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Retinal biomarkers for early Alzheimer's detection: a systematic review of optical coherence tomography (OCT) findings

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ABSTRACT

Objective Retinal biomarkers accessible via non-invasive optical coherence tomography (OCT) could facilitate early detection of Alzheimer's disease (AD), complementing current invasive or costly diagnostic methods. This review evaluates the evidence for spectral-domain OCT (SD-OCT) and OCT angiography (OCT-A) in identifying retinal changes associated with preclinical and early AD.

Methods and analysis We conducted a systematic review registered in PROSPERO and aligned with Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. PubMed/MEDLINE was searched up to April 2025, complemented by reference list screening and citation tracking. Eligible studies assessed SD-OCT and/or OCT-A in biomarker-defined preclinical or early AD, mild cognitive impairment or mild AD. Data were synthesised narratively by disease stage, and methodological quality was appraised with the Newcastle-Ottawa Scale.

Results 22 studies met inclusion criteria. Reported alterations included thinning of the peripapillary retinal nerve fibre layer and retinal ganglion cell layer, macular and choroidal thickness changes and microvascular alterations on OCT-A. However, findings were heterogeneous: some studies observed early thickening or increased vascular density, possibly reflecting inflammatory or compensatory mechanisms, while others reported thinning and rarefaction more consistent with neurodegeneration. Most studies were of moderate quality, limited by small sample sizes, cross-sectional designs and incomplete control for ocular/systemic confounders.

Conclusion SD-OCT and OCT-A hold promise as candidate biomarkers of early AD, but current evidence remains variable, non-specific and methodologically constrained. Further research is needed to standardise imaging protocols, validate findings in biomarker-confirmed longitudinal cohorts and compare OCT-based measures across dementia subtypes. Integration with other biomarkers (eg, plasma or metabolomics) may improve diagnostic specificity and support translation of OCT/OCT-A into clinical practice.

PROSPERO registration number CRD42024600456.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Retinal changes have been reported in Alzheimer's disease (AD), but their value as non-invasive biomarkers for early or preclinical detection remains uncertain due to variability and limited disease specificity.

WHAT THIS STUDY ADDS

⇒ This systematic review synthesises evidence from spectral-domain optical coherence tomography (OCT) and OCT angiography studies, reporting structural and vascular retinal alterations in early and preclinical AD, while highlighting inconsistencies across studies and discussing possible pathophysiological explanations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings support the potential of OCT-based retinal measures as candidate early biomarkers of AD, but emphasise the need for standardised imaging protocols, comparative studies across dementia subtypes and longitudinal validation to establish diagnostic utility.

INTRODUCTION

The current context of Alzheimer's disease and its relationship to the retina

Alzheimer's disease (AD), the most common cause of dementia, is a progressive neurodegenerative disorder (NDD) that increasingly affects ageing populations worldwide. In the USA alone, 6.7 million individuals aged 65 and older are currently living with AD.[1] This prevalence poses a significant public health challenge due to its impact on affected individuals and the associated economic burden on global gross domestic product.[1 2] The classical hallmarks of AD include the accumulation of neurotoxic amyloid β-protein (Aβ) and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein (pTau) in the cerebral cortex and hippocampus. These pathological processes lead to inflammation, cellular metabolic dysfunction, neurodegeneration and progressive cognitive decline.[3 4]

Evidence has demonstrated that Aβ immunisation can mitigate retinal laminar structure loss by reducing Aβ plaque

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formation, highlighting a link between Aβ and retinal changes in AD.[5] Aβ has also been detected in the aqueous humour at comparable levels found in cerebrospinal fluid (CSF).[6] Similarly, pTau accumulation has been observed in the retina, particularly in the inner plexiform layer (IPL) and the retinal ganglion cell layer (RGCL), where it contributes to retinal ganglion cell (RGC) loss and inflammation.[7,8] Furthermore, pTau accumulation in the superior and peripheral retina correlates with cerebral AD pathology, strengthening the connection between retinal and brain changes in AD.[9]

Given the shared embryological, anatomical and physiological characteristics of retinal and cerebral vasculature, the retina has long been considered a 'window' to the brain.[10–13] As a site where ageing theories, disease mechanisms and pathophysiological processes converge, the retina offers valuable insights into systemic conditions affecting non-visible organs. Hypoxia, oxidative stress, inflammation and mitochondrial dysfunction—common causative factors in ageing—are shared between retinal and cerebral pathology.[14] Notably, Aβ deposits in ageing retinas[15] and their presence in drusen deposits (a hallmark of age-related macular degeneration (ARMD))[16] suggest a potential link between early retinal pathology and AD development.[17]

Challenges in AD diagnosis and the need for early detection

Most clinical symptoms of AD appear only at advanced stages, when significant and irreversible neuronal loss has already occurred. Yet, a long preclinical phase—spanning up to 10–15 years—precedes symptom onset and represents a key window for early intervention. The recent approval of lecanemab, which slows cognitive decline in early symptomatic AD,[18] reinforces the importance of detecting AD pathology before clinical symptoms emerge. However, current tools for early detection remain invasive or expensive, and early signs are often mistaken for normal ageing, delaying diagnosis.[19]

Current diagnostic tools, such as Aβ positron emission tomography (PET) and CSF analysis, are both expensive and invasive.[20,21] Cognitive assessments, including the Mini-Mental State Examination (MMSE)[22] and the Montreal Cognitive Assessment, have limited sensitivity for detecting early-stage AD.[19,23] Genetic testing, such as identifying apolipoprotein E epsilon 4 (APOE ε4) variants, only identifies individuals at higher risk.[24] Thus, there is a pressing need for fast, reliable, non-invasive and accessible diagnostic methods to detect AD at its preclinical stage. Such methods could enable personalised interventions and lifestyle modifications to delay symptom onset and maintain quality of life.[19,25]

The role of optical coherence tomography in AD research

Optical coherence tomography (OCT) is a non-invasive, repeatable, in vivo imaging technique based on low-coherence interferometry. It enables the quantification of retinal and choroidal thickness, with analysis at the sublayer level.[26] Advances in OCT technology, notably the transition from time-domain OCT to spectral-domain OCT (SD-OCT), have significantly enhanced image resolution, providing detailed insights into retinal, choroidal and optic nerve architectures.

