Ocular biomarkers for Alzheimer disease dementia: an umbrella review of systematic reviews and meta-analyses

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Ocular biomarkers for Alzheimer's Disease Dementia: An Umbrella Review of Systematic Reviews and Meta-analyses

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Key point

- **Question**: What is the diagnostic accuracy of ocular biomarkers for early diagnosis of Alzheimer's disease (AD), as investigated in systematic reviews?
- **Finding**: Fourteen SRs and meta-analyses were included. OCT peripapillary RNFL thickness, OCTA FAZ measurement and prosaccade latency of saccadic eye movements were extensively investigated and yielded only moderate accuracy. Antisaccade error showed the best accuracy in a smaller number of trials.
- **Meaning**: Ocular biomarkers showed poor to moderate diagnostic accuracy for detection of AD in cross-sectional studies. Longitudinal studies are needed on whether changes in these parameters could yield better predictions of AD onset.

Abstract

Importance: Several ocular biomarkers have been proposed for the early detection of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI), particularly fundus photography, Optical Coherence Tomography (OCT) and OCT-angiography (OCTA).

Objective: Umbrella review of systematic reviews (SRs) on this topic.

Data sources: MEDLINE, EMBASE and PsycINFO from January 2000 to November 2021.

Study selection: Title and abstracts were screened independently by two reviewers. No language restriction was used.

Data extraction and synthesis: The Risk Of Bias in Systematic reviews (ROBIS) tool was used to assess quality. Diagnostic accuracy was presented descriptively and graphically.

Main outcomes and measures: The Area under the Curve (AUC) was derived from Standardised Mean Difference (SMD).

Results: From the 591 titles, we included 14 SRs (median 14 studies in each review, range 5 to 126). OCT and/or OCTA were considered in 9 reviews, fundus photography in 3 SRs and saccadic eye movements (SEM) in 2 SRs, and one review included all tests. Only four reviews were at 'low' risk of bias on all ROBIS domains. Most provided no or limited discussion of the target population and test role in the clinical pathway. Most primary studies were of a case-control nature, but did not account for the risk of overestimating diagnostic performance with this design.

The imaging-derived parameters with most evidence for detecting AD compared to healthy controls (HC), were: OCT peripapillary retinal nerve fiber layer thickness (38 studies, 1883 AD patients and 2510 HC; AUC=0.70; $p<0.001$); OCTA foveal avascular zone (5 studies, 177 AD patients and 371 HC; AUC=0.73; 0.500, 0.893); SEM prosaccade latency (30 studies, 651 AD/MCI patients and 771 HC; AUC=0.64; 0.584, 0.687). Antisaccade error was investigated in fewer studies (12, 424 AD/MCI patients and 382 HC), and yielded the best accuracy (AUC=0.79; 0.695, 0.880).

Conclusions and Relevance: Our umbrella review has highlighted limitations in design and reporting of the existing research on ocular biomarkers for diagnosing AD. Parameters with the best evidence showed poor to moderate diagnostic accuracy in cross-sectional studies. We suggest that future longitudinal studies should investigate whether changes in OCT and OCTA measurements over time can yield accurate predictions of AD onset.

Introduction

The early and accurate diagnosis of Alzheimer's disease (AD) and related-dementias is critical to clinical disease management and for stratification in trials of disease modifying therapies.[1,2]

Biomarkers that directly measure neuropathology are increasingly used to support diagnosis.[3] However, many of such neuroimaging and cerebrospinal fluid biomarkers are invasive, expensive or not widely available.[4] Ocular biomarkers hold the potential to provide objective, affordable and widely available measurements that reflect the underlying neuropathology of dementia, [4,5] also non-invasively using devices as optical coherence tomography (OCT), OCT-angiography (OCTA) and retinal colour fundus photograph,[6] and also with the analysis of saccadic eye movements.

Here we review the progress in translating such ocular biomarkers into clinical practice for the diagnosis of dementia, in particular AD and Mild Cognitive Impairment (MCI), which may represent its earliest stage.

The retina is part of the central nervous system with direct connection with different brain areas; it has even been suggested that axons of the optic nerve facilitate the transport into the brain of amyloid precursor protein (APP) created in retinal ganglion cells (RGCs).[4] Many brain areas are involved in oculomotor control and neurodegenerative diseases present with oculomotor and saccadic abnormalities.[7] Patients with AD and other neurodegenerative diseases may report decreased vision, visual field changes, visual hallucinations and other visual symptoms.[8] The ocular changes that occur in AD include abnormal pupillary reaction, decreased contrast sensitivity, loss of RGCs and retinal nerve fibre layer (RNFL), peripapillary atrophy, and retinal thinning, tortuosity of blood vessels and deposition of beta-amyloid in the retina.[9]

Given these neurobiological associations between the eye and the brain, efforts are underway to establish ocular biomarkers of dementia. A number of small reviews have attempted to synthesise

