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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, PsycINFO 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 evaluation of retinal scanning and cognitive outcomes were excluded. Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies 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 6815 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 with cognitive decline. Study quality was overall moderate.

Conclusion Retinal nerve fibre layer thickness is linked with cognitive performance and therefore may have the potential to detect cognitive impairment in older adults. Further longitudinal studies are required to validate our synthesis and understand underlying mechanisms before recommending implementation of OCT as a dementia screening tool in clinical practice.

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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 six 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 were cross-sectional and have used different retinal imaging devices, 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. With 1 in 10 Australians aged over 65 with dementia and 50 million people affected worldwide,[2] cognitive impairment is a prevalent issue in our ageing population. The worldwide cost of dementia is estimated to be US$818 billion in 2015,[2] 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.[3] 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 minimise preventable hospital visits.[4] However, to date, 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.[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 exhibit brain changes and 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 interindividual differences in the rate of cognitive decline indicate that other age-associated pathologies may be involved, such as macrovascular 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] *Nester et al* demonstrated that cerebral ventricular enlargement due to cerebral atrophy seen characteristically in AD as indicated by MRI 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.[5] The OCT devices often vary, with some users adopting swept-source OCT (SS-OCT) devices while others used spectral-domain 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 an '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 with 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 with 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 with 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 under-represents 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. 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 online supplemental data S1.

Search strategy

A search strategy was developed using medical subject headings 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 on 17 March 2022 prior to the final analysis to ensure up-to-date and relevant articles were included. The search strategy (available in online supplemental 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 handsearched for additional records. This search strategy was then adapted to the other databases.

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 evaluation of cognition and retinal scanning outcomes were excluded.

Participants

Inclusion criteria comprised adults aged 65 years and over with diagnosed cognitive impairment of any form and severity, including AD and MCI, 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 supplemental 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, PsycINFO 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, RS) using a standardised data sheet that was piloted with three papers and revised. All data extraction was verified by JS, and disagreement 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 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 for example, withdrawals. Three reviewers (VJ, RS and 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.

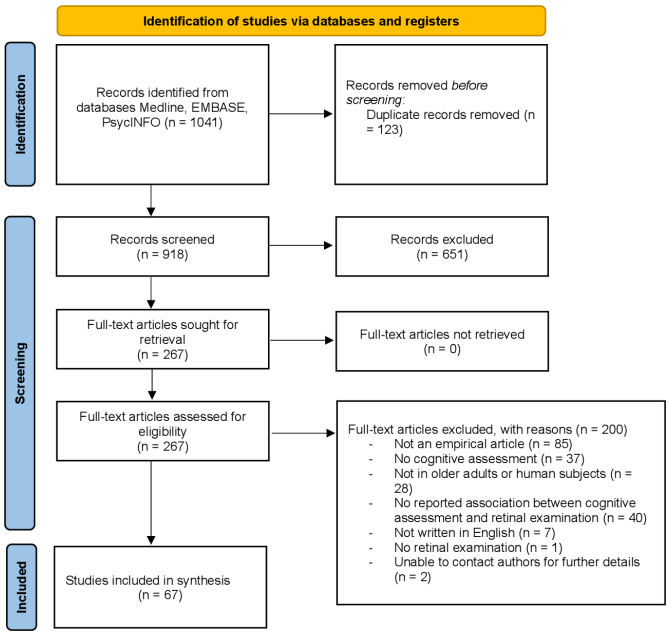

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart describing the process of study selection.