OCT angiography (OCT-A) further expands OCT's capabilities by allowing non-invasive visualisation of vasculature without the need for dye injection.[26–30] OCT-A allows for precise characterisation of vascular structure and perfusion with the retina's capillary layers, the choroid and the optic nerve head.[27] Given the similarities between retinal and cerebral vasculature, OCT-A holds promise as a valuable tool for assessing brain vascular health.[31]

Previous reviews on ocular biomarkers in AD have generally covered the full disease continuum, often pooling results from preclinical, mild cognitive impairment (MCI) and dementia stages.[32] This approach, while comprehensive, has limited the ability to discern whether OCT-based changes emerge early enough for preventive intervention. Moreover, few reviews have specifically integrated findings from OCT-A in biomarker-defined preclinical cohorts, and none have systematically assessed study quality.[17,26] Our review addresses these gaps by (1) restricting the scope to preclinical and early AD, (2) synthesising OCT and OCT-A findings in a stage-stratified manner, (3) explicitly reporting methodological quality and (4) proposing a mechanistic framework to reconcile conflicting results (early inflammation and vascular compensation vs later neurodegeneration and vascular rarefaction). This approach provides novel insights into the translational potential of retinal biomarkers in early AD, while acknowledging that the current evidence base remains limited and requires validation through larger, comparative and longitudinal studies.

This systematic review examines the potential of SD-OCT and OCT-A technologies to identify retinal biomarkers for detecting and monitoring AD during its early or preclinical stages.

MATERIALS AND METHODS

A comprehensive search of MEDLINE articles via PubMed was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines, and the study was registered in National Institute for Health and Care Research-PROSPERO (CRD42024600456). PubMed/MEDLINE was selected as the primary database because of its extensive coverage of biomedical and ophthalmology literature; after internal discussion (with Sylvain), we decided not to extend the search to Embase, Scopus or Web of Science. We acknowledge this as a limitation and now explicitly state it in the manuscript.

The search targeted human studies published up to April 2025 that evaluated one or both standard biomarkers for diagnosing preclinical or early-stage AD using CSF analysis or PET imaging in conjunction with SD-OCT and/or OCT-A. The search strategy combined Boolean operators and Medical Subject Headings terms.

To enhance completeness, we also performed reference list screening of included papers and relevant reviews, as well as forward citation tracking. These additional steps did not identify further eligible clinical studies, but they reinforced the robustness of the selection process. Exclusion criteria included reviews, meta-analyses, case reports, animal studies, studies not published in English and studies involving ocular pathologies or systemic conditions that could interfere with OCT results. One study was excluded because it used OCT solely for controlling ophthalmological parameters in patient assessments. Four articles focusing on early-onset AD rather than early-stage or preclinical AD were excluded (online supplemental table S1).

Two reviewers independently screened all titles and abstracts, removed duplicates and assessed full texts for eligibility using a standardised form. Discrepancies were resolved by consensus. Reasons for exclusion at each stage were recorded. The overall screening workflow, including the number of records identified, duplicates removed and studies excluded at full text, is summarised in online supplemental table S2.

The details extracted included author information, publication year, study design, population characteristics and study outcomes. Cognitive assessment tools and test names are reported exactly as described in the original included publications; they were extracted for descriptive purposes only and were not administered, used, copied, or reproduced by the authors of this systematic review. The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS)[33] (online supplemental table S3).

The findings were summarised in a narrative synthesis of the data. The risk of bias in individual studies was assessed to evaluate the internal validity of the results. Potential biases, including selection bias, information bias and publication bias, were given particular attention to ensure a robust interpretation of the findings.

The study process is summarised in figure 1.

RESULTS

This review included 22 studies (online supplemental table S3). Control groups were age matched, except for van de Kreeke *et al*, which compared monozygotic twins.[34 35] Two studies specifically compared early-stage AD with vascular dementia (VD).[36 37]

Findings in preclinical AD

Peripapillary retinal nerve fibre layer thickness

Three studies reported significant thinning of the peripapillary retinal nerve fibre layer (RNFL) in the early stages of AD (from increased risk to mild to moderate disease) compared with controls.[38 39] However, several studies found no statistically significant differences, though some observed trends. For instance, Mathew *et al*[40] noted progressive RNFL thinning and macular thickening during AD progression, while Kim and Kang[41] detected retinal thinning in mild to moderate AD but not in MCI, suggesting that structural changes may begin early but become detectable only later.

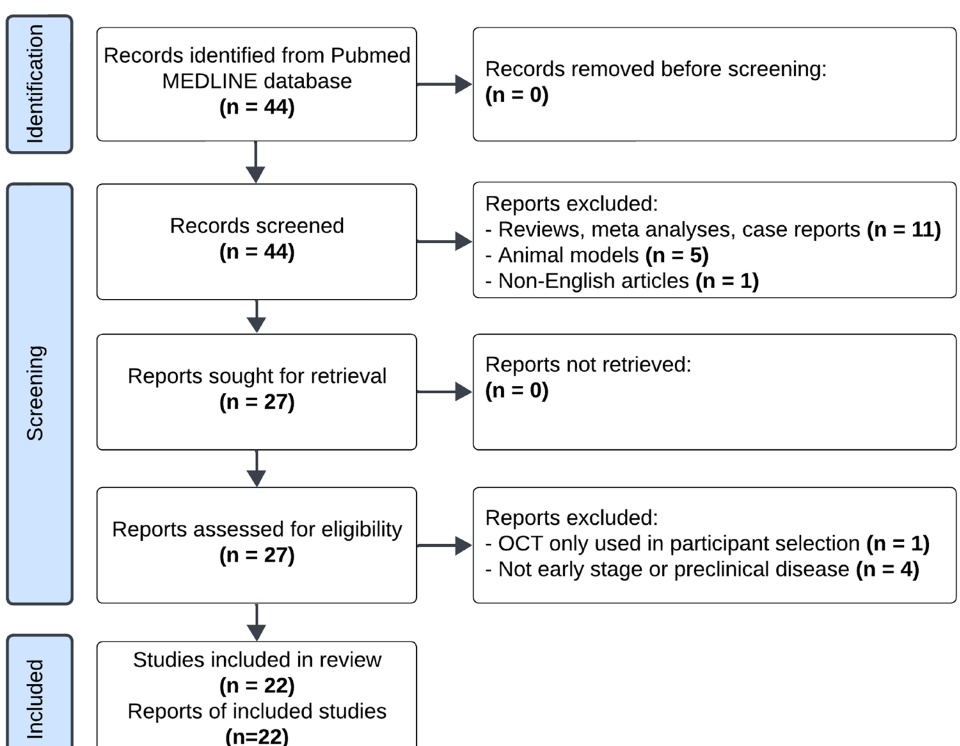

Figure 1 Study selection. A MEDLINE search based on relevant keywords identified 44 articles. These articles were reduced to 22 after excluding animal models, non-English articles, reviews, meta-analyses, case reports and articles not relevant to the topic. OCT, optical coherence tomography.

Interestingly, some studies noted sectorial RNFL thinning, particularly in the nasal sector, aligning with patterns observed in established AD. Nasal fibres, following the papillomacular bundle, are particularly susceptible to degenerative damage due to their high energy requirement.[15 42] Conversely, other studies (eg, van de Kreeke *et al*[35]) found no differences in peripapillary RNFL thickness.