55 specific aspects of the literature. However, the field is still developing and there are potential risks
56 of bias and small sample size that could hamper efforts, so it remains unclear which methods are
57 most promising. The most widely studied parameters from ophthalmic techniques are retinal
58 nerve fiber layer (RNFL) thickness, ganglion cells-inner plexiform layer (GC-IPL) complex, foveal
59 avascular zone (FAZ) area, vessel density (VD) and perfusion density (PD), that are altered in
60 dementia.[4,6,10-21]

61 In addition, the retinal fundus imaging might be used as a surrogate for brain vascular
62 changes,[4,6,22-24] revealing subtle modifications in the cerebral vasculature related to preclinical
63 stages of neurodegenerative diseases, such as arteriolar narrowing and venular widening or e.g., the
64 low complexity or density of retinal vessels expressed as reduction of the fractal
65 dimensions(FD).[23,24] These changes might reflect subtle modifications in the cerebral vasculature
66 related to preclinical stages of neurodegenerative diseases, suggesting that retinal fundus imaging
67 might be used as a surrogate for brain vascular changes.[4,6,22,24,25]

68 Meta-epidemiologic studies have shown that multiple systematic reviews on the same topic
69 have variable quality and their results and conclusions may be only partly overlapping, for to the
70 time span of literature searches, different inclusion criteria and analytic approaches, the use of
71 subgroup analyses and for the interpretation of results. [26-29]

72 The aim of this umbrella review was to summarise the findings of published systematic
73 reviews on the diagnostic performance of ocular biomarkers for detecting dementia and the
74 prognostic significance for assessing the risk of conversion of mild cognitive impairment (MCI) to
75 dementia.

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Methods

This umbrella systematic review, or overview of reviews, is reported following PRISMA guideline.[30] (see PRISMA checklist in the Supplement). A protocol was developed following discussion with topic and methods experts and is registered with PROSPERO (PROSPERO 2021: CRD42021287196). Medline, EMBASE and PsycINFO were searched from January 2000 to November 2021 and the references of included reviews were also searched. Full details of the methods for conducting the review and search strategy are reported in the Supplement.

Systematic reviews were included if they investigated the diagnostic accuracy of ocular biomarkers to detect AD, all-cause dementia or MCI against established clinical criteria or clinical judgement. Eligible reviews assessed the accuracy of any technique related to eyes or vision, including imaging, functional assessment, pathology, or laboratory testing in secondary care or specialist diagnostic services settings such as memory clinics. We excluded studies using questionnaires, even if vision-specific domains were adopted, since we aimed to assess objective biomarkers addressing a single physiologic trait. The methodological quality of the included reviews was assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool.[31]

Primary measures of effect were sensitivity, specificity and area under the curve (AUC). Since none of these were available, we extracted continuous data for each biomarker, with a preference for Standardised Mean Differences (SMD) between diseased and non-diseased groups to account for differences in the measurement scale or calibration of different devices/techniques, using a conversion tables to infer the AUC as a measure of diagnostic accuracy.[32]. If the SMD was not available, we presented Mean Differences (MDs). Based on previous literature,[33] we considered AUC=0.70 as the threshold between poor and acceptable diagnostic accuracy, and 0.80 as the threshold between acceptable and excellent accuracy. However, we suggest an AUC 0.80 should be considered useful for prognostic factors, but still moderate for diagnostic accuracy. In fact, the associated sensitivity and specificity pair with AUC=0.80 at the inverse diagonal (the Q-point) are

104 only 0.72 for a symmetric Receiver Operator Curve (ROC); even a nominally excellent AUC=0.90
105 would generate a moderately good sensitivity and specificity pair at 0.82, meaning that 1 in 5 test
106 positives are false positives and 1 in 5 test negatives are false negatives.

107 We found a large number of parameters for the two main methods, OCT and OCTA. We
108 therefore selected the three parameters with the largest number of studies to provide the best
109 estimation of performance. When the third ranking was shared for more parameters, we presented
110 all of them. When a parameter was collected in different retinal locations, e.g., parafovea, perifovea,
111 fovea, or whole, we followed this order of selection.[34]

112

113 **Results**

114 After duplicates were manually removed, the search retrieved 591 references, of which 32
115 systematic reviews were obtained in full text. Eighteen of these were excluded for one or more of
116 the following reasons: published before 2016 (7 reviews)[35-41]; used surrogates of dementia as a
117 target condition (1 review)[22]; used ocular conditions as biomarker, rather than test technique results
118 (2 reviews)[42,43]; absence of meta-analyses (10 reviews).[4,5,9,11,14,21,22,44-46] Five reviews published
119 before 2016 reported on OCT[35-38,41] and 2 on retinal microvascular changes.[39,40] Consistent with our
120 expectations, the number of included studies in these reviews was much lower than that in the most
121 recent SRs on the same techniques.