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; 89.6%), with a few case–controls (2/67; 3.0%) and longitudinal (6/67; 9.0%) studies (table 1). Longitudinal studies had a range of 2–12 years follow-ups. Studies were mostly conducted in 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 AD and 9 (13.4%) at MCI, and 23 (34.3%) for both conditions. 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**,** online supplemental 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, GCC; choroid and macula.[10] In 12 (17.6%) studies, the Early Treatment of Diabetic Retinopathy Study 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° 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, dilated fundus scan, slit lamp scan of the anterior segment of the eye, intraocular pressure 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 MMSE (59/67; 88%), followed by Montreal Cognitive Assessment (MoCA) (9/67; 13.4%), the global clinical dementia rating score (3/67; 4.5%) and the Alzheimer's Disease Assessment Scale-cognitive subscale (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 the Diagnostic and Statistical Manual of Mental Disorders(DSM-IV) criteria, National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association[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%)

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

				Areas of retinal measured												
Year	Author	Country	Design	RNFL	mRNFL	pRNFL	GCC	GC-IPL	MT/MV	CT	FAZ	VD	RVN	Other	Sample size	Method
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				•			•				•	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			•			•					•†	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											•‡	124	OCT

Continued

Table 1 Continued

Year	Author	Country	Design	Areas of retinal measured											Sample size	Method
				RNFL	mRNFL	pRNFL	GCC	GC-IPL	MT/MV	CT	FAZ	VD	RVN	Other		
2019	Almeida[13]	Brazil	CS		•	•	•	•	•						47	SS-OCT
2019	Cipollini[66]	Italy	CS			•	•		•						42	SD-OCT
2019	Haan[22]	Netherlands	CS			•	•		•					•‡	142	SD-OCT
2019	Haan[67]	Netherlands	CS							•	•	•			86	FP, SD-OCT, OCTA
2019	Kim[68]	South Korea	CS	•				•	•						47	OCT
2019	Salobrar-García[28]	Spain	CS			•	•		•					•§	90	OCT
2019	Tao[29]	China	CS			•	•								191	OCT
2019	Yoon[29]	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	•			•							•‡	930	OCT
2020	Sen[77]	India	CS	•			•							•‡	60	OCT
2020	Uchida[78]	USA	CS											•‡	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

Continued

Table 1 Continued

Year	Author	Country	Design	Areas of retinal measured											Sample size	Method
				RNFL	mRNFL	pRNFL	GCC	GC-IPL	MT/MV	CT	FAZ	VD	RVN	Other		
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	•		•	•	•				•		•‡	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	6415	

*Focal loss volume and global loss volume.
†Time-resolved autofluorescence of the retina by FLIO.
‡Retinal thickness/volume,mean foveal thichness and juxtafoveal thickness.
§[13] IPL, INL, OPL; retinal pigment epithelium thickness.
C, cross-sectional; CC, case–control; CT, Choroidal thickness; FAZ, foveal avascular zone; FLIO, fluorescence lifetime imaging ophthalmoscopy; GCC, macular ganglion cell complex; GC-IPL, ganglion cell-inner plexiform layer; INL, inner nuclear layer; L, longitudinal; mRNFL, macula retinal nerve fibre layer; MT/MV, macular volume/macular thickness; OCT, optical coherence tomography; OCTA, OCT-angiography; OPL, outer plexiform layer; pRNFL, peripapillary retinal nerve fibre layer; RCT, randomised controlled trial; RNFL, retinal nerve fibre layer; RVN, retinal vasculature network; SD-OCT, spectral-domain OCT; VD, vascular/vessel density.

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

Year	Author	Mean age of individuals with AD	Mean age of controls	No. of cognitively impaired subjects		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*	–	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*	–	MMSE	At baseline: 28.0	At baseline: 27.0	–
							At 25 months: 28.0	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],†	MoCA	26.6	21.2	16.0
2016	Trebbastoni[27]	72.0	71.7	–	36	MMSE	At baseline: 28.6	–	At baseline: 22.7
							At 12 months: 28.5		At 12 months:17.9
2017	Ferrari[61]	71.3	68.3	29.0	37‡	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†	MoCA	26.6	20.9	14.7

Continued

Table 2 Continued

Year	Author	Mean age of individuals with AD	Mean age of controls	No. of cognitively impaired subjects		Measure	Mean cognitive score		
				MCI	AD		Controls	MCI	AD
2019	Almeida	–	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§	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¶	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**	70.4/92.4††	–	23**	MMSE	29.0††	–	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‡‡	–	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