Finally, López-Cuenca *et al*[43] observed significantly reduced retinal area volumes, including RNFL, in APOE ε4 high-risk patients, but no difference in peripapillary RNFL thickness.

RGCL thickness

Thinning of the RGCL was reported only by Romagnoli *et al*[44] in mild to moderate AD. Other studies found no differences in asymptomatic at risk for AD or AD-MCI comparisons.[35 45 46] Kim and Kang[41] observed significant RGCL thinning only in severe AD, suggesting progressive changes as the disease advances.

IPL thickness

A non-significant thickening of the IPL in patients with AD was reported, hypothesised to result from retinal inclusion bodies containing fibrillar Aβ deposits, reflecting early inflammation.[47] The initial thickening may mask potential thinning due to neurodegeneration. However, a study by Jorge *et al* found no differences in IPL thickness in patients with mild AD compared with controls.[45]

Findings in MCI

Macular thickness

Marquié *et al*[36] reported sectorial thickening of the inner nasal macular region in individuals with positive Aβ PET scans. However, this did not predict progression from subjective cognitive decline to MCI. Other studies found no changes in macular thickness in asymptomatic at risk for AD,[15 46] though significant thinning was noted in severe AD stages.[41] Ascaso *et al*[38] observed RNFL thinning in patients with MCI and AD. Still, they reported increased macular volume in MCI (vs reduced in AD), potentially reflecting an early inflammatory phase masking neurodegeneration, which transitions to thinning in AD as neuronal loss predominates.

Choroidal thickness

Choroidal thinning was observed in early AD in studies using age-matched participants, even without RNFL changes.[48] This result was not found by Li *et al*,[49] who noted significant thinning only in cases of severe AD. However, longitudinal studies have shown progressive thinning as the disease progresses.[49 50] Moreover, López-de-Eguileta *et al*[50] found a trend in choroidal thinning in MCI, reaching significance when MCI and AD data were combined. Finally, Gharbiya *et al*[48] linked tear Aβ1–42 levels to choroidal thickness and psychometric scores (MMSE and Alzheimer's Disease Assessment Scale-Cognitive Subscale).

Vascular analysis

Biscetti *et al*[51] reported reduced retinal perfusion parameters in patients with MCI compared with controls despite standard retinal thickness and volume. The fractal dimension was increased in MCI, suggesting altered vascular network complexity. Other vascular changes in asymptomatic at-risk patients with AD include increased foveal avascular zone (FAZ) area, choriocapillaris flow deficits[52] and retinal capillary loss, particularly in the deep plexus.[42] However, Sadda *et al*[53] found no significant differences in vascular density in the superficial and deep vascular plexus, potentially due to a small sample size (seven patients with preclinical AD and eight controls), even though ganglion cell layer-IPL integrity was notably reduced in the preclinical AD group.

Conversely, Marquié *et al*[54] observed higher macular vascular density in the temporal quadrant of the MCI-AD group compared with controls but not in the MCI-VD group, suggesting disease vascular changes. Early vascular dysregulation in AD, driven by Aβ deposition, hypoxia and dysregulated angiogenesis, may trigger neuroinflammation, initially increasing vascular density before transitioning to vascular loss in later stages.[55–57] Aβ and collagen deposits within capillaries may induce cell apoptosis and retinal vessel closure over time. Aβ accumulation in the inner retinal layers (IRL) could also contribute to vascular changes. These observations suggest that vascular and structural changes in the retina occur in preclinical AD.

van de Kreeke *et al*[34] also reported significantly higher vascular retinal density in asymptomatic at-risk patients with AD (defined by Aβ PET scans), with no FAZ size differences, while previous studies[58–60] had highlighted reduced retinal vessel density and increased FAZ in established AD. Increased retinal blood flow and vasodilation in early stages due to inflammatory response to early amyloid accumulation (such as observed in the brain) may reveal previously undetectable microvessels on OCT-A, leading to higher vascular density measurements.[57] Over time, the inflammation and Aβ accumulation result in vascular damage and density reductions in advanced AD.[58]

Findings in mild AD

Comparison to other forms of dementia

Only two studies compared early-stage AD with other forms of dementia. Marquié *et al*[36] found greater macular vessel density in the AD group compared with the VD group, in contrast to other studies that reported reduced vascular measures in AD.[42 51 61] Conversely, Mavilio *et al*[37] found no differences in RNFL or RGCL thickness between VD and AD dementia, highlighting the complexity of structural changes across dementia subtypes.

Other putative OCT findings: retinal gliosis

Ravichandran *et al*[62] identified potential epiretinal gliosis in asymptomatic at-risk patients with AD using en face and SD-OCT B-scans, despite no significant RNFL changes.