122 Fourteen included articles were systematic reviews with meta-analyses. Additional studies
123 reported quantitative individual study results with no meta-analysis, and narrative study results
124 (Fig.1). Due to limitations in reporting, data were not extracted and presented for the latter two
125 groups of reviews.

126 Analysed reviews were published between 2016 and 2021, and included 5 to 126 studies
127 (median 14 studies). Included techniques were OCT (n=7), OCTA (n=5), fundus imaging (n=3),

128 and saccadic eye movements (n=2). One review also reported Scanning Laser Ophthalmoscopy
129 (SLO)/polarimetry results, which were not considered since this device is no longer commercially
130 available. Three reviews focused on AD as the target condition,[18,19,23], four on MCI,[13,15,16,24] and
131 seven included both[6,10,12,17,20,47,48].

132 Regarding measures of effect, eight studies used SMD to measure effect
133 sizes,[6,10,12,15,16,19,47,48] and six used the MD,[13,17,18,20,23,24] with one review also using the ratio of
134 means to pool data for meta-analyses.[6]

135 Regarding the risk of bias in studies, three reviews used Quality Assessment of Diagnostic
136 Accuracy Studies (QUADAS) or QUADAS 2,[10,12,16] four used the Newcastle Ottawa Scale
137 (NOS),[17-19,24] one used the Joanna Briggs Institute critical appraisal tools,[6] one used Risk Of Bias In
138 Non-randomized Studies Of Interventions (ROBINS-I),[47] and the other did not adopt validated
139 instruments.[13,20,23,48] One review used Risk-of-bias VISualization (ROBVIS),[15] a visualisation tool,
140 and used questions designed for randomised controlled trials, though some additional items were
141 added.

142 eTable 1 in the Supplement shows the main characteristics of 14 included systematic
143 reviews which reported quantitative estimates, and the risk of bias assessment with ROBIS is
144 detailed in eTable 2 in the Supplement.

145 **Overview of all parameters**

146 Several parameters were reported in the included reviews. As explained in the Methods, for
147 each technique we selected the three parameters with the largest number of studies. These were for
148 OCT; pRNFL[6,10,12,13,15,16], macular RNFL (mRNFL)[6] and GC-IPL complex[6,10,15,16] thickness; for
149 OCTA: FAZ area[6,17-20], PD/VD in the superficial capillary plexus (SCP)[6,17-20] and in the deep
150 capillary plexus (DCP)[6,17,18]; for fundus camera: central retinal venular equivalent caliber
151 (CRVE)[6,23,24], FD total, arterial and venous[6,23,24]; for SEM: prosaccade latency, antisaccade latency

152 and antisaccade error[47,48]. For each parameter we analysed the comparisons between AD vs HC, AD
153 vs MCI and MCI vs HC.

154 All the results for each study and for the different techniques, parameters and comparisons
155 are extensively detailed by reporting all the SMD/MD values, p-values/95%CI and corresponding
156 AUC, in eTable 3 in the Supplement. Of note, perfusion density (PD) was expressed as %, but
157 vessel density (VD), which has a similar clinical significance was used and expressed as mm^2 in
158 four reviews on SCP[6,17-20]. No review used adjusted estimates of test accuracy, e.g., accounting for
159 age-related changes, but they reported studies had matched cases and controls by age and gender.

160 In the following paragraphs we report on the three parameters with the best performance for each
161 technique. These are also presented as forest plots (OCT in Fig.2, OCTA in Fig.3, and SEM in
162 Fig.4).

163 **OCT pRNFL**

164 Mean pRNFL thickness was reported in the largest number of studies in three systematic
165 reviews (Fig.2; eTable 3 in the Supplement). The pooled SMD for detecting AD vs HC was -0.723,
166 corresponding to an AUC=0.70 in the most extensive review (38 studies),[6] which was at low risk of
167 bias. Two reviews[6,12] pooled data comparing AD with MCI for this parameter. The review with low
168 risk of bias and more studies[6] found the SMD was -0.140 (p=0.064), corresponding to an
169 AUC=0.54.

170 Six systematic reviews[6,10,12,13,15,16] pooled data comparing MCI with HC for this parameter.
171 The review with low risk of bias and more studies[6] reported a pooled SMD of -0.324 (p<0.001),
172 corresponding to an AUC=0.59, with high heterogeneity.

173 **OCTA FAZ area**

174 Five reviews [6,17-20] reported on the FAZ in AD vs HC, with 3 to 7 studies each, and found
175 concordant estimates of difference (Fig. 3; eTable 3 in the Supplement). The two reviews using the

176 SMD found SMD=0.87 (95%CI -0.01, 1.76), with imprecision crossing no difference and with high
177 heterogeneity.[6,19] The AUC corresponding to this point estimate was 0.73.