Continued

Table 2 Continued

Year	Author	Mean age of individuals with AD	Mean age of controls	No. of cognitively impaired subjects		Measure	Mean cognitive score		
				MCI	AD		Controls	MCI	AD
2021	Robbins[83]	62.4	68.1	–	15	MMSE	29.3	–	19.36/21.6§§
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¶¶	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	–

*Converted from normal cognition to MCI or MCI to dementia.
†non-AD dementia.
‡Frontotemporal dementia.
§Cognitively abnormal.
¶Subjective cognitive decline, no baseline data available.
**Cognitively impaired nonagenerians.
††Two control groups, one for 65+ and the other for 90+.
‡‡Both MCI and AD were included.
§§MMSE scores for early onset AD and late-onset AD.
¶¶Reported mean for both control groups.
AD, Alzheimer's disease; 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, Trail Making Test; WMS-IV, Wechsler Memory Scale-Fourth Edition.

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 carefully.

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 with 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 used 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 6 (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 (eg, Sánchez *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 baseline 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

Table 3 Associations between diagnosed dementia status (eg, AD) and retinal markers

			Areas of retina measured									
Year	Author	Method	RNFL	mRNFL	pRNFL	GCC	GC-IPL	MT	CT	VD	FAZ	Other
2001	Paris[45]	OCT	✗	–	–	–	–	–	–	–	–	–
2006	Iseri[46]	OCT	✗	–	–	–	–	✓	–	–	–	✗*
2011	Kesler[47]	OCT	✗	–	–	–	–	–	–	–	–	–
2013	Kirbas[48]	SD-OCT	✗	–	✗	–	–	–	–	–	–	–
2013	Shen[37]	OCT	✓	–	–	–	–	–	–	–	–	–
2014	Ascaso[49]	OCT	✓	–	–	–	–	✗	–	–	–	–
2014	Gharbiya[50]	SD-OCT	–	–	✗	–	–	–	✗	–	–	✗†
2014	Polo[51]	OCT	✗	–	–	–	–	–	–	–	–	–
2015	Bambo	OCT	–	–	?	–	–	–	–	–	–	✗‡
2015	Bayhan[52]	SD-OCT	–	–	–	✓	–	–	✗	–	–	–
2015	Feke[19]	Laser Doppler/OCT	–	–	–	–	–	–	–	–	–	✓§
2015	Gao[53]	OCT	–	–	✗	–	–	–	–	–	–	–
2015	Gunes[54]	SD-OCT	–	–	✗	–	–	–	–	–	–	–
2015	Jentsch[21]	OCT / FLIO	–	–	✗	–	–	–	–	–	–	?¶
2015	Oktem[55]	OCT	✓	–	–	–	–	–	–	–	–	–
2015	Salobrar-Garcia[56]	OCT	–	?	✗	–	–	–	–	–	–	✓*, **
2015	Shi[57]	OCT	✓	–	–	–	–	–	–	–	–	–
2016	Choi[42]	OCT	–	–	✗	–	?	?	–	–	–	–
2016	Cunha[26]	OCT	–	✓	✓	✓	✓	✓	–	–	–	✓††
2016	Garcia-Martin[58]	OCT	✓	–	–	✓	–	–	–	–	–	–
2016	Knoll[59]	SD-OCT	–	–	?	–	–	–	–	–	–	–
2016	Pillai[60]	SD-OCT	✗	–	–	–	–	–	–	–	–	–
2016	Trebbastoni[27]	SD-OCT	–	–	✓	–	–	–	–	–	–	–

Continued

Table 3 Continued

Year	Author	Method	Areas of retina measured									
			RNFL	mRNFL	pRNFL	GCC	GC-IPL	MT	CT	VD	FAZ	Other
2017	Ferrari[61]	OCT	–	–	✗	–	AD ✓ MCI ✗	–	–	–	–	–
2017	Mendez-Gomez[38]	SD-OCT	–	–	?	–	–	–	–	–	–	–
2018	Bulut[6]	OCTA	–	–	–	–	–	–	✓	✓	✓	✗‡‡,§§
2018	Jiang[62]	OCTA / OCT	–	–	–	–	–	–	–	–	–	?¶¶
2018	Lahme[63]	OCTA	–	–	–	–	–	–	–	–	–	✓***
2018	Shao[64]	SD-OCT	✓	–	–	–	✓	–	–	–	–	–
2018	Uchida[65]	OCT	–	–	–	–	–	–	–	–	–	✓†††
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	✓	–	–	–	✓	–	–	?	✗	✗‡‡‡ ?§§§
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	✓	–	–	–	✓	–	✓	–	–	–