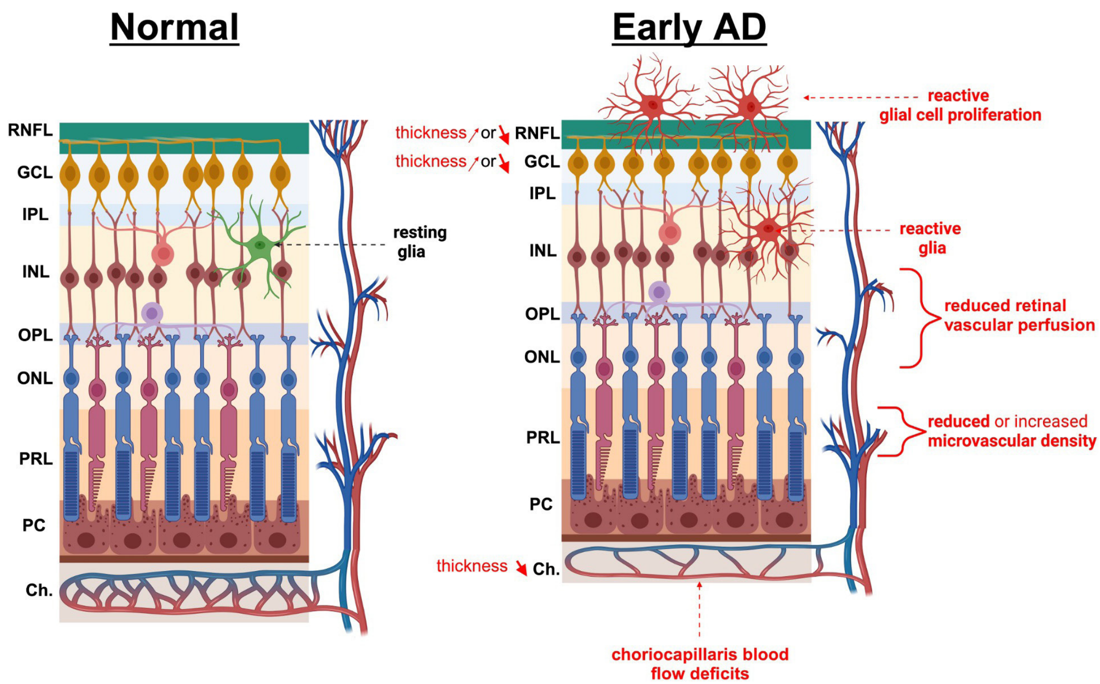

Figure 2 Schematic representation of retinal changes associated with preclinical Alzheimer's disease (AD). Left panel: the normal retinal structure is shown with the major retinal layers—retinal nerve fibre layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), photoreceptor layer (PRL), pigmented cells (PC) and the choriocapillaris (Ch). Glial cells (green) and retinal vasculature (blue and red vessels) are functioning normally, providing adequate blood flow and oxygenation to the retina. The thickness of the retinal layers is preserved, and the choriocapillaris beneath the photoreceptors ensures proper blood supply to the outer retina, supporting healthy visual function. Right panel: retinal pathology associated with preclinical AD. Thinning of the retinal layers is observed, particularly in the RNFL and GCL. Development of reactive glial cell proliferation on the retinal surface (detected by optical coherence tomography (OCT) en face, red) and putative transretinal gliosis (hypertrophy and proliferation), which might explain the macular thickening reported in some cohorts of early AD, have also been reported. The retinal vasculature shows reduced perfusion, with significant changes in microvascular density (studies report both reduced and increased density). Additionally, deficits in choriocapillaris blood flow are evident, further contributing to retinal dysfunction. Red labels and arrows highlight the changes in key pathological features seen in AD, including reduced retinal perfusion, vascular abnormalities, reactive gliosis and thinning of retinal layers.

This finding suggests gliosis as a potential biomarker, though further research is needed to confirm its relevance to retinal and cerebral ageing processes.

Figure 2 illustrates a schematic representation of retinal changes in asymptomatic at-risk AD.

Risk of bias and quality assessment

The methodological quality of the 22 included studies was appraised with the NOS. Overall, quality was predominantly moderate: a minority of studies achieved a 'good' rating (typically those with biomarker-confirmed cohorts and stronger adjustment), while most were 'fair', and a smaller subset 'poor-to-fair'. Ascertainment of AD status was heterogeneous—several studies confirmed diagnosis or risk status with PET/CSF, whereas others relied on clinical criteria alone. The most frequent limitations were small sample sizes, cross-sectional designs (only one longitudinal dataset), incomplete control for ocular/systemic confounders (eg, glaucoma, diabetes, vascular risk) and limited reporting of masking/blinding for image analysis. OCT/OCT-A outcome measurement was generally objective and standardised, but variability in devices/segmentation may introduce measurement bias. A study-by-study NOS breakdown is provided in online supplemental table S3.

DISCUSSION

Retinal changes as biomarkers for AD detection

Evidence from postmortem biopsies of patients with cognitive impairment[9] indicates that retinal and brain alterations occur simultaneously in several NDDs, including AD and Parkinson's disease (PD). This supports retinal changes, as assessed through non-invasive OCT, to detect preclinical and early AD stages. Key findings include thinning of the peripapillary RNFL, IRL and choroidal layers, as well as reduced retinal capillary density and abnormal vasodilatory responses. However, this review also highlights significant discrepancies in OCT biomarkers in asymptomatic at-risk AD, such as thickening versus thinning of retinal and choroidal layers and increased versus reduced vascular density.

Discrepancies in retinal thickness and vascular density

Inflammation within the retinal tissue during early AD stages,[38] particularly in MCI, may partially explain these discrepancies. Reactive changes, such as RGC swelling, Müller glia proliferation or hypertrophy, could mask early neurodegeneration and vascular loss, contributing to observations of increased retinal thickness[63–65] or the absence of detectable changes.[66 67] These phenomena may represent an adaptive response to stress before irreversible damage occurs.

Interindividual variability in ageing processes, such as declines in neuronal, haematopoietic and immune resilience,[14 68 69] could further explain inconsistencies in retinal biomarkers. Ageing-related changes, including oxidative distress, ischaemia and mitochondrial dysfunction, may correspond to different phases of resilience, ranging from 'homeostatic' to 'stress' and finally to 'failure' stages.[70] In established AD, this failure is marked by neuronal and vascular loss. Similarly, isolated epiretinal gliosis observed in some studies, such as Ravichandran *et al*,[62] without corresponding retinal thickening, may indicate an adaptive response of retinal astrocytes to ischaemia rather than a disease-specific hallmark.[68 71]

Variability in vascular biomarkers across NDDs could also reflect differences in primary disease triggers. For instance, vascular parameters are often more significantly affected and earlier in VD than AD.[72–74] These inconsistencies underscore the need for longitudinal studies to track retinal changes in the same patients over time, enabling a deeper understanding of how these parameters evolve towards disease states and identifying opportunities for early interventions.

By stratifying results by disease stage, our review clarifies that OCT/OCT-A changes emerge progressively. In preclinical AD, alterations are inconsistent and sometimes paradoxical (eg, sectoral RNFL thinning, increased vs reduced vascular density), likely reflecting early inflammatory or compensatory mechanisms. In MCI, structural thinning (macular, choroidal) and vascular rarefaction become more consistent. In mild AD, retinal thinning across layers and vascular loss are most robustly demonstrated. This staged synthesis provides a clearer framework for interpreting OCT biomarkers along the AD continuum.

In contrast to the heterogeneous findings in preclinical and MCI cohorts, moderate to severe AD consistently shows marked RNFL, RGCL and macular thinning, as well as vascular rarefaction.[41 49 58] This comparison underscores that early changes are subtle and variable, whereas later stages reveal robust neurodegeneration, highlighting the need for longitudinal validation of early OCT/OCT-A biomarkers.

Study limitations

Many studies have small sample sizes, which limit their ability to detect subtle retinal changes. Additionally, some participants may not ultimately develop AD or harbour other quiescent NDDs, complicating the interpretation of findings.[75] Long-term follow-up is critical to confirm whether preclinical retinal changes progress to AD and to distinguish these changes from normal ageing or other forms of dementia.

Exclusion criteria for confounding ocular or systemic conditions, such as diabetes or glaucoma, were inconsistently reported, which is problematic given that OCT findings are not specific to brain diseases.

Our search was limited to PubMed/MEDLINE; while this provides broad biomedical coverage, omission of Embase, Scopus and Web of Science may have led to missing studies. However, supplementary citation and reference list screening did not yield additional eligible clinical work.

Limitations of OCT

Device-related limitations

Variability in OCT technology and methodologies contributes to inconsistent findings. Differences in image quality segmentation algorithms, scan patterns and protocol updates[27] can result in measurement discrepancies.[76] This is especially critical in preclinical AD, where retinal changes are subtle and require sensitive detection methods.

