre layer thickness associated with cognitive decline. Study quality was overall moderate but limited due to lack of generalisability.

Conclusion Current retinal scanning methods have the potential to detect cognitive impairment in older adults. Further longitudinal studies are required before recommending implementation of OCT as a universal screening tool in clinical practice.

PROSPERO registration number: CRD42020176757

Key words: Retinal scanning, cognitive screening tests, cognitive impairment, optical coherence tomography, ganglion cell complex, choroid, macula

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review provides an in-depth evaluation of the relationship between retinal scanning methods and early detection of cognitive impairment in older adults to inform future clinical practice.
- This review includes a substantially larger number of empirical articles than previous systematic reviews, as well as the inclusion of three longitudinal studies to establish cause-and-effect relationships between retinal scanning and cognitive deterioration.
- These studies were methodologically rated using appropriate tools.
- The included studies may not be representative of the sample population as individuals with chronic conditions were excluded.

INTRODUCTION

The last decade has seen a substantial increase in research focused on the identification, development, and validation of diagnostic and prognostic retinal biomarkers for dementia and Alzheimer's disease (AD).[1] Sensitive retinal biomarkers may be advantageous because they are cost and time efficient, non-invasive, and present a minimal degree of patient risk and a high degree of accessibility.[2] With one in ten Australians aged over 65 with dementia and 50 million people affected worldwide,[3] cognitive impairment is a prevalent issue in our ageing population. With the total estimated worldwide cost of dementia to be US$818 billion in 2015,[3] earlier detection of cognitive impairment will be of high economic benefit. Early diagnosis could also lower mortality,[4] allow timely access to medication, improve quality of life, stabilise cognitive decline, and minimise preventable hospital visits.[4]

As the retina forms as an outgrowth of the brain during embryological development, retinal structure and function reflects that of the brain and spinal cord.[5] Considering this, retinal scanning may allow detection of dementia before symptoms manifest, unlike traditional screening tests which primarily detect cognitive impairment following presentation of warning signs, such as memory loss.[6] Apart from the effects of normal ageing, marked inter-individual differences in the rate of cognitive decline indicate that other age-associated pathologies may be involved, such as macro- or microvascular disease.

Several pathobiological markers have been suggested as potential predictors of cognitive dysfunction and of these, retinal microvascular signs may offer the most promise. A study by Ong et al. (2015) found an association between retinal neuronal damage and grey matter atrophy, which indicates that retinal scanning may reflect cerebral neurodegenerative changes and thus, predict cognitive decline.[7] Yoon et al. (2019) demonstrated that ventricular enlargement due to cerebral atrophy seen characteristically in Alzheimer’s as indicated by previous magnetic resonance imaging

studies,[8] is mirrored in retinal microvasculature changes as measured through retinal scanning tools, such as Optical Coherence Tomography (OCT). OCT is a non-invasive technique that acquires high resolution, cross sectional images of the retina.[2] The OCT devices often vary, with some users adopting swept-source OCT (SS-OCT) devices while others used spectral-domain OCT (SD-OCT), which can impact light source, acquisition speed, and resolution [9]. Therefore, as a common tool in clinical practice, retinal scanning could be used routinely as an accessible alternative to brain imaging that is both faster to administer and less stressful to the patient with the potential to measure and quantify cognitive decline.

A recent cross-sectional observation study has demonstrated the value of OCT in detecting dementia, identifying OCT measurements of the macula as a "useful diagnostic biomarker of cognitive function"[10] (pg. 117). However, there has been conflicting evidence on the effectiveness of ophthalmic scanning in mild cognitive impairment (MCI), the precursor of dementia. Almeida et al. (2019) found a significant correlation between OCT measurements in the inner retinal layers with cognitive screening assessments, whilst Ito et al. saw no changes on OCT in MCI individuals, recommending further research.[11]

Recent systematic reviews have attempted to analyse the association between cognitive functioning and retinal nerve fibre layer thickness (RNFL).[12,13] Thomson et al. conducted a systematic review and meta-analysis of 17 articles and found a statistically significant reduction in RNFL in both AD and MCI patients when compared to healthy controls.[12] This study identified OCT as a potential diagnostic tool in assessing cognitive impairment, particularly for AD and MCI syndromes. Similarly, Wang et al. evaluated the relationship of peripheral RNFL thickness to AD and MCI in 19 studies and found a progressive reduction in total RNFL thickness, particularly in the inferior and superior quadrants, suggesting RNFL thickness to be a candidate biomarker for early detection of AD.[13] However, both systematic reviews appraised only a small number of cross-sectional studies with no consideration of cognitive impairment in forms other than AD and MCI.

The role of the retinal layers other than the nerve fibre layer, including the macula and ganglion cell complex (GCC) as biomarkers in the assessment of cognitive impairment were also not evaluated.

Despite this research, the evidence is limited due to the small sample sizes of the above-mentioned articles making the findings inconclusive as it underrepresents the target population. This is due to the extensive exclusion criteria and high comorbidity rate in the older adult population with the prevalence of concomitant eye and systemic disease such as glaucoma and diabetes making them unsuitable candidates. Nevertheless, retinal scanning may be valuable in monitoring disease progression and response to treatment.

To date, no systematic review has analysed the specific relationship between retinal scanning and cognitive screening tests of all retinal layers, and the efficacy of specific retinal screening tools in diagnosed individuals with dementia. This systematic review aims to summarise the available evidence on the use of retinal scanning methodologies in older adults and provide directions for future research.

METHODS

We drafted a protocol for this review 'a priori' and inclusion criteria were developed prior to commencing the search. This review was registered on PROSPERO. We report according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and a checklist of PRISMA items is presented in the online supplementary data S1.

Ethics approval statement

We used publicly accessible documents as evidence and did not collect individual personal information from participants. As such it was not necessary to seek an institutional ethics approval before commencing our review.

Search strategy

A search strategy was developed using medical subject headings (MeSH) and key search terms related to cognitive impairment and retinal scanning. Studies were identified through Medline (1806 – 2020), PsychINFO (1905 – 2020) and EMBASE (1974 – 2020) databases. An updated literature search was undertaken prior to the final analysis to ensure up-to-date and relevant articles were included. Date last searched was 23 October 2020. The search strategy (available in online supplementary data S2) was deliberately broad in an effort to gather all eligible studies and was developed in collaboration with the clinical librarian and reviewed by the project team. Reference lists of all included studies were hand-searched for additional records. This search strategy was then adapted to the other databases, PsychINFO and EMBASE.

Eligibility Criteria

All peer-reviewed empirical articles in English and using human subjects, including but not limited to cross-sectional, population-based, case-control and longitudinal studies. Studies with no explicit association between cognition and findings on retinal scanning were excluded.

Participants: Inclusion criteria comprised of adults aged 65 years and over with diagnosed cognitive impairment of any form and severity, including AD, Frontotemporal, and Diffuse Lewy Body Dementia, and mild cognitive impairment, and a control group of cognitively healthy participants. The study was limited to subjects aged over 65 as diagnosis of dementia is more prevalent in this age group. Exclusion criteria includes those with pre-existing ophthalmological, metabolic, cardiovascular, cerebrovascular, psychiatric, or other disease that could affect the visual field or neurological system. Other exclusion criteria include previous intraocular surgery or trauma, the inability of the participant to collaborate sufficiently to perform an Optical Coherence Tomography (OCT) scan, and/or use of medications that could affect visual function.

Types of index and reference standard tests: All participants in the chosen studies were screened using standard, traditional cognitive screening tests such as Mini-Mental State Examination

(MMSE) and retinal scanning using Optical Coherence Tomography (OCT), Optical Coherence Tomography Angiography (OCTA) or another technique (available in online supplementary data S2).

Controls or comparators: Cross-sectional and cohort studies will not have a comparator, but a case-control study should have an age- and sex-matched control group of cognitively healthy participants.

Data Extraction

The search results from Medline, PsychINFO and EMBASE were exported to Excel and duplicates were removed. Two authors (VJ and JS) reviewed titles, abstracts and full-text papers for eligibility. Authors resolved disagreement by discussion or, where necessary, a third author (JC) offered their view. Extraction was completed (VJ) using a standardised data sheet that was piloted with three papers and revised. All data extraction was verified by JS, and disagreement was resolved via discussion. Extracted data included, study design, participant demographics (including mean age, country of study), sample size, method of and parameters measured on retinal scanning, measure of cognitive function, type and degree of cognitive impairment, and relevant statistical data.

Risk of bias assessment

The QUADAS Tool [14] was used as it assesses the quality of studies looking at diagnostic accuracy. This covers spectrum, disease progression, partial verification, differential verification, incorporation and review bias, and incomplete data outcomes e.g. withdrawals. Two reviewers (VJ, JS) partook in the studies' quality assessment and any discrepancy between reviewers was resolved through discussion and if an agreement could not be reached, a third individual was consulted (JC).

Statistical Analysis

Owing to a high degree of heterogeneity that exists between studies, including study designs, population type, measures of retinal scanning and cognition, a meta-analysis of study results was not possible. A descriptive synthesis approach was utilised.

Patient and public involvement

No patient involved.

RESULTS

Study design and populations

The search identified 821 articles, of which 47 were eligible (see **Figure 1**). Most studies included were cross-sectional (42/47; 89.4%), with a few case-controls (2/47; 4.3%) and longitudinal (3/47; 6.4%) studies (**Table 1**). Longitudinal studies had a range of two to 12-year follow-ups. One of these longitudinal studies explored the relationship between retinal measures and the evolution of cognitive performance in an elderly population with no formal diagnosis of dementia.

Four (8.5%) studies were population-based with the remainder either clinic- (19/47; 40.4%) or hospital-based (13/47; 27.7%) (**Table 1**). Controls were recruited either from the community or were the spouses of the cases. Studies were mostly conducted in the USA (10/47; 21.3%) and Spain (8/47; 17.0%) followed by Italy (6/47; 12.8%) then Turkey (5/47; 10.6%) and China (4/47; 8.5%), Brazil (3/47; 6.4%) and Korea (3/47; 6.4%), Netherlands (2/47; 4.3%) and Germany (2/47; 4.3%), and finally United Kingdom (1/47; 2.1%), Israel (1/47; 2.1%), Rome (1/47; 2.1%), and France (1/47; 2.1%). The type of cognitive impairment varied between studies with 37 (78.7%) articles looking at Alzheimer's Dementia (AD), 19 (40.4%) at mild cognitive impairment (MCI), five (10.6%) at Parkinson's Dementia (PD), one (2.1%) at Lewy Body Dementia (LBD) and one (2.1%) at Frontotemporal dementia (FTD). Across all studies, the mean age range was 71 years for controls, 73 years for AD, 66 years for FTD, 74 years for LBD, 66 years for PD and 73 years for MCI. The ratio

of males to females was approximately one-to-one across all studies, with a slight female predominance.

Assessment of retinal abnormalities

Retinal scanning was performed using several techniques (**Table 1, Supplementary Material**). The most common was Optical Coherence Tomography (OCT) (44/47, 93.6%; SD-OCT (18/47); SS-OCT (1/47)) followed by Optical Coherence Tomography Angiography (OCTA) (8/47; 17.0%) then Fluorescence Lifetime Imaging Ophthalmoscopy (FLIO) (1/47; 2.1%), laser Doppler flowmetry (1/47; 2.1%) and fundus photography (1/47; 2.1%). OCT is a non-invasive method that obtains cross-sectional images of the retina and calculates the thickness of all retinal layers including the nerve fibre layer, ganglion cell complex, choroid and macula. In 12 (25.5%) studies, the Early Treatment of Diabetic Retinopathy Study (ETDRS) macular map sectors were used to divide the macula into nine segments to produce a retinal thickness map. The retinal nerve fibre layer (RNFL) thickness was calculated globally, and across either four or six segments.

On the other hand, OCTA acquires images of retinal vasculature to calculate perfusion and vascular density (VD), and foveal avascular zone (FAZ) area,[5] whereas laser Doppler flowmetry calculates the retinal blood flow rate.[15] FLIO measures the autofluorescence intensity emitted by endogenous fluorophores contained within the retina to calculate retinal metabolic activity.[16,17] Fundus photography was also employed to obtain detailed images of the fundus within a 50-degree field of view of the macula, and the optic nerve head to evaluate retinal vasculature.[18]

As part of the work-up, a full ophthalmological scan was performed in 28 (59.6%) studies prior to retinal imaging, including assessment of best-corrected visual acuity (BCVA), dilated fundus scan, slit lamp scan of the anterior segment of the eye, intraocular pressure (IOP) measurement, and anatomical ocular measurements with optical biometry. Neuroimaging was performed in 18 (38.3%) studies to exclude alternate diagnoses, and nine (19.1%) studies used standard blood tests to rule out

reversible causes of dementia. A physical neuropsychological examination was part of the initial work-up in 11 (23.4%) studies.

Assessment of cognitive function and impairment

A summary of the assessment of cognitive function is shown in **Table 2**. Cognitive function was always measured using standard cognitive screening tools, such as Mini Mental State Examination (MMSE) (41/47; 87.2%), Montreal Cognitive Assessment (MoCA) (5/47; 10.6%) and the global clinical dementia rating score (CDR) (1/47; 2.1%). These screening tests evaluate various cognitive domains including, orientation, attention, executive functions, memory, language, visuospatial skills, abstract thinking, and calculations. Cognitive screening tests were conducted by either neurologists, psychologists, physicians, or research associates.

AD was diagnosed using DSM-IV criteria (6/47; 12.8%), National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[19] criteria (15/47; 31.9%) or a combination of both (12/47; 25.5%). The most common method to diagnose MCI was through the Peterson's criteria,[20] (6/47; 12.8%) which identifies whether all five criteria are satisfied including, memory complaint corroborated by an informant, objective memory decline, normal general cognitive function, normal functional activities, and absent dementia diagnosis. Rascovsky criteria,[21] (1/47; 2.1%) which consists of a series of persistent or recurrent behavioural and cognitive symptoms was used for the diagnosis of FTD. LBD was diagnosed via the McKeith Criteria,[22] (1/47; 2.1%), which includes dementia coexisting with two of the following symptoms, delirium-like fluctuating cognition, repeated visual hallucinations, REM sleep behaviour disorder and parkinsonism. Diagnosis of PD was through recommendations from the Movement Disorder Society Task Force,[23] (2/47; 4.3%) whether all five criteria are satisfied including, Parkinson's disease diagnosis based on Queen's Square Brain Bank criteria,

Parkinson's disease developed prior to dementia onset, MMSE less than 26, cognitive deficits severe enough to impact ADLs and impairment in more than one cognitive domain.

Association between cognition and retinal measurements

Using OCT, the majority of studies found a significant correlation between RNFL (9/17, 52.9%) and ganglion cell inner plexiform layer (GC-IPL) thinning (6/11, 54.5%) with impaired cognition (**Table 2**). Some studies found a significant correlation between macular (7/17, 41.2%), macular retinal nerve fibre layer (mRNFL) (1/3, 33.3%), GCC (4/12, 33.3%), choroidal thickness (CT) (1/4, 25.0%) and peripapillary retinal nerve fibre layer (pRNFL) thinning (4/22, 18.2%) with cognitive deterioration. These findings did not vary significantly between different OCT devices. Measures of retinal vascular structures using OCTA identified a correlation between VD (2/5, 40.0%), retinal vasculature (1/6, 16.7%) and FAZ area (1/7, 14.3%) with cognitive impairment.