178 Two reviews,[6,20] including two studies each (one overlapping study) compared AD and
179 MCI. One review[6] found an SMD of 0.52 (95%CI -0.38, 1.41) with considerable imprecision and
180 heterogeneity. The corresponding AUC point estimate was 0.64.

181 Three reviews, [6,17,20] including 3 or 4 studies each, included MCI patients and HC. The
182 review using the SMD found a pooled value of 0.83 (95%CI -0.19, 1.85), with considerable
183 imprecision and heterogeneity, corresponding to an AUC=0.72.

184 **Saccadic eye movements**

185 Saccadic eye movements were explored in two systematic reviews with meta-analysis [47,48]
186 which reported significant alterations in AD and MCI patients (Fig.4; eTable 3 in the Supplement).
187 The parameters with the highest number of studies were: prosaccade latency, antisaccade latency
188 and antisaccade error (investigated with gap, overlap or unspecified conditions). Both reviews
189 combined studies on AD with a minority of studies on MCI, all compared with HC. One review[47]
190 compared prosaccade latency in gap and overlap conditions finding SMD=0.30 and 0.50,
191 respectively (95%CI -0.05, -0.01). The antisaccade latency and antisaccade error were reported in
192 gap condition by Opwonya et al.,[47] finding SMD=0.44 and 1.16, with AUC=0.62 and 0.79,
193 respectively and were reported in undefined condition by Kahana Levy et al.,[48] finding SMD=0.37
194 and 1.30, with AUC=0.60 and 0.82, respectively.

195 The parameter with most studies (25 to 30) was prosaccade latency (investigated with gap,
196 overlap or unspecified condition) for which AUCs were 0.58 to 0.64 with sufficient precision.
197 Antisaccade latency yielded similar results to prosaccade latency.

198 Among those selected, the parameter with the best performance was antisaccade error (with
199 gap or unspecified condition) in 8-12 studies, with AUC=0.79, which, however, was imprecisely
200 estimated.

201 **Other biomarkers**

202 Ge et al.[6] reported narratively on studies using retinal blood flow and electrophysiological
203 biomarkers (multifocal or pattern ERG, not presented here). They also reported narratively on
204 several other candidate biomarkers assessed in individual studies, (e.g., retinal blood flow with
205 different instruments, retinal arterial and venous oxygen saturation).

206 Amyloid deposition in one hyperspectral imaging study was found to have an AUC=0.82
207 (0.67-0.97) for 15 AD or MCI subjects compared to HC.[49] A second study confirmed this finding,
208 but estimates were not available.[50] Other imaging studies used Blue-Peak autofluorescence.[25] Ge
209 2021[6] also reported anecdotally on studies using reflective features related to the Müller cells and
210 macular pigment optical density. All these additional biomarkers have not been included in our
211 analyses because no meta-analyses were performed in systematic reviews.

212

213 **Discussion**

214 Our umbrella review found several systematic reviews that have assessed the diagnostic
215 performance of ocular biomarkers, especially OCT and OCTA to detect AD and MCI.

216 We found that the most widely investigated eye biomarkers were pRNFL thickness
217 measured with OCT, FAZ area evaluated with OCTA, and prosaccade or antisaccade latency or
218 error for saccadic eye movements.

219 In two reviews at low risk of bias,[6,10] AUCs were low (about 0.70) for the most widely
220 studied imaging parameters (pRNFL and FAZ area). Results were variable and generally modest
221 and imprecisely estimated for all other OCT parameters. In order to highlight the limited usefulness

222 of such AUC values, we calculated that sensitivity and specificity pairs would be equal at 64.4% at
223 the inverse diagonal (Q point), and that the specificity at 95% would lead to only 19% sensitivity,
224 suggesting a modest performance. This is consistent with the finding by Ge et al.,[6] who reported the
225 ratio of means of pRNFL between AD and HC was 0.93, i.e., only a 7% difference in average
226 RNFL thickness between the two groups.

227 Saccadic eye movements were investigated in a large number of studies included in two
228 reviews, one of which was low risk of bias.[47] Prosaccade and antisaccade latency yielded AUC
229 values below 0.70. The parameter with a better performance was antisaccade error (AUC=0.79),
230 suggesting that it should be considered for further research.

231 Other parameters were CRVE and FD evaluated with retinal photography, yielding
232 imprecise estimates of poor diagnostic performance. Other vascular parameters as Central Retinal
233 Arteriolar equivalent caliber (CRAE), arterial-to-vein ratio (AVR), branching coefficient and
234 tortuosity have been reviewed in AD/MCI population,[6] yielding lower diagnostic accuracy, and
235 have not been included in the present analysis.

236 Several other reviews could have been included but did not provide data. Alber et al.[4] and
237 Mahajan et al.[9] were broad-spectrum but primarily narrative reviews and quantitative data were not
238 considered for meta-analysis. A number of reviews[5,11,14,44] were systematic reviews of OCT data in
239 several neurologic conditions with no meta-analysis. Wu et al.[24] provided quantitative data with
240 OCT and OCTA and reported differences between AD and MCI but did not conduct a meta-
241 analysis.