While SD-OCT and OCT-A show promise, their specificity for AD among NDDs remains unproven. A study comparing retinal measures in AD, amnestic MCI, PD and non-AD dementias found no significant differences in RNFL, RGCL thickness or macular volume.[77] As demonstrated in PD studies, combining multiple parameters with mathematical modelling may enhance specificity.[78]

Operator-dependent limitations

The reproducibility of OCT measurements depends on the operator's expertise. Although modern OCT devices feature 'follow-up' software to align successive scans, accurate baseline measurements by certified operators are essential. Even though the reproducibility of retinal thickness measurements is high with low variability,[79 80] in the context of preclinical AD, subtle changes can be challenging to measure and require precise segmentation methods to distinguish between retinal layers.[81] The positioning of the SD-OCT beam is critical, and Henle's fibre layer inclusion in outer nuclear layer (ONL) measurements can artificially double ONL thickness. Irregular layer boundaries and decentring between the FAZ centre and the centre of the en face image can also introduce errors.[82] Enhanced depth imaging and swept-source OCT technologies improve the deeper choroidal layers and boundary visualisation while combining manual segmentation with the choroidal vascularity index, a quantitative biomarker that evaluates the ratio of vascular lumen area to the total choroidal area,[83] which could provide valuable insights into ischaemic contributions to AD. Finally, a refined manual segmentation method described by Arrigo *et al*, although time consuming, improves the discrimination of the choriocapillaris and, therefore, the evaluation of hypoxia-ischaemia in the pathophysiology.[84]

Patient-dependent limitations

Ocular conditions, such as elevated intraocular pressure, media opacities, dry eye (a feature of ageing, oxidative distress and mitochondrial dysfunction) and ARMD-related fixation errors, can affect image quality. High myopia can introduce magnification errors, and myopic eyes should be excluded unless axial length is accounted for.[85] Motion artefacts and compliance issues in OCT-A further limit the reliability of quantitative vascular measures.[30 82 86]

Interpretation and conceptual limitations

In contrast to earlier reviews that pooled all AD stages, our synthesis focuses exclusively on preclinical and early disease and integrates OCT-A metrics in biomarker-defined cohorts. By stratifying results by disease stage and reporting methodological quality, we highlight both the promise and the limitations of OCT/OCT-A as early biomarkers. We also propose a mechanistic model, from early inflammation and compensatory vascular responses to later neurodegeneration and vascular rarefaction, that helps explain contradictory findings. This structured approach clarifies the unique contribution of OCT-based biomarkers to early AD detection and delineates the evidence still needed for clinical translation.

It is important to note that the OCT and OCT-A alterations reported here are not specific to AD. Similar structural and vascular changes have been described in PD, VD and other NDDs.[63 72 77] The paucity of comparative studies across dementia subtypes further limits our ability to assess diagnostic specificity. Until such head-to-head data are available, OCT-based retinal biomarkers should be regarded as potential markers of neurodegeneration more broadly, rather than AD-specific signatures.

Combined biomarkers and emerging technologies

Combining OCT findings with other biomarkers, such as plasma metabolite profiles (eg, amino acids and purines), could improve diagnostic accuracy. These metabolites have been associated with OCT features observed in early and intermediate stages of ARMD, including hyperreactive intraretinal foci, atrophy and ellipsoid zone disruption.[87] Purine metabolites, altered in AD,[88] suggest that the disease may be triggered by maladaptive use of the fructose-uric acid survival pathway, reflecting oxidative stress.[89] Given the multifactorial nature of NDDs, a single biomarker is unlikely to suffice for predicting preclinical AD. Coupling OCT biomarkers with serum metabolomics offers a perspective to overcome the current limitations of OCT in preclinical AD detection and enhance its specificity.

Emerging OCT technologies offer significant potential. High-resolution SD-OCT enables imaging at the mitochondria level within the photoreceptor's inner segments[90]; spatiotemporal OCT enhances 'en face' imaging for full-thickness visualisation of the choriocapillaris-choroidal complex[91]; and adaptive optics-OCT images provide detailed imaging of cone photoreceptor nuclei and pores in the external limiting membrane, the blood-retinal barrier formed by Müller cell endfeet. These developments extend OCT's capabilities to the cellular and organelle level, enabling the assessment of homeostatic retinal neuronal, vascular and epithelial resilience.[68]

Ultrawide-field colour imaging facilitates the rapid detection of peripheral retinal drusen, which has long been associated with AD.[32] Its application in evaluating retinal and choroidal vasculature in MCI represents a promising addition to the diagnostic toolkit for preclinical AD detection.[67 92]

Strength of evidence

The methodological quality of the included studies was mostly moderate, which limits the strength of the conclusions. Only a subset incorporated biomarker-confirmed cohorts (PET or CSF), while others relied on clinical diagnosis alone, increasing the risk of misclassification. Across the literature, small sample sizes, cross-sectional designs and heterogeneous OCT/OCT-A protocols further reduced reproducibility. These limitations underscore the need for larger, longitudinal, biomarker-defined studies with standardised imaging protocols to establish the reliability and clinical utility of retinal biomarkers in early AD.

Practical implications for clinical translation

Our synthesis highlights several practical considerations for moving OCT/OCT-A from research into clinical use. First, standardised acquisition protocols, segmentation algorithms and vascular metrics are needed to ensure reproducibility across centres. Second, OCT/OCT-A should be evaluated in biomarker-confirmed longitudinal cohorts to determine their predictive value for conversion from preclinical or MCI stages to AD. Third, in clinical settings, OCT/OCT-A could serve as a low-cost, non-invasive screening or enrichment tool to identify individuals who may benefit from further biomarker testing (eg, CSF, PET). Fourth, given the lack of disease specificity, OCT findings should be interpreted in combination with other biomarkers (fluid or imaging) to improve diagnostic accuracy. Together, these steps define a realistic translational pathway for integrating retinal imaging into early AD detection strategies.

Prospects

OCT carries a unique, non-invasive capacity to evaluate hypoxia (capillary loss), inflammation, epithelial dysfunction, glial reactivity and therefore the resulting alterations of tissular health (eg, rupture of barriers), central nervous system-specific loss of function (ie, neuronal loss), and the state of resilience to stress (eg, rheological microcirculation compensation).[68 70 93] It has shown correlations with established AD and other NDDs like PD, paving the way for early detection. However, challenges remain: (1) standardising quantitative techniques to process and analyse the OCT imaging,[84] (2) ensuring clinical reliability, (3) improving specificity for AD among NDDs and (4) gathering longitudinal data to confirm predictive value.