Risk of Bias Assessment

Risk of bias of the 47 studies are provided in **Table 3**. The average QUADAS score was 10.8 with 35 (74.5%) studies scoring 10 or above. In 34 (72.3%) studies it was unclear whether the index test results were interpreted without the knowledge of the reference standard, and vice versa in 32 (68.1%) studies. This could contribute to review bias, and thus impact the diagnostic accuracy of the clinical tool. The time period between conducting the reference standard and index test was unclear in 15 (31.9%) studies, suggesting that the influence of disease progression bias cannot be excluded. All 49 studies were not representative of the target population as patients with comorbidities that may affect the retina, including diabetes mellitus and hypertension were excluded. This lack of generalisability may interfere with the implementation of retinal scanning in clinical practice. However, the majority of studies (93.6%) provided a clear selection criterion, and all studies utilised an accurate reference standard. Partial verification, differential verification, incorporation, and clinical

review bias were minimal across the included studies. Considering this, the overall risk of bias was moderate, and findings should be interpreted with caution.

DISCUSSION

Our review evaluated the relationship between retinal scanning methods and early detection of cognitive impairment in older adults to inform future clinical practice. Over 50% of the studies using OCT identified (25/47, 53.2%) a positive correlation between the thinning of at least one retinal area and cognitive impairment. The future of retinal imaging as a clinically useful tool for measuring cognition in older adults is considered.

Within ophthalmology, retinal imaging devices are primarily used in the diagnosis of retinal disease as well as serial monitoring of retinal conditions such as age-related macular degeneration and response to treatment [9]. We identified two main retinal scanning devices, OCT and OCTA in this review, with a far more sensitive response from OCT. OCTA was primarily used to measure and evaluate retinal vasculature, but measures of retinal thickness via OCT was considerably more effective in detecting cognitive impairment. Studies using OCTA techniques have resulted in mixed findings.[24] This may be due to the varied vessel distribution and morphology, including vessel size and number of anastomoses between participants. The lack of uniformity in vessel size may affect vessel density calculations, as the smaller surface area of capillaries may contribute to a more sensitive measure of perfusion compared to larger vessels [19]. Additionally, fewer anastomoses within a vessel network contributes to a higher risk of vascular dysfunction [19]. Considering this wide variability in vascular network structure between individuals, OCTA may be suitable for detecting later stages of dementia but may not be reliable in detecting the transition between age-related changes and mild cognitive impairment. Furthermore, not all participants with MCI will convert to dementia, some may revert to normal cognition, thus affecting the accuracy of the

results.[19] Retinal layer thickness as measured through OCT does not vary as extensively as OCTA and thus, serves as a suitable alternative in the early detection of dementia.

Although OCT devices have been utilised for the past two decades, there has been no consistent retinal area that is strongly associated with the cognitive function of older adults. This is consistent across all types of OCT devices. Our findings found that thinning of the RNFL and pRNFL were initially associated with poorer cognitive function, however, within the last decade a large proportion of studies have identified a positive correlation. Our review found that since 2016, four (33.3%) of the 12 studies evaluating pRNFL have identified a positive relationship [11, 25, 26, 27]. Similarly, in the last decade, 64.3% of studies using OCT devices to measure RNFL thickness have identified a positive correlation with cognitive impairment, whereas previously no correlation was found. However, researchers have failed to consistently identify a correlation between retinal scanning and cognitive impairment, for example two recent articles identified an association [19, 20] with RNFL whereas two did not [21,22]. This lack of consistency is reflected across all retinal areas and the discrepancies may in part be ascribed to differences in sample size, the severity of cognitive impairment, and the OCT technology used.

Indeed, mean RNFL and macular thickness is largely dependent on the type of OCT device used [23]. The variety of devices may affect the consistency of results across studies. Considering this, OCT thickness measurements from different studies should be compared with caution. Moreover, as MCI represents a transition towards dementia, reductions in pRNFL and macular thickness, if any, are likely to be subtle, perhaps even within the normal range, when compared with healthy age-matched control subjects. Furthermore, these cross-sectional studies present data at a single point in time after the participant has been diagnosed with cognitive impairment. The lack of baselines measures when the participant is well, creates difficulty in detecting these subtle changes. Therefore, findings need to be interpreted with caution.

The inconsistencies between studies can also be attributed to the lack of sensitivity of cognitive screening tools, such as the MMSE which is largely used to assess cognition, but we know is ineffective in identifying cognitive impairment at its early stages [28]. Despite these mixed results, cross-sectional studies present data at a single point in time and therefore, the dynamic change in the relationship between retinal thickness and cognition is unable to be quantified. It seems therefore that with only limited evidence thus far, caution will be needed in interpreting the rate of change of an individual's RNFL thickness in terms of their neurological status. Furthermore, given the physiological variations in RNFL thickness, single time-point measurements in individual participants are likely to have limited value.

Our review innovates by appraising three large longitudinal studies [29,30,31] to further establish cause-and-effect relationships between retinal scanning and cognitive deterioration. We found that OCT measurements of RNFL thickness including inferior quadrant RNFL thickness [29] and pRNFL thickness [30] was able to detect reductions in these areas over time, and was associated with decline in cognitive abilities such as impaired recall [29], immediate and delayed memory [29] and episodic memory [30]. Cognitive decline was found to be associated with longitudinal reduction in inferior quadrant thickness [30]. These results highlight the ability of OCT to detect longitudinal changes in RNFL thickness and declining cognition.

A systematic review by Ding et al. (2008) [32] evaluated six studies and identified a positive relationship between retinal vascular signs, and information processing speed, verbal memory, and executive function. However, the lack of consistency between study findings due to differences in retinal scanning methodology, small sample size, and cognitive screening tools were recognised and limited interpretation. An updated review by Heringa et al. (2013) [33] identified a moderately strong association between microvascular and cerebral changes, and dementia diagnosis across 32 studies. They concluded that although retinal vascular assessment can be incorporated into prediction models, only a minority of dementia cases were attributed to retinal vascular changes. These reviews

support the potential role of retinal vascular changes in the pathophysiology of cognitive impairment but recommend the need for more prospective data. Our review adds to the existing literature by providing greater insight into the role of OCT in the early detection of cognitive impairment through measures of retinal layer thickness.

Our study has several limitations. First, participants in the included studies were not representative of the sample population and individuals with chronic conditions, such as diabetes mellitus, hypertension and neurological conditions were excluded. These comorbidities are common in the older population and affect the generalisability of our findings. Further studies including patients with these comorbidities are required to identify whether retinal scanning is a viable biomarker in cognitive impairment. Second, some studies were missing data in several domains, such as cognition scores or correlation metrics, which excluded their entry in the review and may compromise publication bias. Third, our search strategy was very specific, and this may have excluded studies that were relevant to our review. Fourth, only eight studies evaluating OCTA were included in this review resulting in mixed findings. This may explain why other studies specifically assessing OCTA with a larger sample size may have identified a positive correlation.[24]

Our study has some strengths. This is the first systematic review that has evaluated multiple retinal scanning tools across several forms of cognitive impairment. We reviewed extensively more empirical articles than previous systematic reviews [32,33], comprising of a larger, international sample and summarised the recent results of longitudinal studies, adding substantial insight.

Earlier diagnosis of dementia using non-invasive techniques will improve patient care, quality of life, disease management, and clinical outcome[4]. Cognitive screening tools currently used in routine clinical practice, such as MMSE are not sensitive in detecting cognitive impairment in its earlier stages, are time-consuming and can be stressful for the patient[28]. OCT is a sensitive alternative that provides a rapid assessment of the retina to detect changes consistent with cognitive

impairment, such as RNFL thinning. Advances in OCT technology, especially the advent of Fourier-domain OCT (ED-OCT), and more recently SS-OCT, which improves acquisition speed and resolution of retinal images, will further make accurate quantitative segmented retinal layer analysis possible. Introducing OCT as part of the Medicare Benefits Schedule (MBS) could allow optometrists to additionally provide annual cognitive screening to older adults. This would enable earlier detection of cognitive impairment and thus the provision of both pharmacological and non-pharmacological interventions to slow or stabilise disease progression[4].

In conclusion, whilst cross-sectional studies have inconsistently recognised a link between retinal scanning methods and cognitive impairment, recent longitudinal studies provide stronger evidence on the diagnostic utility of OCT in detecting a declining cognitive status. Further longitudinal studies should be conducted to corroborate these findings before retinal scanning can be introduced into clinical practice as a viable tool for detecting cognitive impairment. Studies using more sensitive cognitive screening tools are required to assess the viability of retinal measures as a biomarker in cognitive decline.

DECLARATIONS

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CONTRIBUTORS

JS conceptualised the study and produced with VJ the first draft of the manuscript. BG reviewed the study design and provided feedback. JS and VJ devised the search strategy which was carried out by VJ. JS completed the blinded 5% review of abstracts with BG acting as arbitrator. VJ reviewed the remainder of the abstracts. JS and VJ carried out the full-text review, followed by the data extraction and quality assessment of included articles. VJ developed the initial frameworks with JS providing feedback. All authors contributed to revisions of subsequent manuscript drafts and approved the final submission,

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COMPETING INTERESTS

The authors declare that they have no conflicts of interest to disclose.

PATIENT CONSENT FOR PUBLICATION

Not required.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. The data are available upon request from the corresponding author (joyce.siette@mq.edu.au)

FIGURES AND TABLES

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart describing the process of study selection.

Table 1. Characteristics of studies included in the systematic review

Year	Author	Country	Design	Areas of retina measured											Sample size	Method	OCT Machine
				RNFL	mRNFL	pRNFL	GCC	GC-IPL	MT/MV	CT	FAZ	VD	RV	Other			
2001	Parisi	Italy	CS	✓											31	OCT	OCT1
2006	Iseri	Turkey	CS	✓					✓						29	OCT	OCT Model 3000 unit
2011	Kesler	Israel	CS	✓											78	OCT	Stratus OCT3
2013	Kirbas	Turkey	CS	✓		✓									80	SD-OCT	SD-OCT
2013	Moreno-Ramos	Spain	CS	✓											40	OCT	TOPCON 3D OCT-1000
2013	Shen	China	Longitudinal	✓											78	OCT	ZEISS Cirrus HD-OCT 4000 OCT
2014	Ascaso	Spain	CS	✓					✓						90	OCT	Stratus OCT3
2014	Gharbiya	Italy	CS			✓				✓				✓[1]	42	SD-OCT	Heidelberg Spectralis with Heidelberg Eye Explorer
2014	Polo	Spain	CS	✓											140	OCT	Cirrus and Spectralis OCT devices
2015	Bambo	Spain	CS			✓									112	OCT	Cirrus OCT
2015	Bayhan	Turkey	CS				✓			✓				✓[2]	61	SD-OCT	RTVue OCT system
2015	Feke	USA	CS			✓							✓[3]		52	Laser Doppler retinal blood flow and OCT	Canon laser Doppler retinal blood flow instrument (CLBF 100, Canon) and Stratus OCT 3000
2015	Gao	China	CS			✓			✓						72	OCT	Cirrus HD-OCT 4000
2015	Gunes	Turkey	Case-control (CC) study			✓									80	SD-OCT	Spectral-domain OCT (Spectral OCT SLO, OPKO / OTI Instrumentation)
2015	Jentsch	Germany	CS			✓			✓					✓[4]	16	OCT and fluorescence	Cirrus OCT 4.0

																lifetime imaging ophthalmoscopy (FLIO)	
2015	Oktem	Turkey	CS	✓											105	OCT	Zeiss Cirrus HD 5000 model OCT device
2015	Salobrar-Garcia	Spain	CS		✓	✓									51	OCT	OCT Model 3D OCT-1000
2015	Shi	China	Longitudinal	✓											78	OCT	ZEISS Cirrus HD-OCT 4000 OCT
2016	Choi	Korea	CS and longitudinal			✓	✓	✓							134	OCT	Cirrus High-Definition OCT (HD-OCT, software version 6.0)
2016	Cunha	Brazil	CS		✓	✓	✓	✓	✓					✓[5]	48	OCT	Frequency domain-OCT (fd-OCT) using 3D OCT-2000, software version 8.11
2016	Garcia-Martin	Spain	CS	✓			✓							✓[6]	225	OCT	Spectralis OCT
2016	Knoll	USA	CS			✓		✓	✓						34	SD-OCT	SD-OCT using Spectralis HRA 1 OCT
2016	Pillai	USA	CS	✓			✓		✓						106	SD-OCT	SD-OCT using Cirrus 4000 HD-OCT
2016	Trebbastoni	Rome	CS			✓									72	SD-OCT	Heidelberg Spectralis with Heidelberg Eye Explorer
2017	Ferrari	Italy	CS			✓		✓							93	OCT	Fourier-domain OCT Heidelberg Spectralis
2017	Mendez-Gomez	France	Longitudinal			✓									427	SD-OCT	SD-OCT using Spectralis

2018	Bulut	Turkey	CS							✓	✓	✓	✓[7]		52	OCT angiography (OCTA)	Commercial spectral domain OCTA
2018	Jiang	USA	CS					✓			✓		✓[8]		52	1. OCTA 2. OCT	1. Zeiss Angioplex OCTA 2. Zeiss OCT
2018	Lahme	Germany	CS								✓		✓[9]		74	OCTA	RTVue XR Avanti with AngioVue
2018	Shao	USA	CS	✓				✓						✓[10]	70	SD-OCT	SD-OCT using Ultrahigh-resolution OCT (UHR-OCT) device
2018	Uchida	USA	CS											✓[11]	124	OCT	Cirrus 4000 HD-OCT
2019	Almeida	Brazil	CS		✓	✓	✓	✓	✓						47	SS-OCT	SS-OCT (DRI OCT Triton)
2019	Cipollini	Italy	CS			✓	✓		✓						42	SD-OCT	SD-OCT RTVue
2019	Haan	Netherlands	CS			✓	✓		✓					✓[12]	142	SD-OCT	Heidelberg Spectralis spectral domain OCT
2019	Haan	Netherlands	CS							✓	✓	✓			86	1. Fundus photography 2. SD-OCT 3. OCTA	1. Topcon TRC 50DX type IA 2. Enhanced Depth Imaging OCT (EDI-OCT) using Heidelberg Spectralis spectral domain-OCT 3. Zeiss Model 5000 spectral domain-OCT with Angioplex
2019	Kim	South Korea	CS	✓				✓	✓						47	OCT	Cirrus HD-OCT software version 6.0.0.599
2019	Salobrar-Garcia	Spain	CS			✓	✓		✓					✓[13]	90	OCT	OCT Model 3D OCT-1000 and OCT Spectralis
2019	Sung	Korea	CS			✓		✓	✓						127	SD-OCT	Cirrus SD-OCT
2019	Tao	China	CS			✓	✓								191	OCT	Optovue AngioVue

																	System
2019	Yoon	USA	CS	✓				✓			✓	✓	✓[14]		209	1. OCTA 2. SD-OCT	1. Zeiss Cirrus HD-5000 SD-OCT with AngioPlex OCTA 2. Cirrus HD-OCT 5000 device
2019	Zhang	USA	CC			✓	✓		✓		✓	✓	✓[15]		32	1. OCT 2. OCTA	RTVue-XR OCT Avanti System with split-spectrum amplitude-decorrelation angiography (SSADA) software
2020	Ashimatey	USA	CS											✓[16]	111	OCTA	Spectral Domain OCTA: Cirrus HD-OCTA
2020	Criscuolo	Italy	CS	✓			✓				✓	✓			83	SD-OCT and OCTA	1. SD-OCT 2. OCTA (XR Avanti AngioVue OCTA)
2020	Leyland	UK	CS						✓[17]						146	SD-OCT	High-resolution SD-OCT (Heidelberg HRA/Spectralis)
2020	Mammadova	USA	CS	✓											20	SD-OCT	High-resolution spectral-domain OCT imaging (Zeiss Cirrus 5000 HD-OCT)
2020	Santangelo	Italy	CS			✓			✓[18]						137	OCT	Heidelberg Spectralis OCT