242 Other reviews included a broad range of diseases, Zhang et al.[21] investigated OCTA in
243 patients with small vessel disease, including stroke and dementia. Lemmens et al.[22] found a
244 significant association between decreased FD and neurodegenerative disease. Youssef et al.[45]
245 reported variation in electroretinography findings in several psychiatric disorders.

246 Overall, several systematic reviews have been produced just in the last five years, the largest
247 of which including over 100 studies. None of these reviews could generate inference that can be
248 used in clinical practice, and only Ge 2021[6] declared they would synthesis these effect measure in
249 the Method section.
250 No included review framed the research question in a clinical pathway, which is key in diagnostic
251 test accuracy reviews, since patient's prior testing and disease spectrum, often related to study
252 setting and test user profile, are known to influence accuracy and also its translation into practice.[51]
253 The quality of the included studies was not taken into account to generate conclusions in the
254 majority of the reviews, neither was the heterogeneity of study findings. Overall, only four[6,10,16,47]
255 out of 14 reviews were at low risk of bias for all ROBIS domains.
256 A further level of complexity is that studies included different devices, using different scales
257 for the measurement of the same biomarker. The comparison between different devices is
258 difficult,[52] and many reviews used SMD as a measure of effect to overcome this problem. The SMD
259 metrics for therapeutic clinical significance commonly assumes small effects if SMD<0.5 and large
260 effects if SMD>0.8. Much larger differences are meaningful in diagnostic accuracy, where an
261 SMD=1.81 equals an AUC=0.90, i.e., a moderately good sensitivity=specificity=0.82 at Q-point.

262 The modest diagnostic performance we found for the two main techniques of greater
263 interest, OCT and OCTA, does not mean these have no use in dementia investigation. First of all,
264 OCTA has not yet been extensively used. Glaucoma research with OCT has shown that, while
265 cross-sectional accuracy is poor due to interindividual variation in normal subjects, the change in
266 OCT parameters over time in the same individual can be helpful for detection.[53] Therefore,
267 longitudinal studies on AD and MCI development might result in better diagnostic accuracy
268 compared to cross-sectional detection. Finally, even biomarkers with weak diagnostic performance
269 could be used in artificial intelligence-based algorithms for case finding or prediction, provided that
270 they contribute independently from other variables.

271 Open issues include testing the sensitivity and specificity of ocular biomarkers compared to
272 more robust and widely accepted biomarkers (e.g., CSF, PET) of amyloid, tau, and neuronal loss.
273 This piece of information, compared to diagnostic yield in populations selected on the basis of a
274 clinical diagnosis would help clarifying whether the weak diagnostic performance is real or due to
275 loose clinical diagnostic criteria across studies. Saccadic eye movements also merit further
276 investigation, possibly regarding antisaccade error.

277 We suggest that future studies on eye-imaging biomarkers in dementia should clearly report:
278 diagnostic criteria for dementia/MCI, whether the diagnosis is clinical or supported by biomarkers,
279 the staging of the disease, longitudinal follow-up (when available), post-mortem neuropathological
280 confirmation. Most importantly, an a-priori diagnostic question should be framed instead of an
281 exploratory design of the study and follow-up data should be obtained in community-based
282 samples, recruiting individuals in the lowest range of normative data for OCT and/or OCTA
283 parameters. In fact, Dong et al.[54] found that this group provides the best opportunity to directly
284 visualize subclinical changes in neurosensory and vascular tissue that are very likely to occur in
285 many prevalent chronic diseases and new methods for detecting these changes are in development.[55]

286 A strength of our overview of reviews was the broad and inclusive approach, encompassing
287 all techniques and conditions related to dementia that had been reported in systematic reviews,
288 based on a research protocol and using a well-established risk of bias tool for systematic reviews
289 (ROBIS), which accommodates different study designs. A limitation of our review is that we did
290 not formally assess study overlap between systematic reviews, and we did not attempt a meta-
291 analysis of original studies, nor did we assess their individual quality. Instead, we presented the
292 quality of the included systematic reviews, meaning that we only assessed whether optimal
293 evidence synthesis methods were used. Nonetheless, we think the consistently moderate diagnostic
294 performance found for ocular biomarkers in all reviews means that results would not change if such
295 a large effort was undertaken. Despite this, the evaluation of non-invasive ocular biomarkers for

296 early AD diagnosis could be useful in artificial intelligence models or in large-scale screening
297 programs selecting patients for specialist referrals.
298

299 **Conclusions**

300 Our overview of reviews showed that research on ocular biomarkers for diagnosing AD,
301 summarised in systematic reviews, was abundant in recent years, but poorly reported and of limited
302 clinical significance. Further studies should adopt a formal diagnostic accuracy framework and
303 follow STARD guidance[56] for reporting results. Longitudinal studies should investigate whether
304 changes in OCT and OCTA measurements over time can yield accurate predictions of AD onset.