OCT changes reflect tissue dysfunction and, potentially soon, cellular-level alterations, providing insights into resilience to chronic disease stressors. This may explain contradictory findings, such as increased versus reduced thickness or vascular perfusion. Integration with proteomics, metabolomics and artificial intelligence could enhance diagnostic precision.[94] While OCT may identify early cognitive decline, its application remains limited to pioneer centres. Further research is essential to establish routine preclinical AD detection.

CONCLUSION

SD-OCT and OCT-A hold potential as non-invasive preclinical AD biomarkers, but further research is needed to develop reliable, sensitive and disease-specific diagnostic tools for routine clinical use.

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REFERENCES

1 2023 Alzheimer's disease facts and figures. *Alzheimer's &Amp; Dementia* 2023;19:1598–695.
2 Rajendran K, Krishnan UM. Biomarkers in Alzheimer's disease. *Clinica Chimica Acta* 2024;562:119857.
3 Swerdlow RH. Pathogenesis of Alzheimer's disease. *Clin Interv Aging* 2007;2:347–59.
4 Wyss-Coray T, Rogers J. Inflammation in Alzheimer disease-a brief review of the basic science and clinical literature. *Cold Spring Harb Perspect Med* 2012;2:a006346.
5 Liu B, Rasool S, Yang Z, *et al*. Amyloid-peptide vaccinations reduce {beta}-amyloid plaques but exacerbate vascular deposition and inflammation in the retina of Alzheimer's transgenic mice. *Am J Pathol* 2009;175:2099–110.
6 Goldstein LE, Muffat JA, Cherny RA, *et al*. Cytosolic β-amyloid deposition and supranuclear cataracts in lenses from people with Alzheimer's disease. *The Lancet* 2003;361:1258–65.
7 Hart NJ, Koronyo Y, Black KL, *et al*. Ocular indicators of Alzheimer's: exploring disease in the retina. *Acta Neuropathol* 2016;132:767–87.
8 Javaid FZ, Brenton J, Guo L, *et al*. Visual and Ocular Manifestations of Alzheimer's Disease and Their Use as Biomarkers for Diagnosis and Progression. *Front Neurol* 2016;7:55.
9 den Haan J, Morrema THJ, Verbraak FD, *et al*. Amyloid-beta and phosphorylated tau in post-mortem Alzheimer's disease retinas. *Acta Neuropathol Commun* 2018;6:147.
10 Cheung CY, Ong YT, Hilal S, *et al*. Retinal ganglion cell analysis using high-definition optical coherence tomography in patients with mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis* 2015;45:45–56.
11 Cvekl A, Vijg J. Aging of the eye: Lessons from cataracts and age-related macular degeneration. *Ageing Res Rev* 2024;99:102407.
12 Wong TY, Klein R, Klein BE, *et al*. Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. *Surv Ophthalmol* 2001;46:59–80.
13 Zhang Y, Wang Y, Shi C, *et al*. Advances in retina imaging as potential biomarkers for early diagnosis of Alzheimer's disease. *Transl Neurodegener* 2021;10:6.
14 Sies H. Oxidative Stress: Concept and Some Practical Aspects. *Antioxidants (Basel)* 2020;9:852.
15 Asanad S, Felix CM, Fantini M, *et al*. Retinal ganglion cell dysfunction in preclinical Alzheimer's disease: an electrophysiologic biomarker signature. *Sci Rep* 2021;11:6344.
16 Vujosevic S, Limoli C, Kozak I. Hallmarks of aging in age-related macular degeneration and age-related neurological disorders: novel insights into common mechanisms and clinical relevance. *Eye (Lond)* 2025;39:845–59.