[1]Central subfield (CSF) retinal thickness; [2]Focal loss volume and global loss volume; [3]Blood column diameter, centreline blood speed, retinal blood flow rate; [4] Time-resolved autofluorescence of the retina by FLIO; [5]Average RNFL + GC-IPL = GCL++; [6]Papillomacular bundle thickness, Inner plexiform layer (IPL) and outer nuclear layer (ONL) thickness; [7]Outer retinal flow rate and choroidal flow rate; [8]Superficial vascular plexus (SVP), Deep vascular plexus (DVP), Total retinal vascular network (RVN); [9]Flow density in the Optic Nerve Head (ONH), Superficial retinal OCTA of the macula; [10]Inner nuclear layer (INL), ONL, outer plexiform layer (OPL), Retinal photoreceptor (PR); [11]Retinal thickness/volume, mean foveal thickness and juxtafoveal thickness; [12]IPL thickness; inner retinal layer thickness; total retinal thickness; [13]IPL, INL, OPL; retinal pigment epithelium (RPE) thickness; [14]Perfusion density (PD); central subfield thickness (CST); [15]Radial peripapillary capillary (RPC) layer, Superficial vascular complex (SVC), Superficial capillary plexus (SCP), Deep capillary plexus (DCP), Adjusted Flow Index (AFI), Micropapillary VD of RPC; [16]Retinal vessel skeleton density (VSD) – measure of retinal capillary perfusion; [17]Macular thickness and volume of RNFL, Ganglion cell layer (GCL) and IPL; [18]Macular volume of GCL, IPL and INL;

Table 2. Study characteristics of cognitive assessment and score

Year	Author	Mean age of individuals with diagnosed AD[1]	Mean age range of controls	No. of cognitively impaired subjects[2]		Cognition measure	Mean cognitive score		
				MCI	AD		Controls	MCI	AD
2001	Parisi	70.4	-	-	17	MMSE	23	-	16.4
2006	Iseri	70.1	65.1	-	14	MMSE	29.4	-	18.5
2011	Kesler	73.7	70.9	24	30	MMSE	-	28.1	23.6
2013	Kirbas	69.3	68.9	-	40	MMSE	28.7	-	21.2
2013	Moreno-Ramos	73.0	70.2	-	10[3,4]	MMSE	29.2	-	16.4
2013	Shen	-	74.1	18[5]	-	MMSE	At 25 months: 27.7	At 25 months: 24.6	-
2014	Ascaso	72.1	72.9	21	18	MMSE	28.8	-	19.3
2014	Gharbiya	73.1	70.3	-	21	MMSE	28.2	-	22.2
2014	Polo	74.2	74.0	-	70	MMSE	-		16.0
2015	Bambo	74.0	76.4		56	MMSE	-	-	16.6
2015	Bambo	74.0	76.4		56	MMSE	-	-	16.6
2015	Bayhan	75.8	74.9	-	31	MMSE	29.3	-	17.4
2015	Feke	74.3	69.1	21	10	CDR	0.0	0.5	1.0 or 2.0
2015	Gao	74.7	72.1	26	25	MMSE	28.6	25.8	19.2
2015	Gunes	75.0	74.2	-	40	MMSE	-	-	21.9
2015	Jentsch	77.2	-	-	16	MMSE	-	-	24.0
2015	Oktem	75.4	70.2	35	35	MMSE	29.0	28.0	18.0
2015	Salobrar-Garcia	79.3	72.3	-	23	MMSE	28.2	-	23.3
2015	Shi	-	74.1	18[5]	-	MMSE	At baseline: 28.0 At 25 months: 28.0	At baseline: 27.0 At 25 months: 24.0	-
2016	Choi	76.8	73.8	26	42	MMSE	-	23.1	14.1

2016	Cunha	74.8	72.3	-	24	MMSE	29.1	-	17.0
2016	Garcia-Martin	75.3	74.8	-	150	MMSE	29.8	-	18.4
2016	Knoll	-	74.0	17	-	MMSE	29.0	27.0	-
2016	Pillai	65.8	65.1	21	21[4,6]	MoCA	26.6	21.2	16.0
2016	Trebbastoni	72.0	71.7	-	36	MMSE	At baseline: 28.6 At 12 months 28.5	-	At baseline: 22.7 At 12 months: 17.9
2017	Ferrari	71.26	68.3	29	37[7]	MMSE	-	26.6	16.6
2017	Mendez-Gomez	-	N/A	-	-	MMSE	27.8	-	-
2018	Bulut	74.2	72.6	-	26	MMSE	26.8	-	16.9
2018	Jiang	73.3	67.6	19	12	MMSE	29.5	25.7	19.9
2018	Lahme	68.0	66.1	-	36	MMSE	-	-	22.3
2018	Shao	74.0	68.0	24	25	MMSE	29.0	28.0	22.0
2018	Uchida	65.3	65.1	22	24[4,6]	MoCA	26.6	20.9	14.7
2019	Almeida	-	64.6	23	-	MMSE	-	27.9	-
2019	Cipollini	74.0	70.0	-	25	MMSE	29.2	-	24.2
2019	Haan	65.0	67.9	-	57	MMSE	29 .0	-	22.0
2019	Haan	65.4	60.6	-	48	MMSE	29.0	-	23.0
2019	Kim	74.2	73.6	14	16	MMSE	-	24.2	12.1
2019	Salobrar-Garcia	-	-	-	50	MMSE	28.6		19.9
2019	Sung	65.3	64.7	-	74[4]	MMSE	-	-	25.7[9]
2019	Tao	71.4	68.9	51	73	MMSE	28.7	28.3	19.7
2019	Yoon	72.8	69.2	37	39	MMSE	29.2	22.6	20.1
2019	Zhang	73.0	73.6	13	3	MoCA	27.1		20.3
2020	Ashimatey	-	68.4	-	15[8]	MoCA	23.0	-	20.0
2020	Criscuolo	-	73.1	54	-	MMSE	28.0	26.5	-
2020	Leyland	-	64.8	-	112[4]	MoCA	28.7	-	27.9
2020	Mammadova	-	N/A	N/A	N/A	MMSE	29.2	-	-
2020	Santangelo	70.9	69.4	37	43	MMSE	-	24.9	19.0

[1] Mean age of AD group reported only; [2] Other groups studied listed in footnotes; [3] Lewy Body Dementia; [4] Parkinson's Dementia; [5] Converted (converted from normal cognition to MCI or MCI to dementia); [6] non-AD dementia; [7] Frontotemporal Dementia; [8] Cognitively abnormal; [9] Dementia

Table 3. Summary of QUADAS score of the 47 include studies.

Year	Author	RS[1]	CSC[2]	ARS[3]	DPB[4]	PVB[5]	DVB[6]	IB[7]	ITE[8]	RSE[9]	ITRB[10]	RSRB[11]	CRB[12]	UTRR[13]	WE[14]	Total
2001	Parisi	N	N	Y	U	U	U	Y	Y	N	U	U	Y	Y	N	5/14
2006	Iseri	N	Y	Y	Y	Y	Y	Y	Y	N	U	U	Y	Y	Y	10/14
2011	Kesler	N	Y	Y	U	Y	Y	U	U	N	Y	Y	Y	Y	Y	9/14
2013	Kirbas	N	Y	Y	U	Y	Y	Y	N	N	U	U	Y	Y	Y	8/14
2013	Moreno-Ramos	N	Y	Y	Y	Y	Y	Y	Y	N	U	U	Y	Y	Y	10/14
2013	Shen	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2014	Ascaso	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	11/14
2014	Gharbiya	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	13/14
2014	Polo	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2015	Bambo	N	Y	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	Y	10/14
2015	Bambo	N	Y	Y	Y	U	Y	Y	Y	Y	U	U	Y	Y	Y	10/14
2015	Bayhan	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2015	Feke	N	Y	Y	U	Y	Y	Y	Y	N	U	U	Y	Y	Y	10/14
2015	Gao	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2015	Gunes	N	Y	Y	Y	Y	Y	Y	N	N	U	U	Y	Y	Y	9/14
2015	Jentsch	N	Y	Y	U	U	Y	Y	Y	Y	U	U	Y	Y	Y	9/14
2015	Oktem	N	N	Y	Y	Y	Y	Y	N	Y	U	U	Y	Y	Y	9/14
2015	Shi	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2015	Solabrar-Garcia	N	Y	Y	U	Y	Y	Y	Y	N	U	U	Y	Y	Y	9/14
2016	Choi	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	12/14
2016	Cunha	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2016	Garcia-Martin	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2016	Knoll	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	12/14
2016	Pillai	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2016	Trebbastoni	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2017	Ferrari	N	Y	Y	U	Y	Y	Y	Y	N	U	U	Y	Y	Y	9/14
2017	Mendez-Gomez	N	N	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	10/14
2018	Bulut	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2018	Jiang	N	Y	Y	U	Y	Y	Y	Y	N	U	U	U	N	N	6/14
2018	Lahme	N	Y	Y	U	Y	Y	Y	Y	N	U	U	Y	Y	Y	9/14
2018	Shao	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	11/14
2018	Uchida	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2019	Almeida	N	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	12/14
2019	Cipollini	N	Y	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	Y	10/14
2019	Haan	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2019	Haan	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2019	Kim	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2019	Solabrar-Garcia	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14

2019	Sung	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2019	Tao	N	Y	Y	N	Y	Y	Y	Y	N	U	U	Y	Y	Y	9/14
2019	Yoon	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2019	Zhang	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2020	Ashimatey	N	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12/14
2020	Criscuolo	N	Y	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	Y	10/14
2020	Leyland	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2020	Mammadova	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2020	Santangelo	N	Y	Y	U	Y	Y	Y	Y	N	U	U	Y	Y	Y	9/14

Y: Yes (green); N: No (red); U: unknown (yellow)

[1]Representative spectrum, [2]Clear selection criteria, [3]Accurate reference standard, [4]Disease progression bias, [5]Partial verification bias, [6]Differential verification bias, [7]Incorporation bias, [8]Index test execution well described, [9]Reference standard execution well described, [10]Index test review bias, [11]Reference standard review bias, [12]Clinical review bias, [13]Uninterpretable results reported, [14]Withdrawals explained

Table 3. Associations between diagnosed dementia status (e.g., AD) and retinal function

Year	Author	Method	Areas of retina measured									
			RNFL	mRNFL	pRNFL	GCC	GC-IPL	MT	CT	VD	FAZ	Other
2001	Parisi	OCT	x	-	-	-	-	-	-	-	-	
2006	Iseri	OCT	x	-	-	-	-	✓	-	-	-	x[1]
2011	Kesler	OCT	x	-	-	-	-	-	-	-	-	
2013	Kirbas	SD-OCT	x	-	x	-	-	-	-	-	-	
2013	Moreno-Ramos	OCT	✓	-	-	-	-	-	-	-	-	
2013	Shen	OCT	✓	-	-	-	-	-	-	-	-	
2014	Ascaso	OCT	✓	-	-	-	-	x	-	-	-	
2014	Gharbiya	SD-OCT	-	-	x	-	-	-	x	-	-	x[2]
2014	Polo	OCT	x	-	-	-	-	-	-	-	-	
2015	Bambo	OCT	-	-	?	-	-	-	-	-	-	x[3]
2015	Bayhan	SD-OCT	-	-	-	✓	-	-	x	-	-	
2015	Feke	1. Laser Doppler retinal blood flow measurements 2. OCT	-	-	-	-	-	-	-	-	-	✓[4]
2015	Gao	OCT	-	-	x	-	-	-	-	-	-	
2015	Gunes	SD-OCT	-	-	x	-	-	-	-	-	-	
2015	Jentsch	OCT and FLIO	-	-	x	-	-	-	-	-	-	?[5]
2015	Oktem	OCT	✓	-	-	-	-	-	-	-	-	
2015	Salobrar-Garcia	OCT	-	?	x	-	-	-	-	-	-	✓[1, 6]
2015	Shi	OCT	✓	-	-	-	-	-	-	-	-	
2016	Choi	OCT	-	-	x	-	?	?	-	-	-	
2016	Cunha	OCT	-	✓	✓	✓	✓	✓	-	-	-	✓[7]
2016	Garcia-Martin	OCT	✓	-	-	✓	-	-	-	-	-	
2016	Knoll	SD-OCT	-	-	?	-	-	-	-	-	-	
2016	Pillai	SD-OCT	x	-	-	-	-	-	-	-	-	
2016	Trebbastoni	SD-OCT	-	-	✓	-	-	-	-	-	-	
2017	Ferrari	OCT	-	-	x	-	AD ✓ MCI and FTD x	-	-	-	-	
2017	Mendez-Gomez	SD-OCT	-	-	?	-	-	-	-	-	-	
2018	Bulut	OCTA	-	-	-	-	-	-	✓	✓	✓	x[8] x[9]
2018	Jiang	1. OCTA	-	-	-	-	-	-	-	-	-	?[10]

		2. OCT										
2018	Lahme	OCTA	-	-	-	-	-	-	-	-	-	x[11]
2018	Shao	SD-OCT	✓	-	-	-	✓	-	-	-	-	
2018	Uchida	OCT	-	-	-	-	-	-	-	-	-	✓[12]
2019	Almeida	SS-OCT	-	x	✓	✓	✓	?	-	-	-	
2019	Cipollini	SD-OCT	-	-	x	x	-	x	-	-	-	
2019	Haan	SD-OCT	-	-	x	-	-	x	-	-	-	
2019	Haan	1. SD-OCT 2. OCTA	-	-	-	-	-	-	x	x	x	
2019	Kim	OCT	?	-	-	-	?	✓	-	-	-	
2019	Salobrar-Garcia	OCT	-	-	✓	-	-	✓	-	-	-	
2019	Sung	SD-OCT	-	-	x	-	✓	✓	-	-	-	x[13]
2019	Tao	OCT	-	-	x	x	-	-	-	-	-	
2019	Yoon	1. OCTA 2. SD-OCT	✓	-	-	-	✓	-	-	?	x	x[14] ?[15]
2019	Zhang	1. OCT 2. OCTA	-	-	-	-	-	-	-	?	-	? [16] x[17]
2020	Ashimatey	OCTA	-	-	-	-	-	-	-	✓	-	
2020	Criscuolo	1. SD-OCT 2. OCTA	x	-	-	x	-	-	-	-	-	
2020	Leyland	SD-OCT	-	-	-	-	-	✓	-	-	-	
2020	Mammadova	SD-OCT	✓	-	-	-	-	-	-	-	-	
2020	Santangelo	OCT	x	-	-	-	-	✓	-	-	-	

[1] Foveal thickness; [2] Retinal CSF thickness;3 Retinal haemoglobin levels; [4] Retinal blood flow; [5] T2, α2 and Q2 in ch2; [6] Macular volume; [7] GCL++; [8] Choroidal flow rate; [9] Outer retinal flow rate; [10] Superficial vascular plexus (SVP), Deep vascular plexus (DVP) and Total retinal vascular network (RVN); [11] Flow density; [12] Retinal pigment epithelium (RPE); [13] Central foveal thickness (CFT); [14] Central subfield thickness (CST); [15]Perfusion Density (PD); [16] Vessel length density (VLD); [17] Adjusted flow index (AFI);

Key:

✓	Correlation identified
x	No correlation identified
-	Not specified

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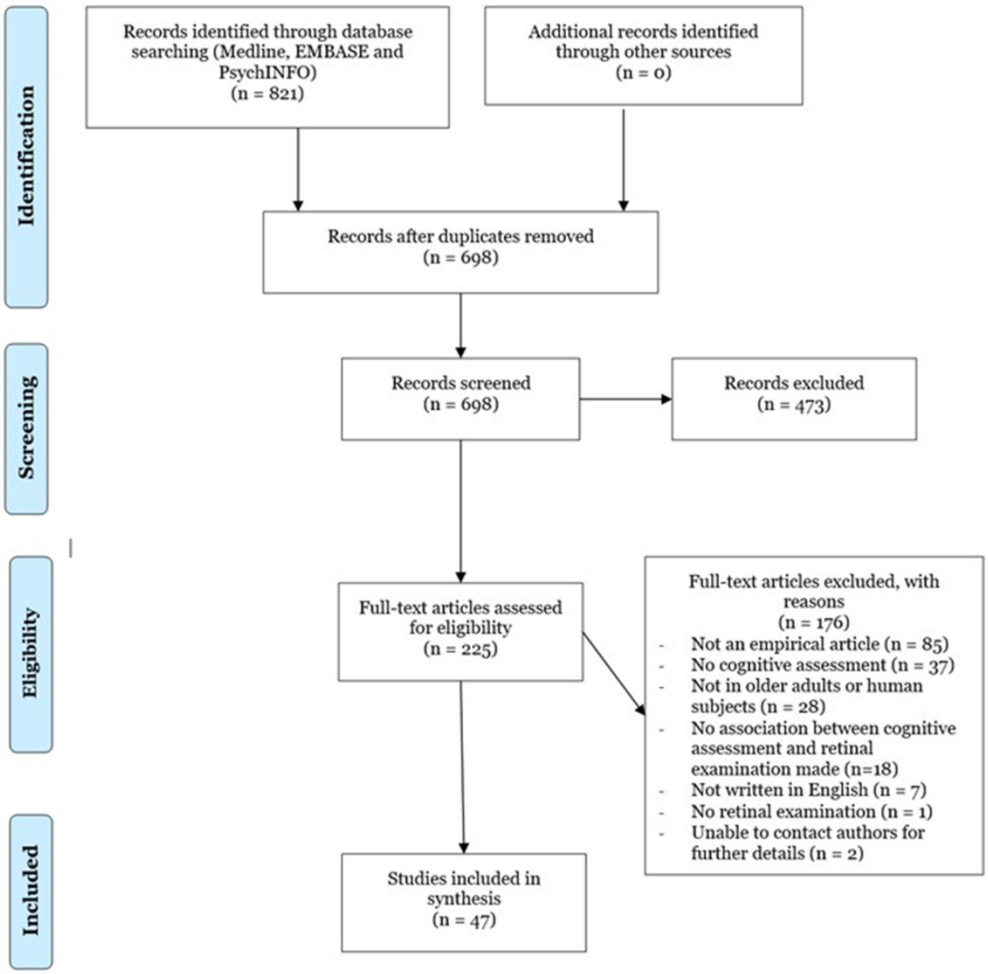

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart describing the process of study selection.

184x182mm (300 x 300 DPI)

Supplementary Appendix S1

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 – 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3 – 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6 – 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6 – 7

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	15 – 19
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	22 – 23
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	(a) 20 – 21 (b) 24 – 26
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10 – 14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

Supplementary Appendix S2

Additional Methods

Search strategy used in Medline database

(1) "Diagnostic techniques, ophthalmological/ or electroretinography/ or eye movement measurements/ or electronystagmography/ or electrooculography/", (2) "Tomography, Optical Coherence/", (3) "Optical coherence tomography.ti,ab.", (4) "(eye-track* or eye track*).mp.", (5) "Retina* exam*.ti,ab.", (6) "Ophthalmic assessment*.ti,ab.", (7) "1 or 2 or 3 or 4 or 5 or 6", (8) "Exp Retina/", (9) "Retina*.ti,ab.", (10) "8 or 9", (11) "7 and 10", (12) "Exp Dementia/", (13) "(dementia or cognitive impairment*).ti,ab.", (14) "12 or 13", and (15) "11 and 14"

Supplementary Table 1. Definitions of terminology used in the included studies

Terminology	Number of Articles that Utilised these Terms	Definition	Reference(s)
Optical Coherence Tomography (OCT)	41	Non-invasive technique to acquire high resolution, cross-sectional images of the retina	Almeida 2019
SD-OCT	18	Uses a light source with a longer-wavelength to promote deeper tissue penetration. It detects light echoes through an interferometer with a spectrometer.	Adhi 2013
SS-OCT	1	Measures light echoes using photodetectors, thus improving the signal quality in deep tissue to enhance choroid visualisation.	Adhi 2013
Fluorescence Lifetime Imaging Ophthalmoscopy (FLIO)	1	Measures the autofluorescence intensity emitted by endogenous fluorophores contained within the retina to determine retinal metabolic activity.	Dysli 2017; Jentsch 2014
Laser Doppler Retinal Blood Flow	1	Measures the retinal blood flow rate, centreline blood speed and blood column diameter in a major temporal retinal vein. As the vein with the largest diameter drains the largest portion of the total retinal blood flow, the blood flow measured within this retinal vein will be representative of total retinal blood flow.	Feke 2015
Alzheimer's dementia (AD)	37	Most common form of dementia characterised by progressive deterioration in cognition, executive functioning, learning and episodic memory	Gao 2015
Mild cognitive impairment (MCI)	19	Preclinical phase of AD characterised by cognitive decline that is significant for their	Gao 2015; Almeida 2019

		age but does not compromise functioning or activities of daily living	
Choroid	4	Vascular layer located between the sclera and retina of the eye which supplies oxygen and nutrients to the outer third of the retina, retinal pigment epithelium and part of the optic nerve.	Tan 2017
Retinal pigment epithelium (RPE)	1	Single layer of pigmented, cuboidal cells which regulates the transport of nutrients, ions, and water, absorbs scattered light and partakes in phagocytosis of shed photoreceptors.	Sparrow 2010
Outer nuclear layer of the retina (ONL)	1	Contains cell bodies of photoreceptors, the rods and cones	Balasubramaniam 2014
Outer plexiform layer (OPL)	2	Synapse between the cells located in the INL (bipolar and horizontal cells) and ONL (rods and cones) occurs in the OPL.	Kolb 1995
Inner nuclear layer of the retina (INL)	2	Composed of the cell bodies of bipolar, horizontal, interplexiform, amacrine and Müller cells, and occasionally displaced ganglion cells	Balasubramaniam 2014
Ganglion cell inner plexiform layer (GC-IPL)	10	Comprised of the dendrites and cell bodies of retinal ganglion cells	Öztürker 2016
Ganglion cell complex (GCC)	11	Composed of the retinal nerve fibre layer (RNFL), ganglion cell layer (GCL) and inner plexiform layer (IPL)	Öztürker 2016
Retinal nerve fibre layer (RNFL)	25	Comprised of nonmyelinated retinal ganglion cell axons that form the optic nerve	Shi 2019
Macula	17	Central, oval-shaped region of the retina comprising of a highest density of cone photoreceptions which is responsible for visual acuity	Lima 2016
Foveal Avascular Zone (FAZ)	6	Central region of the fovea, characterised by an absence of blood vessels, rods, inner retinal tissue and peak cone density. The fovea is the central area of the macula.	Chui 2012

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Association between retinal markers and cognition in older adults: a systematic review

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ABSTRACT

Objectives 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.

Design Systematic review of peer-reviewed empirical articles investigating the association of retinal markers in assessing cognitive impairment.

Data sources Three electronic databases, Medline, PsychINFO, and EMBASE were searched from inception until March 2022.

Eligibility criteria All empirical articles in English investigating the association between retinal markers and cognition in humans aged ≥ 65 years using various retinal scanning methodologies were included. Studies with no explicit association between retinal scanning findings and cognition were excluded. Risk of bias was assessed using the QUADAS Tool.

Data extraction and synthesis Data extraction was conducted by two authors (VJ, RS) and reviewed by another author (JS). Results were synthesised and described narratively.

Results Sixty-seven eligible studies examining 6,815 older adults were included. Majority of studies were cross-sectional (n=60; 89.6%). Optical coherence tomography (OCT) was the most commonly used retinal scanning methodology to measure the thickness of retinal nerve fibre layer, the ganglion cell complex, choroid, and macula. 51.1% of cross-sectional studies using OCT reported an association between the thinning of at least one retinal parameter and poor cognition. Longitudinal studies (n=6) using OCT also mostly identified significant reductions in retinal nerve fibre layer thickness as associated with cognitive decline. Study quality was overall moderate.

Conclusion Retinal nerve fibre layer thickness is associated with cognitive performance and therefore may have the potential to detect cognitive impairment in older adults. Further longitudinal studies are

required to validate our systematic review synthesis and understand underlying mechanisms before recommending implementation of OCT as a dementia screening tool in clinical practice.

PROSPERO registration number: CRD42020176757

Key words: Retinal scanning, cognitive screening tests, cognitive impairment, optical coherence tomography, ganglion cell complex, choroid, macula

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review provides an in-depth evaluation of the relationship between retinal markers identified using various scanning methods and early detection of cognitive impairment in older adults to inform future research and clinical practice.
- This review includes a substantially larger number of empirical articles than previous systematic reviews, as well as the inclusion of three longitudinal studies to establish cause-and-effect relationships between retinal scanning and cognitive performance.
- The included studies were methodologically rated using appropriate tools.
- Majority of the included studies are cross-sectional and have used different retinal imaging devices and therefore it is not possible to compare measurements across devices.

INTRODUCTION

The last decade has seen a substantial increase in research focused on the identification, development, and validation of diagnostic and prognostic retinal biomarkers for dementia, particularly Alzheimer's disease (AD)[1]. AD is the most common form of dementia and affects 60-70% dementia cases. There is no cost-effective, clinically established early AD diagnostic marker. Retinal biomarkers may be advantageous because they are cost and time efficient, can be assessed non-invasively, and present a minimal degree of patient risk and a high degree of accessibility[2]. With one in ten Australians aged over 65 with dementia and 50 million people affected worldwide[3], cognitive impairment is a prevalent issue in our ageing population. The worldwide cost of dementia is estimated to be US$818 billion in 2015[3], and therefore, early detection of AD that could reflect the deposition of amyloid-beta (Aβ, a pathological hallmark feature found in AD brain) in the brain and the resulting cognitive impairment will be of high economic benefit. It is now evident that deposition of Aβ in the brain occurs 15-20 years earlier than the onset of cognitive decline[4]. Early diagnosis could help develop preventive or delaying strategies, lower mortality rates, allow timely access to medication, improve quality of life, stabilise cognitive decline, and/or minimise preventable hospital visits[5].

As the retina forms as an outgrowth of the brain during embryological development, retinal cells reflects that of the brain and spinal cord[6]. Therefore, retinal changes may reflect brain changes and may allow detection of dementia before symptoms manifest, unlike traditional neuropsychological screening tests which primarily detect cognitive impairment following presentation of warning signs, such as memory loss[7]. Apart from the effects of normal ageing, marked inter-individual differences in the rate of cognitive decline indicate that other age-associated pathologies may be involved, such as macro- or microvascular disease.

Several pathobiological markers have been suggested as potential predictors of cognitive dysfunction and of these, retinal microvascular signs may offer the most promise. A study by Ong *et*

al. found an association between retinal neuronal damage and grey matter atrophy, which indicates that retinal changes may reflect cerebral neurodegenerative changes and thus, predict cognitive decline[8]. Yoon *et al.* demonstrated that cerebral ventricular enlargement due to cerebral atrophy seen characteristically in AD as indicated by magnetic resonance imaging studies[9], is mirrored in retinal microvasculature changes as measured through retinal scanning tools, such as optical coherence tomography (OCT). OCT is a non-invasive technique that acquires high-resolution, cross-sectional images of the retina and is the most common tool used clinically to assess neurodegenerative changes in the retina[2]. The OCT devices often vary, with some users adopting swept-source OCT (SS-OCT) devices while others used spectral-domain OCT (SD-OCT), which can impact light source, acquisition speed, and resolution[10]. Therefore, as a common tool in clinical practice, retinal OCT scanning could be used routinely as an accessible alternative to brain imaging that is both, faster to administer and less stressful to the patient with the potential to measure and quantify cognitive decline.

A recent cross-sectional observation study has demonstrated the value of OCT in detecting dementia, identifying OCT measurements of the macula as a "useful diagnostic biomarker of cognitive function"[11] (pg. 117). However, there has been conflicting evidence on the effectiveness of ophthalmic scanning in mild cognitive impairment (MCI), the precursor of dementia. A significant correlation between OCT measurements in the inner retinal layers with cognitive screening assessments[12] has been reported, although Ito *et al*. saw no changes on OCT in MCI individuals, recommending further research[11 13].

Recent systematic reviews have attempted to analyse the association between cognitive functioning and retinal nerve fibre layer thickness (RNFL)[12 14]. Thomson *et al.* conducted a systematic review and meta-analysis of 17 articles and found a statistically significant reduction in RNFL in both AD and MCI patients when compared to healthy controls[12]. This study identified OCT as a potential diagnostic tool in assessing cognitive impairment, particularly for AD and MCI syndromes. However, the study did not consider the direct comparisons of RNFL thickness to that of cognitive domains

assessed using neuropsychological assessments and which the respective studies included in the review would have used to make a diagnosis of AD and MCI. Similarly, in another meta-analysis study, Wang *et al.* evaluated the relationship of peripheral RNFL thickness in AD and MCI from 19 studies and found a progressive reduction in total RNFL thickness, particularly in the inferior and superior quadrants, suggesting RNFL thickness as a candidate biomarker for early detection of AD[14]. However, both reviews conducted in 2015 appraised only a small number of cross-sectional studies with no consideration of cognitive impairment in forms other than AD and MCI. The role of the retinal layers other than the nerve fibre layer such as the ganglion cell complex (GCC) thickness and macular thickness as biomarkers in the assessment of cognitive impairment were also not evaluated.

More recent systematic reviews and meta-analysis studies have reported similar findings as per the aforementioned 2015 reviews. The study by Chan *et al.*[15] identified 30 cross-sectional studies to report that the thickness of ganglion cell and inner plexiform layer (GC-IPL), GCC, macular volume was significantly different between AD and the control group. AD group also showed reduced peripapillary RNFL (pRNFL) thickness and choroidal thickness[15]. In another systematic review and meta-analysis study by Mejia-Vergara *et al.*[16], 15 studies that included MCI individuals only were included to report that pRNFL and macular GCL-IPL thinning with reduced macular volume was prominent in MCI when compared to the controls. A large effect size was observed for reduced macular thickness in MCI individuals with significant heterogeneity for macular thickness. The study concluded that more standardised and longitudinal studies were needed to support the role of OCT in identifying reduced retinal layer and/or macular thickness as a biomarker for MCI due to AD[16]. The study by Ge *et al.*[17] was broader in scope as the authors included retinal markers *per se* and not just the RNFL thickness assessed using OCT. The study aimed to identify signature retinal markers in AD, MCI and preclinical AD population. Of the 126 studies included in this systematic review and meta-analysis, the authors reported reduced pRNFL, subfoveal choroid and total macular thickness in the AD and MCI groups when compared to the control group. Overall, the study concluded that structural

retinal changes such as RNFL, choroidal thinning; optic nerve degeneration and possibly Aβ deposition; vascular retinal changes such as blood flow, vessel density and morphology and electrophysiological changes showing dysfunction of the retinal layers could be helpful markers in the diagnosis, prognosis and/or risk assessment for AD, MCI and/or preclinical AD population[17]. While the study findings are broad and inconclusive, it gives an indication of studies that have explored retinal markers other than the RNFL and reported an association in AD, MCI and/or preclinical AD population.