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Author contributions:

Eliana Costanzo: conceptualization of the work, data analysis and interpretation of the results, manuscript drafting and final approval. Imre Lengyel: conceptualization of the study, data

interpretation, manuscript drafting and critical revision. Mariacristina Parravano: data analysis and interpretation of results. Ilaria Biagini: data analysis and tables' creation. Michele Veldsman, AmanPreet Badhwar, Matthew Betts, Antonio Cherubini, David Llewellyn, Ilianna Lourida, Tom MacGillivray, Timothy Rittman, Stefano Tamburin, Xin You Tai: critically revision of manuscript. Gianni Virgili: conceptualization and design of the work, data analysis and interpretation of the results, manuscript drafting and final approval.

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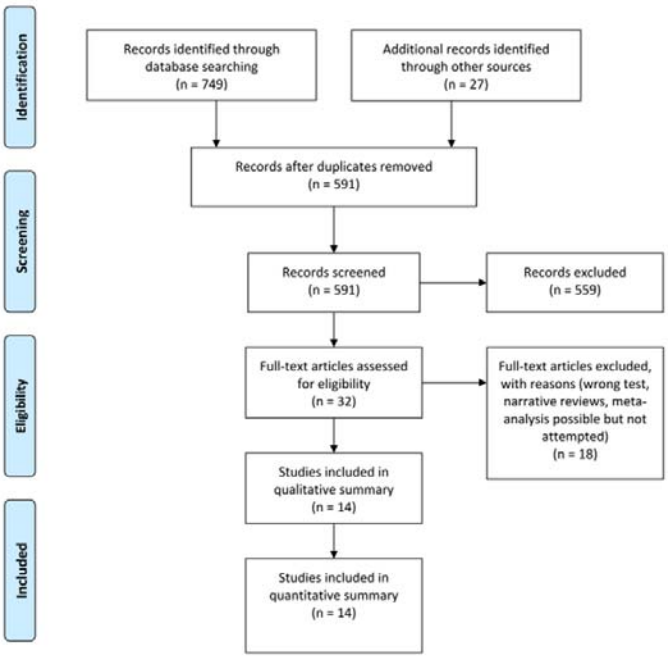
481 **Figure 1.**



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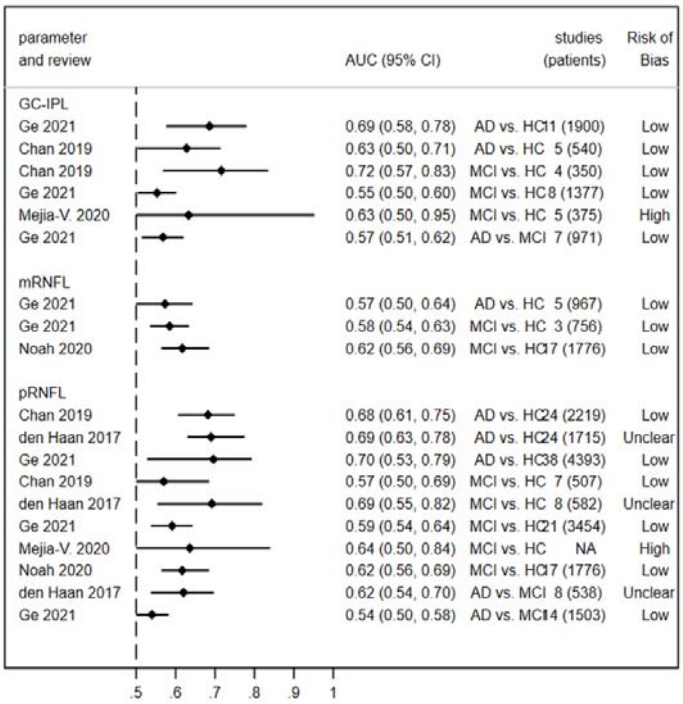
483 **Figure 2.**



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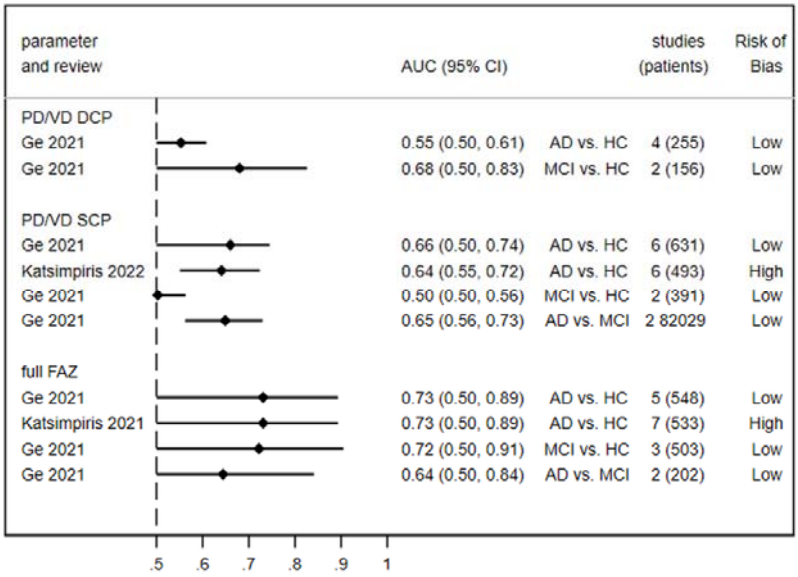