Continued

Table 3 Continued

Year	Author	Method	Areas of retina measured									
			RNFL	mRNFL	pRNFL	GCC	GC-IPL	MT	CT	VD	FAZ	Other
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	✗	–	✗	✗	✓¶¶	–	–	✓	✓¶¶,***	–
2021	Zhao[88]	OCT	–	✓	–	–	–	–	–	–	–	–
2022	Montorio[89]	OCTA	✓	–	–	✓	–	–	–	✗	–	–

Continued

Table 3 Continued

Year	Author	Method	Areas of retina measured									
			RNFL	mRNFL	pRNFL	GCC	GC-IPL	MT	CT	VD	FAZ	Other
			15/30	3/5	6/21	8/19	9/15	5/10	4/9	7/14	3/9	

Key: ✓ = correlation identified; ✗ = no correlation identified; ? = unclear
*Foveal thickness.
†Retinal central subfield thickness.
‡Retinal haemoglobin levels.
§Retinal blood flow.
¶T2, α2 and Q2 in ch2.
**Macular volume.
††GCL++.
‡‡Choroidal flow rate.
§§Outer retinal flow rate.
¶¶Superficial vascular plexus, deep vascular plexus and total retinal vascular network.
***Flow density.
†††Retinal pigment epithelium.
‡‡‡Central subfield thickness.
§§§Perfusion density.
AD, Alzheimer's disease; CSF, central subfield retinal thickness; FAZ, foveal avascular zone; FLIO, Fluorescence Lifetime Imaging Ophthalmoscopy; GCC, ganglion cell complex; GC-IPL, ganglion cell and inner plexiform layer; mRNFL, macular retinal nerve fibre layer; MT/MV, macular volume/macular thickness; OCT, optical coherence tomography; OCTA, optical coherence tomography-angiography; PRNFL, peripapillary RNFL; RNFL, retinal nerve fibre layer thickness; SD-OCT, spectral-domain OCT; VD, vascular density.

Table 4 Summary of QUADAS score of the 67 included studies

Year	Author	RS	CSC	ARS	DPB	PVB	DVB	IB	ITE	RSE	ITRB	RSRB	CRB	UTRR	WE	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	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

Continued

Table 4 Continued

Year	Author	RS	CSC	ARS	DPB	PVB	DVB	IB	ITE	RSE	ITRB	RSRB	CRB	UTRR	WE	Total
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	Salobrar-García[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

Continued

Table 4 Continued

Year	Author	RS	CSC	ARS	DPB	PVB	DVB	IB	ITE	RSE	ITRB	RSRB	CRB	UTRR	WE	Total
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

.ARS, Accurate reference standard; CRB, Clinical review bias; DPB, Disease progression bias; DVB, Differential verification bias; IB, Incorporation bias; ITE, Index test execution; ITRB, Index test review bias; N, No; PVB, Partial verification bias; QUADAS, Quality Assessment of Diagnostic Accuracy Studie; RS, Representative spectrum; RSE, Reference standard execution; RSRB, Reference standard review bias; U, Unknown; UTRR, Uninterpretable results reported; WE, Withdrawals explained; Y, Yes.

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] While 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 17 (25.4%) 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.[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.[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 a Government's health-subsidised care (e.g., Australia's Medicare Benefits Schedule) 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, while cross-sectional studies show moderate support 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.

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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. 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 RS provided essential write-up and feedback on early drafts. All authors contributed to critical revisions of subsequent manuscript drafts and approved the final submission. JS is responsible for the overall content as the guarantor.

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