Despite the aforementioned review studies, the evidence is limited due to the small sample sizes and comparison of retinal markers directly to AD and/or MCI diagnosis, making the findings inconclusive as it underrepresents the target population and does not reflect the associated cognitive domains. Another limitation is the extensive exclusion criteria and high comorbidity rate in the older adult population with the prevalence of concomitant eye and systemic disease such as glaucoma and diabetes respectively making them unsuitable candidates. Nevertheless, retinal scanning may be valuable in monitoring disease progression and response to treatment.

To date, no systematic review and/or meta-analysis study has analysed the specific relationship between retinal markers and cognitive screening tests that assess the functions of respective cognitive domains. This systematic review aims to summarise the available evidence on the use of retinal markers using various retinal scanning methodologies in older adults as an alternative to comprehensive cognitive assessments used in dementia diagnosis and provide directions for future research and clinical practice.

METHODS

We drafted a protocol for this review '*a priori*' and inclusion criteria were developed prior to commencing the search. This review was registered on PROSPERO (CRD42020176757). We report

according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines, and a checklist of PRISMA items is presented in the online supplementary data S1.

Ethics approval statement

We used publicly accessible documents as evidence and did not collect individual personal information from participants. As such it was not necessary to seek an institutional ethics approval before commencing our review.

Search strategy

A search strategy was developed using medical subject headings (MeSH) and key search terms related to cognitive impairment and retinal scanning. Studies were identified through Medline (1806 – 2022), PsycINFO (1905 – 2022) and EMBASE (1974 – 2022) databases. An updated literature search was undertaken prior to the final analysis to ensure up-to-date and relevant articles were included. Date last searched was 17 March 2022. The search strategy (available in online supplementary data S2) was deliberately broad in an effort to gather all eligible studies and was developed in collaboration with the clinical librarian and reviewed by the project team. Reference lists of all included studies were hand-searched for additional records. This search strategy was then adapted to the other databases namely, PsychINFO and EMBASE.

Eligibility Criteria

All peer-reviewed empirical articles in English and using human subjects, including but not limited to cross-sectional, population-based, case-control and longitudinal studies. Studies with no explicit association between cognition and findings on retinal scanning were excluded.

Participants: Inclusion criteria comprised of adults aged 65 years and over with diagnosed cognitive impairment of any form and severity, including AD and mild cognitive impairment, and a control group of cognitively healthy participants. The study was limited to subjects aged over 65 as

diagnosis of dementia is more prevalent in this age group. Exclusion criteria includes those with pre-existing ophthalmological, metabolic, cardiovascular, cerebrovascular, psychiatric, or other disease that could affect the visual field or neurological system. Other exclusion criteria include previous intraocular surgery or trauma, the inability of the participant to collaborate sufficiently to perform an OCT scan, and/or use of medications that could affect visual function.

Types of index and reference standard tests: All participants in the chosen studies were screened using standard, traditional cognitive screening tests such as Mini-Mental State Examination (MMSE) and retinal scanning using OCT, OCT-Angiography (OCTA) or another technique (available in online supplementary data S2).

Controls or comparators: Cross-sectional and cohort studies will not have a comparator, but a case-control study should have an age- and sex-matched control group of cognitively healthy participants.

Data Extraction

The search results from Medline, PsychINFO and EMBASE were exported to Microsoft Excel sheet and duplicates were removed. Two authors (VJ and JS) reviewed titles, abstracts and full-text papers for eligibility. Authors resolved disagreement by discussion or, where necessary, a third author (JC) offered their view. Extraction was completed (VJ) using a standardised data sheet that was piloted with three papers and revised. All data extraction was verified by JS, and disagreement was resolved via discussion. Extracted data included, study design, participant demographics (including mean age, country of study), sample size, method of and parameters measured on retinal scanning, measure of cognitive function, type and degree of cognitive impairment, and relevant statistical data.

Risk of bias assessment

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool[18] was used as it assesses the quality of studies looking at diagnostic accuracy. This covers spectrum, disease

progression, partial verification, differential verification, incorporation and review bias, and incomplete data outcomes e.g. withdrawals. Three reviewers (VJ, RS, JS) partook in the studies' quality assessment and any discrepancy between reviewers was resolved through discussion and if an agreement could not be reached, a third individual was consulted (JC).

Statistical Analysis

Owing to a high degree of heterogeneity that exists between studies, including study designs, population type, measures of retinal scanning and cognition, a meta-analysis of study results was not possible. A descriptive synthesis approach was utilised.

Patient and public involvement

No patient involved.

RESULTS

Study design and population

The search identified 821 articles, of which 67 studies were eligible (see **Figure 1**). Most studies included were cross-sectional (60/67; 89.5%), with a few case-controls (2/67; 3.0%) and longitudinal (6/67; 9.0%) studies (**Table 1**). Longitudinal studies had a range of two to 12-year follow-ups. Studies were mostly conducted in these following countries: USA (13/67; 19.4%), China (9/67; 13.4%), Spain (9/67; 13.4%) and Italy (7/67; 10.4%). The type of cognitive impairment varied between studies with 35 (52.2%) articles looking only at Alzheimer's Dementia (AD) and 9 (13.4%) at mild cognitive impairment (MCI), and 23 (34.3%) for both groups. Across all studies, the mean age range was 70.9 years for controls, 72.4 years for AD, and 73.0 years for MCI. The ratio of males to females was approximately one-to-one across all studies, with a slight female predominance.

Assessment of retinal abnormalities

Retinal scanning was performed using several techniques (**Table 1, Supplementary Material**). The most common method used was OCT (40/67, 59.1%); SD-OCT (17/67); SS-OCT (1/67)) followed by OCTA (18/67; 26.9%) then fundus photography (3/67; 4.5%), Fluorescence Lifetime Imaging Ophthalmoscopy (FLIO) (1/67; 1.5%) and laser Doppler flowmetry (1/67; 1.5%). OCT is a non-invasive method that obtains cross-sectional images of the retina and calculates the thickness of all retinal layers including the nerve fibre layer, ganglion cell complex; choroid and macula[10]. In 12 (17.6%) studies, the Early Treatment of Diabetic Retinopathy Study (ETDRS) macular map sectors were used to divide the macula into nine segments to produce a retinal thickness map. The retinal nerve fibre layer (RNFL) thickness was calculated globally, and across either four or six segments.

OCTA acquires images of retinal vasculature to calculate perfusion and vascular density (VD), and foveal avascular zone (FAZ) area[6] whereas laser Doppler flowmetry calculates the retinal blood flow rate[19]. FLIO measures the autofluorescence intensity emitted by endogenous fluorophores contained within the retina to calculate retinal metabolic activity[20 21]. Fundus photography was also employed to obtain detailed images of the fundus within a 50-degree field of view of the macula, and the optic nerve head to evaluate retinal vasculature[22].

As part of the work-up, a full ophthalmological scan was performed in 28 (59.6%) studies prior to retinal imaging, including assessment of best-corrected visual acuity (BCVA), dilated fundus scan, slit lamp scan of the anterior segment of the eye, intraocular pressure (IOP) measurement, and anatomical ocular measurements with optical biometry. Neuroimaging was performed in 20 (29.4%) studies to exclude alternate diagnoses, and nine (19.1%) studies used standard blood tests to rule out reversible causes of dementia. A comprehensive neuropsychological examination assessing cognitive performance was part of the initial work-up in 11 (23.4%) studies.

Assessment of cognitive function and impairment

A summary of the assessment of cognitive function is shown in **Table 2**. Cognitive function was always measured using standard cognitive screening tools, with the most popular one being as Mini Mental State Examination (MMSE) (59/67; 88%), followed by Montreal Cognitive Assessment (MoCA) (9/67; 13.4%), the global clinical dementia rating score (CDR) (3/67; 4.5%) and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) (2/67; 3%). These screening tests evaluate various cognitive domains including, orientation, attention, executive functions, memory, language, visuospatial skills, abstract thinking, and calculations. Cognitive screening tests were conducted by either neurologists, psychologists, physicians, or trained research associates.

AD was diagnosed using DSM-IV criteria, National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[23] criteria or generally through a combination of both approaches. The most common method to diagnose MCI was through the Peterson's criteria[24] which identifies whether all five criteria are satisfied including, memory complaint corroborated by an informant, objective memory decline, normal general cognitive function, normal functional activities, and absent dementia diagnosis.

Association between cognition and retinal measurements

Half of the studies found a significant correlation between RNFL (9/17, 52.9%) and GC-IPL thinning (6/11, 54.5%) with impaired cognition (**Table 3**). Some studies found a significant correlation between macular (14/30, 46.7%), macular retinal nerve fibre layer (mRNFL) (3/5, 60.0%), GCC (8/19, 42.1%), choroidal thickness (CT) (4/9, 44.4%) and pRNFL thinning (5/21, 23.8%) with cognitive performance. These findings did not vary significantly between different OCT devices. Measures of retinal vascular structures using OCTA identified a correlation between VD (7/14, 50.0%), and FAZ area (3/9, 33.3%) with cognitive impairment.

Risk of Bias Assessment

Risk of bias of the 67 studies are provided in **Table 4**. For over half the studies (39/67, 58.2%) it was unclear whether the index test results were interpreted without the knowledge of the reference standard, and vice versa (37/67, 55.2%). This could contribute to review bias, and thus impact the diagnostic accuracy of the respective clinical tool. The time period between conducting the reference standard and index test was unclear in 17 (25.3%) studies, suggesting that the influence of disease progression bias cannot be excluded. All 67 studies were not representative of the target population as patients with comorbidities that may affect the retina, including diabetes mellitus and hypertension were excluded. This lack of generalisability may interfere with the implementation of retinal scanning in clinical practice. However, the majority of studies (95.5%) provided a clear selection criterion and all studies utilised an accurate reference standard. Partial verification, differential verification, incorporation, and clinical review bias were minimal across the included studies. Considering this, the overall risk of bias was moderate, and findings should be interpreted with caution.

DISCUSSION

Our review evaluated the relationship between retinal scanning methods and early detection of cognitive impairment in older adults to inform future clinical practice. Over 50% of the studies using OCT identified an association between the thinning of at least one retinal area and cognitive impairment. The future of retinal imaging as a clinically useful tool for measuring cognition in older adults is considered.

Within ophthalmology, retinal imaging devices are primarily used in the diagnosis of retinal disease as well as serial monitoring of retinal conditions such as age-related macular degeneration and response to treatment[10]. We identified two main retinal scanning methods, OCT and OCTA in this review, with a more sensitive response from OCT. OCTA was primarily used to measure and evaluate retinal vasculature, but measures of retinal thickness via OCT was considerably more effective in

detecting cognitive impairment. Studies using OCTA techniques have resulted in mixed findings[25]. This may be due to the varied vessel distribution and morphology, including vessel size and number of anastomoses between participants. The lack of uniformity in vessel size may affect vessel density calculations, as the smaller surface area of capillaries may contribute to a more sensitive measure of perfusion compared to larger vessels[23]. Additionally, fewer anastomoses within a vessel network contributes to a higher risk of vascular dysfunction[23]. Considering this wide variability in vascular network structure between individuals, OCTA may be suitable for detecting later stages of dementia but may not be reliable in detecting the transition between age-related changes and MCI. Furthermore, not all participants with MCI will convert to dementia, some may revert to normal cognition, thus affecting the accuracy of the results[23]. Retinal layer thickness as measured through OCT does not vary as extensively as OCTA and thus, serves as a suitable alternative for the early detection of dementia.

Although OCT devices have been utilised for the past two decades, there has been no consistent retinal area that is strongly associated with the cognitive function of older adults. This is consistent across all types of OCT devices. Our findings indicate that thinning of the RNFL and pRNFL may be associated with poorer cognitive function, however, within the last decade, studies have found more varied results for pRNFL, with only six (out of 21, 28.6%) studies identifying an association[13 26-30]. On the other hand, 45.5% of studies using OCT devices to measure RNFL thickness have identified a positive correlation with cognitive impairment, although studies with larger sample sizes (e.g., Sanchez *et al.*[31], 930; Van De Kreeke *et al.*[32], 298) found no significant correlation. Indeed, researchers have failed to consistently identify a correlation between retinal scanning and cognitive impairment, for example two recent articles identified an association[23 24] with RNFL whereas two articles did not[33 34]. This lack of consistency is reflected across all retinal areas and the discrepancies may in part be ascribed to differences in sample size, the severity of cognitive impairment, and the OCT technology used in various devices.

Mean RNFL and macular thickness maybe largely dependent on the type of OCT device used[35]. The variety of devices identified in this review may thus affect the consistency of results across studies. Moreover, as MCI represents a transition towards dementia, reductions in pRNFL and macular thickness, if any, are likely to be subtle, perhaps even within the normal range, when compared with healthy age-matched control subjects. Furthermore, these cross-sectional studies present data at a single point in time after the participant has been diagnosed with cognitive impairment. The lack of baselines measures from cognitively healthy participants creates difficulty in detecting subtle changes in their cognitive performance. Therefore, our findings need to be interpreted with caution.

The inconsistencies between studies can also be attributed to the lack of sensitivity of cognitive screening tools, such as the MMSE which is largely used to assess cognition, but we know is ineffective in identifying cognitive impairment at its early stages[36]. Despite these mixed results, cross-sectional studies present data at a single point in time and therefore, the dynamic change in the relationship between retinal thickness and cognition is unable to be quantified. It seems therefore that with only limited evidence thus far, caution will be needed in interpreting the rate of change of an individual's RNFL thickness in terms of their cognitive status. Furthermore, given the physiological variations in RNFL thickness, single time-point measurements in individual participants are likely to have limited value.

Our review innovates by appraising six well-sized longitudinal studies[37-41] (sample size 78-427), to further establish cause-and-effect relationships between retinal scanning and cognitive deterioration. We found that OCT measurements of RNFL thickness including inferior quadrant RNFL thickness[37 39 40] and pRNFL thickness[38] was able to detect reductions in these areas over time, and was associated with decline in cognitive abilities such as impaired recall[37], immediate and delayed memory[37] and episodic memory[38]. Whilst cognitive decline was found to be associated with longitudinal reduction in inferior quadrant thickness[38], the association is less clear for other retinal regions around the GCC[42] and macular thickness[42]. Our results suggest the ability of OCT to

potentially detect longitudinal changes in RNFL thickness and declining cognition, although further longitudinal efforts need to be carried out to determine the true nature of cognitive decline with retinal changes.

A systematic review by Ding *et al.* [43] evaluated six studies and identified a positive relationship between retinal vascular signs, and information processing speed, verbal memory, and executive function. However, the lack of consistency between study findings due to differences in retinal scanning methodology, small sample size, and cognitive screening tools were recognised and limited interpretation. An updated review by Heringa *et al*[44] identified a moderately strong association between microvascular and cerebral changes, and dementia diagnosis across 32 studies. They concluded that although retinal vascular assessment can be incorporated into prediction models, only a minority of dementia cases were attributed to retinal vascular changes. These reviews support the potential role of retinal vascular changes in the pathophysiology of cognitive impairment but recommend the need for more prospective data. Our review adds to the existing literature by providing greater insight into the role of OCT in the early detection of cognitive impairment through measures of retinal layer thickness.