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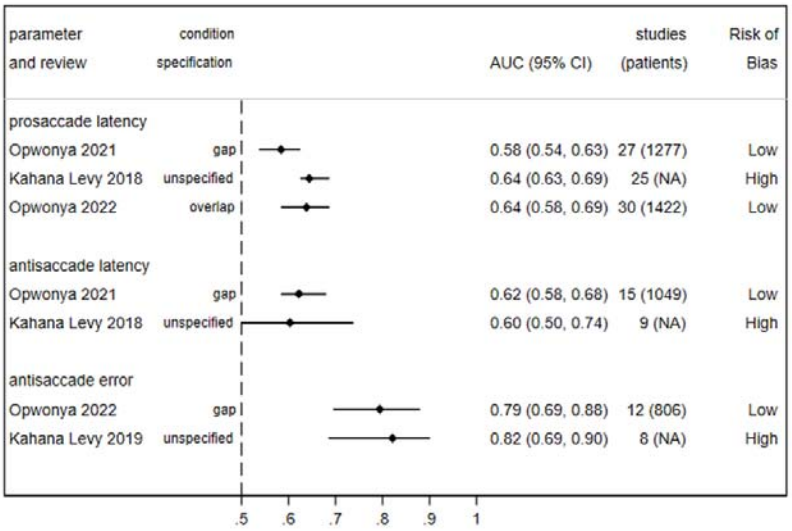

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489

490 **Figure legend**

491 Figure 1.

492 Flow diagram of the literature search (PRISMA diagram)

493 Figure 2.

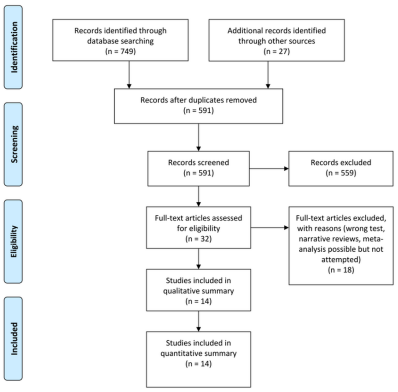
494 Forest plot of optical coherence tomography parameters for AD and MCI versus HC. All values are
495 extensively reported in Supplementary file 3. Abbreviations: AD, Alzheimer's disease; MCI, Mild
496 Cognitive Impairment; HC, health controls; AUC, Area Under the Curve; GC-IPL, ganglion cell-
497 inner plexiform layer complex; mRNFL, macular retinal nerve fiber layer; pRNFL, peripapillary
498 retinal nerve fiber layer.

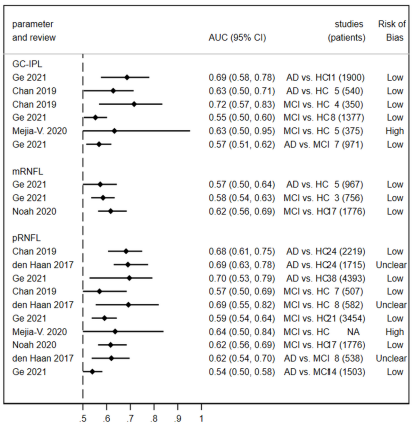
499 Figure 3.

500 Forest plot of optical coherence tomography angiography parameters for AD and MCI versus HC.
501 All values are extensively reported in Supplementary file 3. Abbreviations: AD, Alzheimer's
502 disease; MCI, Mild Cognitive Impairment; HC, health controls; AUC, Area Under the Curve; PD,
503 perfusion density; VD, vessel density; DCP, deep capillary plexus; SCP, superficial capillary
504 plexus; FAZ, foveal avascular zone.

505 Figure 4.

506 Forest plot of saccadic eye movements' parameters for AD and MCI versus HC. All values are
507 extensively reported in eTable 3 in the Supplement.