17 García-Bermúdez MY, Vohra R, Freude K, *et al*. Potential Retinal Biomarkers in Alzheimer's Disease. *Int J Mol Sci* 2023;24:15834.
18 van Dyck CH, Swanson CJ, Aisen P, *et al*. Lecanemab in Early Alzheimer's Disease. *N Engl J Med* 2023;388:9–21.
19 Porsteinsson AP, Isaacson RS, Knox S, *et al*. Diagnosis of Early Alzheimer's Disease: Clinical Practice in 2021. *J Prev Alzheimers Dis* 2021;8:371–86.
20 Sperling RA, Aisen PS, Beckett LA, *et al*. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's &Amp; Dementia* 2011;7:280–92.
21 Thal LJ, Kantarci K, Reiman EM, *et al*. The Role of Biomarkers in Clinical Trials for Alzheimer Disease. *Alzheimer Disease & Associated Disorders* 2006;20:6–15.
22 Folstein MF, Folstein SE, McHugh PR. Mini-mental state. *J Psychiatr Res* 1975;12:189–98.
23 Costa A, Bak T, Caffarra P, *et al*. The need for harmonisation and innovation of neuropsychological assessment in neurodegenerative dementias in Europe: consensus document of the Joint Program for Neurodegenerative Diseases Working Group. *Alz Res Therapy* 2017;9:27.
24 Di Resta C, Ferrari M. New molecular approaches to Alzheimer's disease. *Clin Biochem* 2019;72:81–6.
25 Gauthier SG. Alzheimer's disease: the benefits of early treatment. *Euro J of Neurology* 2005;12:11–6.
26 López-Cuenca I, Salobrar-García E, Elvira-Hurtado L, *et al*. The Value of OCT and OCTA as Potential Biomarkers for Preclinical Alzheimer's Disease: A Review Study. *Life (Basel)* 2021;11:712.
27 Chan VTT, Sun Z, Tang S, *et al*. Spectral-Domain OCT Measurements in Alzheimer's Disease. *Ophthalmology* 2019;126:497–510.
28 Choi W, Mohler KJ, Potsaid B, *et al*. Choriocapillaris and Choroidal Microvasculature Imaging with Ultrahigh Speed OCT Angiography. *PLoS ONE* 2013;8:e81499.
29 Cohen AA, Ferrucci L, Fülöp T, *et al*. A complex systems approach to aging biology. *Nat Aging* 2022;2:580–91.
30 Spaide RF, Klancnik JM, Cooney MJ. Retinal Vascular Layers Imaged by Fluorescein Angiography and Optical Coherence Tomography Angiography. *JAMA Ophthalmol* 2015;133:45.
31 Patton N, Aslam T, MacGillivray T, *et al*. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. *J Anat* 2005;206:319–48.
32 Cheung CY, Mok V, Foster PJ, *et al*. Retinal imaging in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2021;92:983–94.
33 Lo CK-L, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol* 2014;14:45.
34 van de Kreeke JA, Nguyen H-T, Konijnenberg E, *et al*. Optical coherence tomography angiography in preclinical Alzheimer's disease. *Br J Ophthalmol* 2020;104:157–61.
35 van de Kreeke JA, Nguyen HT, Konijnenberg E, *et al*. Longitudinal retinal layer changes in preclinical Alzheimer's disease. *Acta Ophthalmol* 2021;99:538–44.
36 Marquié M, Valero S, Castilla-Marti M, *et al*. Association between retinal thickness and β-amyloid brain accumulation in individuals with subjective cognitive decline: Fundació ACE Healthy Brain Initiative. *Alzheimers Res Ther* 2020;12:37.
37 Mavilio A, Sisto D, Prete F, *et al*. RE-PERG in early-onset Alzheimer's disease: A double-blind, electrophysiological pilot study. *PLoS ONE* 2020;15:e0236568.
38 Ascaso FJ, Cruz N, Modrego PJ, *et al*. Retinal alterations in mild cognitive impairment and Alzheimer's disease: an optical coherence tomography study. *J Neurol* 2014;261:1522–30.
39 Bambo MP, Garcia-Martin E, Gutierrez-Ruiz F, *et al*. Analysis of optic disk color changes in Alzheimer's disease: a potential new biomarker. *Clin Neurol Neurosurg* 2015;132:68–73.
40 Mathew S, WuDunn D, Mackay DD, *et al*. Association of Brain Volume and Retinal Thickness in the Early Stages of Alzheimer's Disease. *J Alzheimers Dis* 2023;91:743–52.
41 Kim J-I, Kang B-H. Decreased retinal thickness in patients with Alzheimer's disease is correlated with disease severity. *PLoS ONE* 2019;14:e0224180.
42 Asanad S, Fantini M, Sultan W, *et al*. Retinal nerve fiber layer thickness predicts CSF amyloid/tau before cognitive decline. *PLoS ONE* 2020;15:e0232785.
43 López-Cuenca I, Marcos-Dolado A, Yus-Fuertes M, *et al*. The relationship between retinal layers and brain areas in asymptomatic first-degree relatives of sporadic forms of Alzheimer's disease: an exploratory analysis. *Alzheimers Res Ther* 2022;14:79.
44 Romagnoli M, Amore G, Avanzini P, *et al*. Chromatic pupillometry for evaluating melanopsin retinal ganglion cell function in Alzheimer's disease and other neurodegenerative disorders: a review. *Front Psychol* 2023;14:1295129.
45 Jorge L, Canário N, Martins R, *et al*. The Retinal Inner Plexiform Synaptic Layer Mirrors Grey Matter Thickness of Primary Visual Cortex with Increased Amyloid β Load in Early Alzheimer's Disease. *Neural Plast* 2020;2020:8826087.
46 Wu SZ, Nolan-Kenney R, Moehringer NJ, *et al*. Exploration of Rapid Automatized Naming and Standard Visual Tests in Prodromal Alzheimer Disease Detection. *J Neuroophthalmol* 2022;42:79–87.
47 Isas JM, Luibl V, Johnson LV, *et al*. Soluble and Mature Amyloid Fibrils in Drusen Deposits. *Invest Ophthalmol Vis Sci* 2010;51:1304.
48 Gharbiya M, Visioli G, Trebbastoni A, *et al*. Beta-Amyloid Peptide in Tears: An Early Diagnostic Marker of Alzheimer's Disease Correlated with Choroidal Thickness. *Int J Mol Sci* 2023;24:2590.
49 Li M, Li R, Lyu J-H, *et al*. Relationship Between Alzheimer's Disease and Retinal Choroidal Thickness: A Cross-Sectional Study. *J Alzheimers Dis* 2021;80:407–19.
50 López-de-Eguileta A, Lage C, López-García S, *et al*. Evaluation of choroidal thickness in prodromal Alzheimer's disease defined by amyloid PET. *PLoS ONE* 2020;15:e0239484.
51 Biscetti L, Lupidi M, Luchetti E, *et al*. Novel noninvasive biomarkers of prodromal Alzheimer disease: The role of optical coherence tomography and optical coherence tomography–angiography. *Euro J of Neurology* 2021;28:2185–91.
52 Corradetti G, Oncel D, Kadomoto S, *et al*. Choriocapillaris and Retinal Vascular Alterations in Presymptomatic Alzheimer's Disease. *Invest Ophthalmol Vis Sci* 2024;65:47.
53 Sadda SR, Borrelli E, Fan W, *et al*. A pilot study of fluorescence lifetime imaging ophthalmoscopy in preclinical Alzheimer's disease. *Eye (Lond)* 2019;33:1271–9.
54 Marquié M, Valero S, Martínez J, *et al*. Differences in macular vessel density in the superficial plexus across cognitive impairment: the NORFACE cohort. *Sci Rep* 2022;12:16938.
55 Alvarez-Vergara MI, Rosales-Nieves AE, March-Diaz R, *et al*. Non-productive angiogenesis disassembles Aß plaque-associated blood vessels. *Nat Commun* 2021;12:3098.
56 Iturria-Medina Y, Sotero RC, Toussaint PJ, *et al*. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat Commun* 2016;7:11934.
57 Sousa DC, Leal I, Moreira S, *et al*. Hypoxia challenge test and retinal circulation changes – a study using ocular coherence tomography angiography. *Acta Ophthalmol (Copenh)* 2018;96.
58 Bulut M, Kurtuluş F, Gözkaya O, *et al*. Evaluation of optical coherence tomography angiographic findings in Alzheimer's type dementia. *Br J Ophthalmol* 2018;102:233–7.
59 Grewal DS, Polascik BW, Hoffmeyer GC, *et al*. Assessment of Differences in Retinal Microvasculature Using OCT Angiography in Alzheimer's Disease: A Twin Discordance Report. *Ophthalmic Surg Lasers Imaging Retina* 2018;49:440–4.
60 Jiang H, Wei Y, Shi Y, *et al*. Altered Macular Microvasculature in Mild Cognitive Impairment and Alzheimer Disease. *J Neuroophthalmol* 2018;38:292–8.
61 Wu J, Zhang X, Azhati G, *et al*. Retinal microvascular attenuation in mental cognitive impairment and Alzheimer's disease by optical coherence tomography angiography. *Acta Ophthalmol (Copenh)* 2020;98.
62 Ravichandran S, Snyder PJ, Alber J, *et al*. Quantifying Putative Retinal Gliosis in Preclinical Alzheimer's Disease. *Invest Ophthalmol Vis Sci* 2024;65:5.
63 Ferrari L, Huang S-C, Magnani G, *et al*. Optical Coherence Tomography Reveals Retinal Neuroaxonal Thinning in Frontotemporal Dementia as in Alzheimer's Disease. *J Alzheimers Dis* 2017;56:1101–7.
64 Oktem EO, Derle E, Kibaroglu S, *et al*. The relationship between the degree of cognitive impairment and retinal nerve fiber layer thickness. *Neurol Sci* 2015;36:1141–6.
65 Wu Y, Wang X-N, Wang N, *et al*. Regularity changes of the retinal nerve fiber layer and macular ganglion cell complex in patients with the amnestic mild cognitive impairment. *Int J Neurosci* 2018;128:849–53.
66 Almeida ALM, Pires LA, Figueiredo EA, *et al*. Correlation between cognitive impairment and retinal neural loss assessed by swept-source optical coherence tomography in patients with mild cognitive impairment. *Alz &Amp; Dem Diag Ass &Amp; Dis Mo* 2019;11:659–69.
67 Pead E, Thompson AC, Grewal DS, *et al*. Retinal Vascular Changes in Alzheimer's Dementia and Mild Cognitive Impairment: A Pilot Study Using Ultra-Widefield Imaging. *Trans Vis Sci Tech* 2023;12:13.