Our study has several limitations. First, participants in the included studies were not representative of the sample population and individuals with chronic conditions, such as diabetes mellitus, hypertension and neurological conditions were excluded. These comorbidities are common in the older population and affect the generalisability of our findings. Further studies including patients with these comorbidities are required to identify whether retinal scanning is a viable biomarker in cognitive impairment. Second, some studies were missing data in several domains, including global cognition scores or correlation metrics, which excluded their entry in the review and may compromise publication bias. 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 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. Third, our search strategy was very specific, and this may have excluded studies that were relevant to our review. Fourth, only sixteen (23.9%) studies evaluating OCTA were included in this review resulting in mixed findings. This may explain why other studies specifically assessing OCTA with a larger sample size may have identified a positive correlation[25]. 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.

Our study has some strengths. This is the first systematic review that has evaluated multiple retinal scanning tools across several forms of cognitive impairment. We reviewed extensively more empirical articles than previous systematic reviews[43 44], comprising of a larger, international sample and summarised the recent results of longitudinal studies, adding substantial insight.

Earlier diagnosis of dementia using non-invasive techniques will improve patient care, quality of life, disease management, and clinical outcome[5]. Cognitive screening tools currently used in routine clinical practice, such as MMSE are not sensitive in detecting cognitive impairment in its earlier stages, are time-consuming and can be stressful for the patient[36]. OCT is a sensitive alternative that provides a rapid assessment of the retina to detect changes consistent with cognitive impairment, such as RNFL thinning. Advances in OCT technology, especially the advent of Fourier-domain OCT (ED-OCT), and more recently SS-OCT, which improves acquisition speed and resolution of retinal images, will further make accurate quantitative segmented retinal layer analysis possible. Introducing OCT as part of the Medicare Benefits Schedule (MBS) could allow optometrists to additionally provide annual cognitive screening to older adults. This would enable earlier detection of cognitive impairment and thus the

provision of both pharmacological and non-pharmacological interventions to slow or stabilise disease progression[5].

In conclusion, whilst cross-sectional studies have inconsistently recognised a link between retinal scanning methods and cognitive impairment, recent longitudinal studies provide stronger evidence on the diagnostic utility of OCT in detecting a declining cognitive status. Further longitudinal studies should be conducted to corroborate these findings before retinal scanning can be introduced into clinical practice as a viable tool for detecting cognitive impairment. Studies using more sensitive cognitive screening tools are required to assess the viability of retinal measures as a biomarker in cognitive decline.

DECLARATIONS

CONTRIBUTORS

JS conceptualised the study and produced with VJ the first draft of the manuscript. BG reviewed the study design and provided feedback. JS and VJ devised the search strategy which was carried out by VJ. JS completed the blinded 5% review of abstracts with BG acting as arbitrator. VJ reviewed the remainder of the abstracts. JS and VJ carried out the full-text review, followed by the data extraction and quality assessment of included articles. VJ developed the initial frameworks with JS providing feedback. JS and RS conducted the full-text review and data extraction of an updated search in March 2022. JC contributed to identification of OCT machines and critical revisions. GL and TS provided essential write-up and feedback on early drafts. All authors contributed to critical revisions of subsequent manuscript drafts and approved the final submission.

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The authors declare that they have no conflicts of interest to disclose.

PATIENT CONSENT FOR PUBLICATION

Not required.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. The data are available upon request from the corresponding author (joyce.siette@westernsydney.edu.au)

FIGURES AND TABLES

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart describing the process of study selection.

Table 1. Characteristics of studies included in the systematic review (n=67).

Table 2. Study characteristics of cognitive assessment and score (n=67).

Table 3. Associations between diagnosed dementia status (e.g., AD) and retinal markers

Table 4. Summary of QUADAS score of the 67 included studies.

Table 1. Characteristics of studies included in the systematic review (n=67).

Year	Author	Country	Design	Areas of retinal measured											Sample size	Method
				RNFL	mRNFL	pRNFL	GCC	GC-IPL	MT/MV	CT	FAZ	VD	RVN	Other		
2001	Parisi[45]	Italy	CS	•											31	OCT
2006	Iseri[46]	Turkey	CS	•					•						29	OCT
2011	Kesler[47]	Israel	CS	•											78	OCT
2013	Kirbas[48]	Turkey	CS	•		•									80	SD-OCT
2013	Shen[37]	China	L	•											78	OCT
2014	Ascaso[49]	Spain	CS	•					•						90	OCT
2014	Gharbiya[50]	Italy	CS			•				•					42	SD-OCT
2014	Polo[51]	Spain	CS	•											140	OCT
2015	Bambo[1]	Spain	CS			•									112	OCT
2015	Bayhan[52]	Turkey	CS				•			•				•[1]	61	SD-OCT
2015	Feke[19]	USA	CS			•							•		52	Laser Doppler, OCT
2015	Gao[53]	China	CS			•			•						72	OCT
2015	Gunes[54]	Turkey	CC			•									80	SD-OCT
2015	Jentsch[21]	Germany	CS			•			•					•[2]	16	OCT, FLIO
2015	Oktem[55]	Turkey	CS	•											105	OCT
2015	Salobrar-Garcia[56]	Spain	CS		•	•									51	OCT
2015	Shi[57]	China	L	•											78	OCT
2016	Choi[42]	Korea	L			•		•	•						134	OCT
2016	Cunha[26]	Brazil	CS		•	•	•	•	•						48	OCT
2016	Garcia-Martin[58]	Spain	CS	•			•								225	OCT
2016	Knoll[59]	USA	CS			•		•	•						34	SD-OCT
2016	Pillai[60]	USA	CS	•			•		•						106	SD-OCT
2016	Trebbastoni[27]	Rome	CS			•									72	SD-OCT
2017	Ferrari[61]	Italy	CS			•		•							93	OCT
2017	Mendez-Gomez[38]	France	L			•									427	SD-OCT
2018	Bulut[6]	Turkey	CS							•	•	•	•		52	OCTA
2018	Jiang[62]	USA	CS					•			•		•		52	OCTA, OCT
2018	Lahme[63]	Germany	CS								•		•		74	OCTA
2018	Shao[64]	USA	CS	•				•							70	SD-OCT
2018	Uchida[65]	USA	CS											•[3]	124	OCT
2019	Almeida[13]	Brazil	CS		•	•	•	•	•						47	SS-OCT
2019	Cipollini[66]	Italy	CS			•	•		•						42	SD-OCT
2019	Haan[22]	Netherlands	CS			•	•		•					•[3]	142	SD-OCT
2019	Haan[67]	Netherlands	CS							•	•	•			86	FP, SD-OCT, OCTA
2019	Kim[68]	South Korea	CS	•				•	•						47	OCT
2019	Salobrar-Garcia[28]	Spain	CS			•	•		•					•[4]	90	OCT
2019	Tao[29]	China	CS			•	•								191	OCT
2019	Yoon[23]	USA	CS	•				•			•	•	•		209	OCTA, SD-OCT

2019	Zhang[69]	USA	CC			•	•		•		•	•	•		32	OCT, OCTA
2020	Ashimatey[70]	USA	CS									•			111	OCTA
2020	Chua[71]	Singapore	CS								•	•			90	OCTA
2020	Criscuolo[33]	Italy	CS	•			•				•	•			83	SD-OCT, OCTA
2020	Jindahra[72]	Thailand	CS	•				•							58	OCT
2020	Jorge[73]	Portugal	CS					•							41	OCT
2020	Karakahya[40]	Germany	RCT; L	•				•		•					93	OCT
2020	Lemmens[74]	Belgium	CS	•											39	OCT
2020	Mammadova[24]	USA	CS	•											20	SD-OCT
2020	Marquie[41]	Spain	L	•			•								129	OCT
2020	Mavilio[75]	Italy	CS	•			•								52	OCT
2020	Salobra-Garcia[76]	Switzerland	CS							•	•				32	OCT, OCTA
2020	Sanchez[31]	Spain	CS	•			•							•[3]	930	OCT
2020	Sen[77]	India	CS	•			•							•[3]	60	OCT
2020	Uchida[78]	USA	CS											•[3]	64	OCT
2020	Van De Kreeke[32]	Netherlands	CS	•			•	•				•			298	OCT, FP
2020	Wu[79]	China	CS								•	•			60	OCTA
2021	Biscetti[80]	Italy	CS				•	•			•	•			37	OCT, OCTA
2021	Janez-Garcia[30]	Spain	CS	•	•	•	•	•							43	OCT OCTA
2021	Li[81]	China	CS							•					71	OCT
2021	Mei[82]	China	CS	•			•					•			39	OCTA
2021	Robbins[83]	USA	CS	•				•		•					122	OCTA
2021	Robbins[84]	USA	CS							•					278	OCT
2021	Wang[85]	China	CS			•	•				•	•			158	OCTA, FP
2021	Wong[86]	Hong Kong	CS									•			40	OCTA
2021	Zabel[87]	Poland	CS	•		•	•	•				•		•[3]	108	SD-OCT OCTA
2021	Zhao[88]	China	CS		•										59	OCT
2022	Montorio[89]	Italy	CS	•			•					•			108	SD-OCT OCTA
			Total	29	5	23	22	17	14	9	12	15	6	9	6,415	

Design abbreviations: CC=case-control, C=cross-sectional, L=longitudinal, RCT=randomised controlled trial.

Retinal markers abbreviations: CSF=central subfield retinal thickness; CT= Choroidal thickness; FAZ=foveal avascular zone; FD, fractal dimension; GCC=macular ganglion cell complex; GC-IPL= ganglion cell-inner plexiform layer; mRNFL=macula retinal nerve fibre layer; MT/MV=macular volume/macular thickness; pRNFL=peripapillary retinal nerve fibre layer; RNFL= retinal nerve fibre layer; RVN=retinal vasculature network; VD=vascular/vessel density (including CC-VLD, choriocapillaris plexus vessel length density; CC-VPD, choriocapillaris plexus vessel perfusion density; DCP-VLD, deep capillary plexus vessel length density; DCP-VPD, deep capillary plexus vessel perfusion density; ICP-VLD, intermediate capillary plexus vessel length density; ICP-VPD, intermediate capillary plexus vessel perfusion density).

Footnotes: [1] Focal loss volume and global loss volume; [2] Time-resolved autofluorescence of the retina by FLIO; [3]Retinal thickness/volume, mean foveal thickness and juxtafoveal thickness; [4] [13]IPL, INL, OPL; retinal pigment epithelium (RPE) thickness.

Table 2. Study characteristics of cognitive assessment and score (n=67).

Year	Author	Mean age of individuals with AD[1]	Mean age of controls	No. of cognitively impaired subjects[2]		Measure	Mean cognitive score		
				MCI	AD		Controls	MCI	AD
2001	Parisi[45]	70.4	-	-	17	MMSE	23	-	16.4
2006	Iseri[46]	70.1	65.1	-	14	MMSE	29.4	-	18.5
2011	Kesler[47]	73.7	70.9	24	30	MMSE	-	28.1	23.6
2013	Kirbas[48]	69.3	68.9	-	40	MMSE	28.7	-	21.2
2013	Shen[37]	-	74.1	18[5]	-	MMSE	At 25 months:27.7	At 25 months: 24.6	-
2014	Ascaso[49]	72.1	72.9	21	18	MMSE	28.8	-	19.3
2014	Gharbiya[50]	73.1	70.3	-	21	MMSE	28.2	-	22.2
2014	Polo[51]	74.2	74.0	-	70	MMSE	-	-	16.0
2015	Bambo[1]	74.0	76.4	-	56	MMSE	-	-	16.6
2015	Bayhan[52]	75.8	74.9	-	31	MMSE	29.3	-	17.4
2015	Feke[19]	74.3	69.1	21	10	CDR	0.0	0.5	1.0 or 2.0
2015	Gao[53]	74.7	72.1	26	25	MMSE	28.6	25.8	19.2
2015	Gunes[54]	75.0	74.2	-	40	MMSE	-	-	21.9
2015	Jentsch[21]	77.2	-	-	16	MMSE	-	-	24.0
2015	Oktem[55]	75.4	70.2	35	35	MMSE	29.0	28.0	18.0
2015	Salobrar-Garcia[56]	79.3	72.3	-	23	MMSE	28.2	-	23.3
2015	Shi[57]	-	74.1	18[5]	-	MMSE	At baseline: 28.0 At 25 months: 28.0	At baseline: 27.0 At 25 months: 24.0	-
2016	Choi[42]	76.8	73.8	26	42	MMSE	-	23.1	14.1
2016	Cunha[26]	74.8	72.3	-	24	MMSE	29.1	-	17.0
2016	Garcia-Martin[58]	75.3	74.8	-	150	MMSE	29.8	-	18.4
2016	Knoll[59]	-	74.0	17	-	MMSE	29.0	27.0	-
2016	Pillai[60]	65.8	65.1	21	21[4,6]	MoCA	26.6	21.2	16.0
2016	Trebbastoni[27]	72.0	71.7	-	36	MMSE	At baseline: 28.6 At 12 months: 28.5	-	At baseline: 22.7 At 12 months:17.9
2017	Ferrari[61]	71.3	68.3	29.0	37[7]	MMSE	-	26.6	16.6
2017	Mendez-Gomez[38]	-	N/A	-	-	MMSE	27.8	-	-
2018	Bulut[6]	74.2	72.6	-	26	MMSE	26.8	-	16.9
2018	Jiang[62]	73.3	67.6	19	12	MMSE	29.5	25.7	19.9
2018	Lahme[63]	68.0	66.1	-	36	MMSE	-	-	22.3
2018	Shao[64]	74.0	68.0	24	25	MMSE	29.0	28.0	22.0
2018	Uchida[65]	65.3	65.1	22	24[4,6]	MoCA	26.6	20.9	14.7
2019	Almeida[13]	-	64.6	23	-	MMSE	-	27.9	-
2019	Cipollini[66]	74.0	70.0	-	25	MMSE	29.2	-	24.2
2019	Haan[22]	65.0	67.9	-	57	MMSE	29 .0	-	22.0
2019	Haan[67]	65.4	60.6	-	48	MMSE	29.0	-	23.0
2019	Kim[68]	74.2	73.6	14	16	MMSE	-	24.2	12.1
2019	Salobrar-Garcia[28]	-	-	-	50	MMSE	28.6		19.9
2019	Tao[29]	71.4	68.9	51	73	MMSE	28.7	28.3	19.7
2019	Yoon[23]	72.8	69.2	37	39	MMSE	29.2	22.6	20.1

2019	Zhang[69]	73.0	73.6	13	3	MoCA	27.1	-	20.3
2020	Ashimatey[70]	-	68.4	-	15[8]	MoCA	23.0	-	20.0
2020	Chua[71]	74.9	76.7	37	24	MMSE	24.8	23.9	20.3
2020	Criscuolo [33]	-	73.1	54	-	MMSE	28.0	26.5	-
2020	Jindahra[72]	75.6	75.8	29	29	MoCA	26.6	-	14.5
2020	Jorge[73]	65.3	66.3	-	20	MoCA	24.9	-	14.4
2020	Karakahya[40]	76.8	77.2	-	13	MMSE	28.2	-	21.0
2020	Lemmens[74]	71.9	68.6	-	17	MMSE	29.3	-	17.6
2020	Mammadova [24]	-	N/A	N/A	N/A	MMSE	29.2	-	-
2020	Marquie[41]	-	65.8	15	-	MMSE	At follow-up: 29.3[10]	At follow-up: 28.3	-
2020	Mavilio[75]	71.2	69.1	16	17	MMSE	27.1	25.1	24.8
2020	Sanchez[31]	79.0	66.0	192	324	MMSE	29.3	25.1	20.3
2020	Santangelo [34]	70.9	69.4	37	43	MMSE	-	24.9	19.0
2020	Salobrar-Garcia[76]	-	-	-	17	MMSE	30.0	-	26.0
2020	Sen[77]	61.5	60.9	-	40	MMSE	28.0	-	17.5
2020	Uchida[78]	64.7	65.1	-	14	MoCA WMS-IV HVLT-R PVF SVF	27.0 30.5 23.5 40.0 21.0	- - - - -	15.5 14.0 12.0 26.0 8.0
2020	Van De Kreeke[32]	91.9[12]	70.4 / 92.4[13]	-	23[12]	MMSE	29.0[13]	-	24.0
2020	Wu[79]	69.9	69.0	21	19	MMSE	27.1	24.8	19.7
2021	Biscetti[80]	72.1	73.6	24[9]	-	MMSE	28.9	25.9	-
2021	Janez-Carcia[30]	79.2	75.7	-	19	MMSE	28.38	-	23.4
2021	Li[81]	83.1	79.7	-	37	MMSE ADAS-cog CDR	29.1 3.0 0	- - -	7.9 48.4 2.54
2021	Mei[82]	73.8	74.3	-	19	MMSE	28.1	-	12.8
2021	Robbins[83]	62.4	68.1	-	15	MMSE	29.3	-	19.36/21.6[11]
2021	Robbins[84]	72.8	69.2	74	67	MMSE	29.0	24.5	19.8
2021	Wang[85]	71.8	69.5	47	62	MMSE CDR	28.7 0.03	28.0 0.5	19.9 1.3
2021	Wong[86]	64.9[14]	64.5	11	-	MoCA	26.9	22.8	-
2021	Zabel[87]	74.4	71.4	-	31	MMSE	29	-	20.5
2021	Zhao[88]	70.2	66.6	23	17	MMSE MoCA ADAS-cog	28.8 24.9 14.2	26.9 20.6 18.0	21.2 15.7 31.9
2022	Monotorio[89]	-	72.7	54	-	MMSE	28.4	26.5	-

[1] Mean age of AD group reported only; [2] Other groups studied listed in footnotes; [3] Lewy Body Dementia;; [5] Converted (converted from normal cognition to MCI or MCI to dementia); [6] non-AD dementia; [7] Frontotemporal Dementia; [8] Cognitively abnormal; [9] Both MCI and AD were included. [10] Subjective cognitive decline, no baseline data available. [11] MMSE scores for early onset AD and late-onset AD. [12] Cognitively impaired nonagenerians. [13] Two control groups, one for 65+ and the other for 90+. [14] Reported mean for both control groups.