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 749)
Additional records identified through other sources (n = 27)
Records after duplicates removed (n = 591)
Records screened (n = 591)
Records excluded (n = 559)
Full-text articles assessed for eligibility (n = 32)
Full-text articles excluded, with reasons (wrong test, narrative reviews, meta-analysis possible but not attempted) (n = 18)
Studies included in qualitative summary (n = 14)
Studies included in quantitative summary (n = 14)


parameter and review
AUC (95% CI)
studies (patients)
Risk of Bias
GC-IPL
Ge 2021 0.69 (0.58, 0.78) AD vs. HC 11 (1900) Low
Chan 2019 0.63 (0.50, 0.71) AD vs. HC 5 (540) Low
Chan 2019 0.72 (0.57, 0.83) MCI vs. HC 4 (350) Low
Ge 2021 0.55 (0.50, 0.60) MCI vs. HC 8 (1377) Low
Mejia-V. 2020 0.63 (0.50, 0.95) MCI vs. HC 5 (375) High
Ge 2021 0.57 (0.51, 0.62) AD vs. MCI 7 (971) Low
mRNFL
Ge 2021 0.57 (0.50, 0.64) AD vs. HC 5 (967) Low
Ge 2021 0.58 (0.54, 0.63) MCI vs. HC 3 (756) Low
Noah 2020 0.62 (0.56, 0.69) MCI vs. HC 7 (1776) Low
pRNFL
Chan 2019 0.68 (0.61, 0.75) AD vs. HC 24 (2219) Low
den Haan 2017 0.69 (0.63, 0.78) AD vs. HC 24 (1715) Unclear
Ge 2021 0.70 (0.53, 0.79) AD vs. HC 38 (4393) Low
Chan 2019 0.57 (0.50, 0.69) MCI vs. HC 7 (507) Low
den Haan 2017 0.69 (0.55, 0.82) MCI vs. HC 8 (582) Unclear
Ge 2021 0.59 (0.54, 0.64) MCI vs. HC 21 (3454) Low
Mejia-V. 2020 0.64 (0.50, 0.84) MCI vs. HC NA High
Noah 2020 0.62 (0.56, 0.69) MCI vs. HC 7 (1776) Low
den Haan 2017 0.62 (0.54, 0.70) AD vs. MCI 8 (538) Unclear
Ge 2021 0.54 (0.50, 0.58) AD vs. MCI 4 (1503) Low
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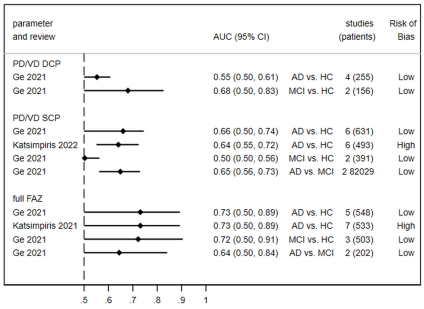
parameter and review
AUC (95% CI)
studies (patients)
Risk of Bias
PD/VD DCP
Ge 2021 0.55 (0.50, 0.61) AD vs. HC 4 (255) Low
Ge 2021 0.68 (0.50, 0.83) MCI vs. HC 2 (156) Low
PD/VD SCP
Ge 2021 0.66 (0.50, 0.74) AD vs. HC 6 (631) Low
Katsimpiris 2022 0.64 (0.55, 0.72) AD vs. HC 6 (493) High
Ge 2021 0.50 (0.50, 0.56) MCI vs. HC 2 (391) Low
Ge 2021 0.65 (0.56, 0.73) AD vs. MCI 2 82029 Low
full FAZ
Ge 2021 0.73 (0.50, 0.89) AD vs. HC 5 (548) Low
Katsimpiris 2021 0.73 (0.50, 0.89) AD vs. HC 7 (533) High
Ge 2021 0.72 (0.50, 0.91) MCI vs. HC 3 (503) Low
Ge 2021 0.64 (0.50, 0.84) AD vs. MCI 2 (202) Low
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.6
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.8
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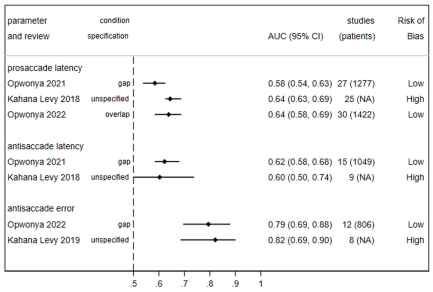
1


parameter and review
condition specification
AUC (95% CI)
studies (patients)
Risk of Bias
prosaccade latency
Opwonya 2021 gap 0.58 (0.54, 0.63) 27 (1277) Low
Kahana Levy 2018 unspecified 0.64 (0.63, 0.69) 25 (NA) High
Opwonya 2022 overlap 0.64 (0.58, 0.69) 30 (1422) Low
antisaccade latency
Opwonya 2021 gap 0.62 (0.58, 0.68) 15 (1049) Low
Kahana Levy 2018 unspecified 0.60 (0.50, 0.74) 9 (NA) High
antisaccade error
Opwonya 2022 gap 0.79 (0.69, 0.88) 12 (806) Low
Kahana Levy 2019 unspecified 0.82 (0.69, 0.90) 8 (NA) High
.5 .6 .7 .8 .9 1