68 López-Otín C, Kroemer G. Hallmarks of health. *Cell* 2021;184:1929–39.
69 Ubaida-Mohien C, Moaddel R, Moore AZ, *et al*. Proteomics and Epidemiological Models of Human Aging. *Front Physiol* 2021;12:674013.
70 Love AC, Wagner GP. Co-option of stress mechanisms in the origin of evolutionary novelties. *Evolution* 2022;76:394–413.
71 Masson E. Modalités réactionnelles de la gliose rétinienne dans les maladies oculaires et relations avec l'œdème cystoïde de la macula. EM-Consulte. Available: https://www.em-consulte.com/es/article/89168/article/modalites-reactionnelles-de-la-gliose-retinienne-d [Accessed 30 Dec 2024].
72 Custodero C, Ciavarella A, Panza F, *et al*. Role of inflammatory markers in the diagnosis of vascular contributions to cognitive impairment and dementia: a systematic review and meta-analysis. *Geroscience* 2022;44:1373–92.
73 Dhoat S, Ali K, Bulpitt CJ, *et al*. Vascular compliance is reduced in vascular dementia and not in Alzheimer's disease. *Age Ageing* 2008;37:653–9.
74 Sabayan B, Jansen S, Oleksik AM, *et al*. Cerebrovascular hemodynamics in Alzheimer's disease and vascular dementia: A meta-analysis of transcranial Doppler studies. *Ageing Res Rev* 2012;11:271–7.
75 Granholm EL, Panizzon MS, Elman JA, *et al*. Pupillary Responses as a Biomarker of Early Risk for Alzheimer's Disease. *Journal of Alzheimer's Disease* 2017;56:1419–28.
76 Polo V, Garcia-Martin E, Bambo MP, *et al*. Reliability and validity of Cirrus and Spectralis optical coherence tomography for detecting retinal atrophy in Alzheimer's disease. *Eye (Lond)* 2014;28:680–90.
77 Pillai JA, Bermel R, Bonner-Jackson A, *et al*. Retinal Nerve Fiber Layer Thinning in Alzheimer's Disease: A Case-Control Study in Comparison to Normal Aging, Parkinson's Disease, and Non-Alzheimer's Dementia. *Am J Alzheimers Dis Other Demen* 2016;31:430–6.
78 Ding Y, Spund B, Glazman S, *et al*. Application of an OCT data-based mathematical model of the foveal pit in Parkinson disease. *J Neural Transm (Vienna)* 2014;121:1367–76.
79 Hu J, Gottlieb CB, Barajas DJ, *et al*. Improved repeatability of retinal thickness measurements using line-scan ophthalmoscope image-based retinal tracking. *Ophthalmic Surg Lasers Imaging Retina* 2015;46:310–4.
80 Obis J, Garcia-Martin E, Orduna E, *et al*. Reproducibility of retinal and choroidal measurements using swept-source optical coherence tomography in patients with Parkinson's disease. *Arq Bras Oftalmol* 2020;83:19–27.
81 Lujan BJ, Roorda A, Knighton RW, *et al*. Revealing Henle's Fiber Layer Using Spectral Domain Optical Coherence Tomography. *Invest Ophthalmol Vis Sci* 2011;52:1486.
82 Kashani AH, Asanad S, Chan JW, *et al*. Past, present and future role of retinal imaging in neurodegenerative disease. *Prog Retin Eye Res* 2021;83:100938.
83 Agrawal R, Gupta P, Tan K-A, *et al*. Choroidal vascularity index as a measure of vascular status of the choroid: Measurements in healthy eyes from a population-based study. *Sci Rep* 2016;6:21090.
84 Arrigo A, Amato A, Barresi C, *et al*. Choroidal Modifications Preceding the Onset of Macular Neovascularization in Age-Related Macular Degeneration. *Ophthalmol Ther* 2022;11:377–86.
85 Kang SH, Hong SW, Im SK, *et al*. Effect of Myopia on the Thickness of the Retinal Nerve Fiber Layer Measured by Cirrus HD Optical Coherence Tomography. *Invest Ophthalmol Vis Sci* 2010;51:4075.
86 Spaide RF, Fujimoto JG, Waheed NK, *et al*. Optical coherence tomography angiography. *Prog Retin Eye Res* 2018;64:1–55.
87 Lains I, Han X, Gil J, *et al*. Plasma Metabolites Associated with OCT Features of Age-Related Macular Degeneration. *Ophthalmol Sci* 2024;4:100357.
88 Ansoleaga B, Jové M, Schlüter A, *et al*. Deregulation of purine metabolism in Alzheimer's disease. *Neurobiol Aging* 2015;36:68–80.
89 Johnson RJ, Tolan DR, Bredesen D, *et al*. Could Alzheimer's disease be a maladaptation of an evolutionary survival pathway mediated by intracerebral fructose and uric acid metabolism? *Am J Clin Nutr* 2023;117:455–66.
90 Reche J, Stocker AB, Henchoz V, *et al*. High-Resolution Optical Coherence Tomography in Healthy Individuals Provides Resolution at the Cellular and Subcellular Levels. *Transl Vis Sci Technol* 2023;12:12.
91 Auksorius E, Borycki D, Wegrzyn P, *et al*. Spatio-temporal optical coherence tomography provides full thickness imaging of the chorioretinal complex. *iScience* 2022;25:105513.
92 Joseph S, Haystead A, Robbins CB, *et al*. Analysis of the Retinal and Choroidal Vasculature Using Ultrawidefield Fundus Imaging in Mild Cognitive Impairment and Normal Cognition. *Ophthalmol Sci* 2024;4:100480.
93 Boscher C, Erol O, Luscan R. Remodeling of the choroidal vasculature and the role of choriocapillaris perfusion drop in pachychoroid diseases: a global rheological approach. *Graefes Arch Clin Exp Ophthalmol* 2023;261:3045–6.
94 Ashayeri H, Jafarizadeh A, Yousefi M, *et al*. Retinal imaging and Alzheimer's disease: a future powered by Artificial Intelligence. *Graefes Arch Clin Exp Ophthalmol* 2024;262:2389–401.