Abbreviations: AFT=Animal Fluency Test; CDR= clinical dementia rating; CFT=Complex Figure Test; HVLT-R=Hopkins Verbal Learning Test-Revised; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; PVF=Phonemic verbal fluency; SCWT=Stroop Colour Word Test; SVF=Semantic verbal fluency; TMT=Trial Making Test; WMS-IV=Wechsler Memory Scale-Fourth Edition.

Table 3. Associations between diagnosed dementia status (e.g., AD) and retinal markers.

Year	Author	Method	Areas of retina measured									
			RNFL	mRNFL	pRNFL	GCC	GC-IPL	MT	CT	VD	FAZ	Other
2001	Paris[45]	OCT	✗	-	-	-	-	-	-	-	-	-
2006	Iseri[46]	OCT	✗	-	-	-	-	✓	-	-	-	✗ 1
2011	Kesler[47]	OCT	✗	-	-	-	-	-	-	-	-	-
2013	Kirbas[48]	SD-OCT	✗	-	✗	-	-	-	-	-	-	-
2013	Shen[37]	OCT	✓	-	-	-	-	-	-	-	-	-
2014	Ascaso[49]	OCT	✓	-	-	-	-	✗	-	-	-	-
2014	Gharbiya[50]	SD-OCT	-	-	✗	-	-	-	✗	-	-	✗ 2
2014	Polo[51]	OCT	✗	-	-	-	-	-	-	-	-	-
2015	Bambo[1]	OCT	-	-	?	-	-	-	-	-	-	✗ 3
2015	Bayhan[52]	SD-OCT	-	-	-	✓	-	-	✗	-	-	-
2015	Feke[19]	Laser Doppler / OCT	-	-	-	-	-	-	-	-	-	✓ 4
2015	Gao[53]	OCT	-	-	✗	-	-	-	-	-	-	-
2015	Gunes[54]	SD-OCT	-	-	✗	-	-	-	-	-	-	-
2015	Jentsch[21]	OCT / FLIO	-	-	✗	-	-	-	-	-	-	?[5]
2015	Oktem[55]	OCT	✓	-	-	-	-	-	-	-	-	-
2015	Salobrar-Garcia[56]	OCT	-	?	✗	-	-	-	-	-	-	✓ 1,6
2015	Shi[57]	OCT	✓	-	-	-	-	-	-	-	-	-
2016	Choi[42]	OCT	-	-	✗	-	?	?	-	-	-	-
2016	Cunha[26]	OCT	-	✓	✓	✓	✓	✓	-	-	-	✓ 7
2016	Garcia-Martin[58]	OCT	✓	-	-	✓	-	-	-	-	-	-
2016	Knoll[59]	SD-OCT	-	-	?	-	-	-	-	-	-	-
2016	Pillai[60]	SD-OCT	✗	-	-	-	-	-	-	-	-	-
2016	Trebbastoni[27]	SD-OCT	-	-	✓	-	-	-	-	-	-	-
2017	Ferrari[61]	OCT	-	-	✗	-	AD ✓ MCI ✗	-	-	-	-	-
2017	Mendez-Gomez[38]	SD-OCT	-	-	?	-	-	-	-	-	-	-
2018	Bulut[6]	OCTA	-	-	-	-	-	-	✓	✓	✓	✗ 8,9
2018	Jiang[62]	OCTA / OCT	-	-	-	-	-	-	-	-	-	?[10]
2018	Lahme[63]	OCTA	-	-	-	-	-	-	-	-	-	✓ 11
2018	Shao[64]	SD-OCT	✓	-	-	-	✓	-	-	-	-	-
2018	Uchida[65]	OCT	-	-	-	-	-	-	-	-	-	✓ 12
2019	Almeida[13]	SS-OCT	-	✗	✓	✓	✓	?	-	-	-	-
2019	Cipollini[66]	SD-OCT	-	-	✗	✗	-	✗	-	-	-	-
2019	Haan[22]	SD-OCT	-	-	✗	-	-	✗	-	-	-	-
2019	Haan[67]	SD-OCT / OCTA	-	-	-	-	-	-	✗	✗	✗	-
2019	Kim[68]	OCT	?	-	-	-	?	✓	-	-	-	-

2019	Salobrar-Garcia[28]	OCT	-	-	✓	-	-	✓	-	-	-	-
2019	Tao[29]	OCT	-	-	✓	✗	-	-	-	-	-	-
2019	Yoon[23]	OCTA / SD-OCT	✓	-	-	-	✓	-	-	?	✗	✗[14] ?[15]
2019	Zhang[69]	OCT / OCTA	-	-	-	-	-	-	-	?	-	-
2020	Ashimatey[70]	OCTA	-	-	-	-	-	-	-	✓	-	-
2020	Chua[71]	OCT	-	-	-	-	-	-	-	✓	✓	-
2020	Criscuolo[33]	SD-OCT / OCTA	✗	-	-	✗	-	-	-	-	-	-
2020	Jindahra[65]	OCT	✓	-	-	-	✓	-	-	-	-	-
2020	Jorge[73]	OCT	-	-	-	-	✗	-	-	-	-	-
2020	Karakahya[40]	OCT	✓	-	-	-	✓	-	✓	-	-	-
2020	Lemmens[74]	OCT	✓	-	-	-	-	-	-	-	-	-
2020	Mammadova[24]	SD-OCT	✓	-	-	-	-	-	-	-	-	
2020	Marquie[41]	OCT	✗	-	-	✗	-	-	-	-	-	-
2020	Mavilio[75]	OCT	✗	-	-	✗	-	-	-	-	-	-
2020	Salobra-Garcia[76]	OCT, OCTA	-	-	-	-	-	-	✓	-	✗	✗
2020	Sanchez[31]	OCT	✗	-	-	✗	-	-	-	-	-	✗
2020	Santangelo [34]	OCT	✗	-	-	-	-	✓	-	-	-	-
2020	Sen[77]	OCT	✗	-	-	✗	-	-	-	-	-	✗
2020	Uchida[78]	OCT	-	-	-	-	-	-	-	-	-	✗
2020	Van De Kreeke[32]	OCT	✗	-	-	✗	✗	-	-	✗	-	-
2020	Wu[79]	OCTA	-	-	-	-	-	-	-	?	?	-
2021	Biscetti[80]	OCT	-	-	-	✗	✗	-	-	✓	✗	-
2021	Janez-Garcia[30]	OCT, OCTA	✓	✓	✓	✓	✓	-	-	-	-	-
2021	Li[81]	OCT	-	-	-	-	-	-	✓	-	-	-
2021	Lian	OCT	✓	-	-	✓	-	-	-	-	-	-
2021	Mei[82]	OCTA	✓	-	-	✓	-	-	-	✓	-	-
2021	Robbins[83]	OCTA	✗	-	-	-	✗	-	✗	-	-	-
2021	Robbins[84]	OCT	-	-	-	-	-	-	?	-	-	-
2021	Wang[85]	OCTA	-	-	✗	✗	-	-	-	✗	✗	-
2021	Wong[86]	OCTA	-	-	-	-	-	-	-	✓	-	-
2021	Zabel[87]	OCT, OCTA	✗	-	✗	✗	✓[10]	-	-	✓	✓[10, 11]	-
2021	Zhao[88]	OCT	-	✓	-	-	-	-	-	-	-	-
2022	Montorio[89]	OCTA	✓	-	-	✓	-	-	-	✗	-	-
			15/30	**3/5**	**6/21**	**8/19**	**9/15**	**5/10**	**4/9**	**7/14**	**3/9**	

[1] Foveal thickness; [2] Retinal CSF thickness; [3] Retinal haemoglobin levels; [4] Retinal blood flow; [5] T2, α2 and Q2 in ch2; [6] Macular volume; [7] GCL++; [8] Choroidal flow rate; [9] Outer retinal flow rate; [10] Superficial vascular plexus, deep vascular plexus and total retinal vascular network; [11] Flow density; [12] Retinal pigment epithelium; [13] Central foveal thickness; [14] Central subfield thickness; [15]Perfusion density; [16] Vessel length density; [17] Adjusted flow index; Vessel perfusion density; [18] Peripapillary Radial Peripapillary Capillary. Key: ✓ = correlation identified; ✗= no correlation identified; **?** = unclear.

Table 4. Summary of QUADAS score of the 67 included studies.

Year	Author	RS[1]	CSC[2]	ARS[3]	DPB[4]	PVB[5]	DVB[6]	IB[7]	ITE[8]	RSE[9]	ITRB[10]	RSRB[11]	CRB[12]	UTRR[13]	WE[14]	Total
2001	Parisi[45]	N	N	Y	U	U	U	Y	Y	N	U	U	Y	Y	N	5/14
2006	Iseri[46]	N	Y	Y	Y	Y	Y	Y	Y	N	U	U	Y	Y	Y	10/14
2011	Kesler[47]	N	Y	Y	U	Y	Y	U	U	N	Y	Y	Y	Y	Y	9/14
2013	Kirbas[48]	N	Y	Y	U	Y	Y	Y	N	N	U	U	Y	Y	Y	8/14
2013	Shen[37]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2014	Ascaso[49]	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	11/14
2014	Gharbiya[50]	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	13/14
2014	Polo[51]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2015	Bambo[1]	N	Y	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	Y	10/14
2015	Bayhan[52]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2015	Feke[19]	N	Y	Y	U	Y	Y	Y	Y	N	U	U	Y	Y	Y	10/14
2015	Gao[53]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2015	Gunes[54]	N	Y	Y	Y	Y	Y	Y	N	N	U	U	Y	Y	Y	9/14
2015	Jentsch[21]	N	Y	Y	U	U	Y	Y	Y	Y	U	U	Y	Y	Y	9/14
2015	Oktem[55]	N	N	Y	Y	Y	Y	Y	N	Y	U	U	Y	Y	Y	9/14
2015	Shi[57]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2015	Solabrar-Garcia[56]	N	Y	Y	U	Y	Y	Y	Y	N	U	U	Y	Y	Y	9/14
2016	Choi[42]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	12/14
2016	Cunha[26]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2016	Garcia-Martin[58]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2016	Knoll[59]	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	12/14
2016	Pillai[60]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2016	Trebbastoni[27]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2017	Ferrari[61]	N	Y	Y	U	Y	Y	Y	Y	N	U	U	Y	Y	Y	9/14
2017	Mendez-Gomez[38]	N	N	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	10/14
2018	Bulut[6]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2018	Jiang[62]	N	Y	Y	U	Y	Y	Y	Y	N	U	U	U	N	N	6/14
2018	Lahme[63]	N	Y	Y	U	Y	Y	Y	Y	N	U	U	Y	Y	Y	9/14
2018	Shao[64]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	11/14
2018	Uchida[65]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2019	Almeida[13]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	12/14
2019	Cipollini[66]	N	Y	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	Y	10/14
2019	Haan[22]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2019	Haan[67]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2019	Kim[68]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2019	Solabrar-Garcia[28]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2019	Tao[29]	N	Y	Y	N	Y	Y	Y	Y	N	U	U	Y	Y	Y	9/14
2019	Yoon[23]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2019	Zhang[69]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2020	Ashimatey[70]	N	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12/14

2020	Chua[71]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2020	Criscuolo[33]	N	Y	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	Y	10/14
2020	Jindahra[72]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2020	Jorge[73]	N	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12/14
2020	Karakahya[40]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2020	Lemmens[74]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2020	Mammadova[24]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2020	Marguie[41]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2020	Mavilio[75]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2020	Sanchez[31]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2020	Santangelo[34]	N	Y	Y	U	Y	Y	Y	Y	N	U	U	Y	Y	Y	9/14
2020	Salobrar-Garcia[76]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2020	Sen[77]	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	12/14
2020	Uchida[78]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2020	Van De Kreeke[32]	N	Y	Y	Y	U	Y	Y	Y	N	U	U	Y	Y	Y	9/14
2020	Wu[79]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2021	Biscetti[80]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2021	Janez-Garcia[30]	N	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2021	Li[81]	N	Y	Y	Y	Y	Y	Y	Y	N	U	U	Y	Y	Y	10/14
2021	Mei[82]	N	Y	Y	U	Y	Y	Y	Y	N	U	U	Y	Y	Y	9/14
2021	Robbins[83]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2021	Robbins[84]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11/14
2021	Wang[85]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2021	Wong[86]	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	12/14
2021	Zabel[87]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2021	Zhao[88]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14
2022	Montorio[89]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/14

Y: Yes (green); N: No (red); U: unknown (yellow)

[1]Representative spectrum, [2]Clear selection criteria, [3]Accurate reference standard, [4]Disease progression bias, [5]Partial verification bias, [6]Differential verification bias, [7]Incorporation bias, [8]Index test execution well described, [9]Reference standard execution well described, [10]Index test review bias, [11]Reference standard review bias, [12]Clinical review bias, [13]Uninterpretable results reported, [14]Withdrawals explained.

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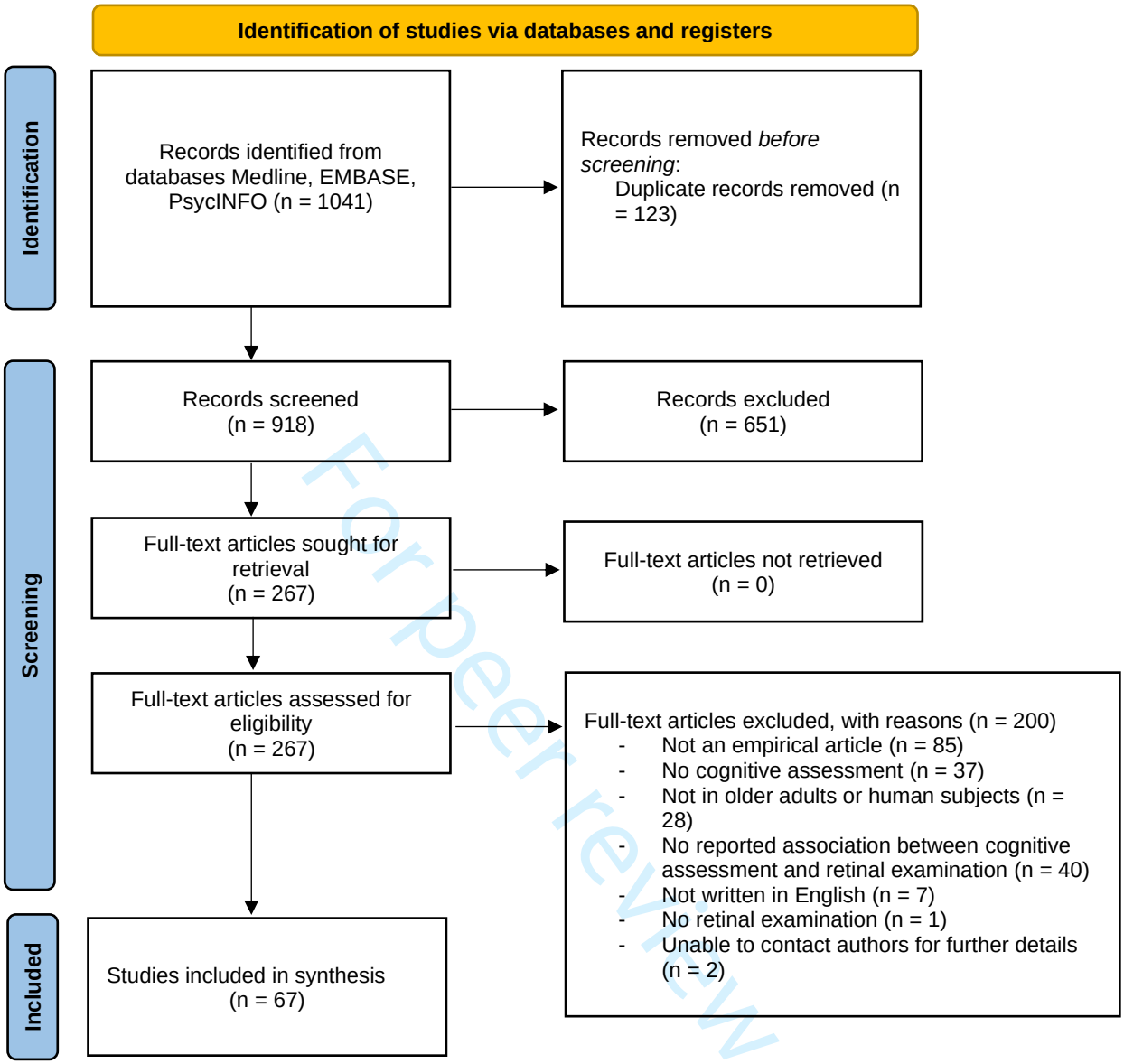

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-7
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	9
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	9-10
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8-9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Tables 2,3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	10-13
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	10-13
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	12-13
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13-15
	23b	Discuss any limitations of the evidence included in the review.	16
	23c	Discuss any limitations of the review processes used.	16
	23d	Discuss implications of the results for practice, policy, and future research.	17-18
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	7
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	19
Competing interests	26	Declare any competing interests of review authors.	30061990
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	19

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary Appendix S2

Additional Methods

Search strategy used in Medline and EMBASE database

(1) "Diagnostic techniques, ophthalmological/ or electroretinography/ or eye movement measurements/ or electronystagmography/ or electrooculography/", (2) "Tomography, Optical Coherence/", (3) "Optical coherence tomography.ti,ab.", (4) "(eye-track* or eye track*).mp.", (5) "Retina* exam*.ti,ab.", (6) "Ophthalmic assessment*.ti,ab.", (7) "1 or 2 or 3 or 4 or 5 or 6", (8) "Exp Retina/", (9) "Retina*.ti,ab.", (10) "8 or 9", (11) "7 and 10", (12) "Exp Dementia/", (13) "(dementia or cognitive impairment*).ti,ab.", (14) "12 or 13", and (15) "11 and 14"

Search strategy used in PsycINFO

☐	1	Diagnostic techniques, ophthalmological/ or electroretinography/ or eye movement measurements/ or electronystagmography/ or electrooculography.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	2580	Advanced
☐	2	Tomography/	5330	Advanced
☐	3	Optical coherence tomography.ti,ab.	536	Advanced
☐	4	(eye-track* or eye track*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	7728	Advanced
☐	5	Retina* exam*.ti,ab.	44	Advanced
☐	6	Ophthalmic assessment*.ti,ab.	12	Advanced
☐	7	1 or 2 or 3 or 4 or 5 or 6	15890	Advanced
☐	8	exp Retina/	8932	Advanced
☐	9	Retina*.ti,ab.	18697	Advanced
☐	10	8 or 9	20257	Advanced
☐	11	7 and 10	939	Advanced
☐	12	exp Dementia/	85053	Advanced
☐	13	(dementia or cognitive impairment*).ti,ab.	96290	Advanced
☐	14	12 or 13	124970	Advanced
☐	15	11 and 14	70	Advanced

Supplementary Table 1. Definitions of terminology used in the included studies

Terminology	Number of Articles that Utilised these Terms	Definition	Reference(s)
Optical Coherence Tomography (OCT)	41	Non-invasive technique to acquire high resolution, cross-sectional images of the retina	Almeida 2019
SD-OCT	18	Uses a light source with a longer-wavelength to promote deeper tissue penetration. It detects light echoes through an interferometer with a spectrometer.	Adhi 2013
SS-OCT	1	Measures light echoes using photodetectors, thus improving the signal quality in deep tissue to enhance choroid visualisation.	Adhi 2013
Fluorescence Lifetime Imaging Ophthalmoscopy (FLIO)	1	Measures the autofluorescence intensity emitted by endogenous fluorophores contained within the retina to determine retinal metabolic activity.	Dysli 2017; Jentsch 2014
Laser Doppler Retinal Blood Flow	1	Measures the retinal blood flow rate, centreline blood speed and blood column diameter in a major temporal retinal vein. As the vein with the largest diameter drains the largest portion of the total retinal blood flow, the blood flow measured within this retinal vein will be representative of total retinal blood flow.	Feke 2015
Alzheimer's dementia (AD)	37	Most common form of dementia characterised by progressive deterioration in cognition, executive functioning, learning and episodic memory	Gao 2015
Mild cognitive impairment (MCI)	19	Preclinical phase of AD characterised by cognitive decline that is significant for their age but does not compromise functioning or activities of daily living	Gao 2015; Almeida 2019
Choroid	4	Vascular layer located between the sclera and retina of the eye which supplies oxygen and nutrients to the outer third of the retina, retinal pigment epithelium and part of the optic nerve.	Tan 2017
Retinal pigment epithelium (RPE)	1	Single layer of pigmented, cuboidal cells which regulates the transport of nutrients, ions, and water, absorbs scattered light and partakes in phagocytosis of shed photoreceptors.	Sparrow 2010
Outer nuclear layer of the retina (ONL)	1	Contains cell bodies of photoreceptors, the rods and cones	Balasubramaniam 2014
Outer plexiform layer (OPL)	2	Synapse between the cells located in the INL (bipolar and horizontal cells) and ONL (rods and cones) occurs in the OPL.	Kolb 1995
Inner nuclear layer of the retina (INL)	2	Composed of the cell bodies of bipolar, horizontal, interplexiform, amacrine and	Balasubramaniam 2014

		Müller cells, and occasionally displaced ganglion cells	
Ganglion cell inner plexiform layer (GC-IPL)	10	Comprised of the dendrites and cell bodies of retinal ganglion cells	Öztürker 2016
Ganglion cell complex (GCC)	11	Composed of the retinal nerve fibre layer (RNFL), ganglion cell layer (GCL) and inner plexiform layer (IPL)	Öztürker 2016
Retinal nerve fibre layer (RNFL)	25	Comprised of nonmyelinated retinal ganglion cell axons that form the optic nerve	Shi 2019
Macula	17	Central, oval-shaped region of the retina comprising of a highest density of cone photoreceptions which is responsible for visual acuity	Lima 2016
Foveal Avascular Zone (FAZ)	6	Central region of the fovea, characterised by an absence of blood vessels, rods, inner retinal tissue and peak cone density. The fovea is the central area of the macula.	Chui 2012

Supplementary Table 2. Summary of studies and machine used.

Year	Author	Method	OCT Machine
2001	Parisi	OCT	OCT
2006	Iseri	OCT	OCT Model 3000 unit
2011	Kesler	OCT	Stratus OCT3
2013	Kirbas	SD-OCT	SD-OCT
2013	Shen	OCT	ZEISS Cirrus HD-OCT 4000 OCT
2014	Ascaso	OCT	Stratus OCT3
2014	Gharbiya	SD-OCT	Heidelberg Spectralis with Heidelberg Eye Explorer
2014	Polo	OCT	Cirrus and Spectralis OCT devices
2015	Bambo	OCT	Cirrus OCT
2015	Bayhan	SD-OCT	RTVue OCT system
2015	Feke	Laser Doppler retinal blood flow and OCT	Canon laser Doppler retinal blood flow instrument (CLBF 100, Canon) and Stratus OCT 3000
2015	Gao	OCT	Cirrus HD-OCT 4000
2015	Gunes	SD-OCT	Spectral-domain OCT (Spectral OCT SLO, OPKO / OTI Instrumentation)
2015	Jentsch	OCT and fluorescence lifetime imaging ophthalmoscopy (FLIO)	Cirrus OCT 4.0
2015	Oktem	OCT	Zeiss Cirrus HD 5000 model OCT device
2015	Salobrar-Garcia	OCT	OCT Model 3D OCT-1000
2015	Shi	OCT	ZEISS Cirrus HD-OCT 4000 OCT
2016	Choi	OCT	Cirrus High-Definition OCT (HD-OCT, software version 6.0)
2016	Cunha	OCT	Frequency domain-OCT (fd-OCT) using 3D OCT-2000, software version 8.11
2016	Garcia-Martin	OCT	Spectralis OCT
2016	Knoll	SD-OCT	SD-OCT using Spectralis HRA 1 OCT
2016	Pillai	SD-OCT	SD-OCT using Cirrus 4000 HD-OCT
2016	Trebbastoni	SD-OCT	Heidelberg Spectralis with Heidelberg Eye Explorer
2017	Ferrari	OCT	Fourier-domain OCT Heidelberg Spectralis
2017	Mendez-Gomez	SD-OCT	SD-OCT using Spectralis
2018	Bulut	OCT angiography (OCTA)	Commercial spectral domain OCTA
2018	Jiang	1. OCTA OCT	1. Zeiss Angioplex OCTA 2. Zeiss OCT
2018	Lahme	OCTA	RTVue XR Avanti with AngioVue
2018	Shao	SD-OCT	SD-OCT using Ultrahigh-resolution OCT (UHR-OCT) device
2018	Uchida	OCT	Cirrus 4000 HD-OCT

2019	Almeida	SS-OCT	SS-OCT (DRI OCT Triton)
2019	Cipollini	SD-OCT	SD-OCT RTVue
2019	Haan	SD-OCT	Heidelberg Spectralis spectral domain OCT
2019	Haan	1. Fundus photography 2. SD-OCT 3. OCTA	1. Topcon TRC 50DX type IA 2. Enhanced Depth Imaging OCT (EDI-OCT) using Heidelberg Spectralis spectral domain-OCT 3. Zeiss Model 5000 spectral domain-OCT with Angioplex
2019	Kim	OCT	CirrusHD-OCTsoftwareversion 6.0.0.599
2019	Salobrar-Garcia	OCT	OCT Model 3D OCT-1000 and OCT Spectralis
2019	Tao	OCT	Optovue AngioVue System
2019	Yoon	1. OCTA SD-OCT	1. Zeiss Cirrus HD-5000 SD-OCT with AngioPlex OCTA 2. Cirrus HD-OCT 5000 device
2019	Zhang	1. OCT OCTA	RTVue-XR OCT Avanti System with split-spectrumamplitude-decorrelation angiography (SSADA) software
2020	Ashimatey	OCTA	Spectral Domain OCTA: Cirrus HD-OCTA
2020	Chua	OCTA	Zeiss Cirrus HD-5000 Spectral-Domain OCT with AngioPlex Octa (Carl Zeiss Meditec)
2020	Criscuolo	SD-OCT and OCTA	1. SD-OCT 2. OCTA (XR Avanti AngioVue OCTA)
2020	Jindahra	OCT	Cirrus HD-OCT Model 4000 (Carl Zeiss Meditec)
2020	Jorge	OCT	Cirrus HD-OCT System (Carl Zeiss Meditec)
2020	Karakahya	OCT	OCT Cirrus HD-OCT, Carl Zeiss Ophthalamic System Inc
2020	Lemmens	OCT	RTVue XR Avanti (Optovue, Fremont, CA, USA; software version 2015.1.1.98)
2020	Mammadova	SD-OCT	High-resolution spectral-domain OCT imaging (Zeiss Cirrus 5000 HD-OCT)
2020	Marquie	OCT	3D − OCT Maestro
2020	Mavilio	OCT	Zeiss Cirrus HD OCT-500 (Carl Zeiss Meditec)
2020	Salobra-Garcia	OCT OCTA	Spectralis OCT, RTYue XR OCTA and Cirrus 5000 Angioplex
2020	Sanchez	OCT	3D-OCT Maestro, Fast map software version 8.40
2020	Sen	OCT	Cirrus HD-OCT Model 4000, Carl Zeiss Meditex
2020	Uchida	OCT	Cirrus 4000 HD-OCT (Zeiss, Oberkochen, Germany)
2020	Van De Kreeke	OCT	Spectralis, Heidelberg

		Fundas photography	Topcon TRC 50DX type IA
2020	Wu	OCTA	RTVue XR Avanti spectral domain OCT system (Optovue) with AngioVue software
2021	Biscetti	OCT, OCTA	Specttralis HRA + CT2 (Heidelberg Engineering)
2021	Janez-Garcia	OCT OCTA	3D OCT-1000 Topcon, Japan
2021	Li	OCT	Heidelberg Spectralis OCT
2021	Mei	OCTA	Cirruss 5000 Angioplex, Zeiss Meditex
2021	Robbins	OCTA	Zeiss Cirrus HD-OCT 5000 with Angioplex OCTA
2021	Robbins	OCT	Zeiss Cirrus HD-OCT 5000 Spectral Domain OCT With Angioplex OCT Angiography
2021	Wang	OCTA Fundas photography	Optovue Angiovie System (software ReVue version 2017.1.0.155) Version 1.5.0.0, NIDEK CO, LTD
2021	Wong	OCTA	Zeiss CIRRUS HD-OCT 5000,
2021	Zabel	SD-OCT OCTA	RTVue XR Avanti SD-OCT device wit\h AngioVue software
2021	Zhao	OCT	Stratus Oct Model 3000 (Carl Zeiss Meditec)
2022	Montorio	SD-OCT OCTA	RTVue XR Avanti with AngioVue XR Avanti AngioVue OCTA (software ReVue ver-sion 2017.1.0.151, Optovue Inc., Fremont, CA, USA)