Imaging the Retina in Alzheimer's Disease

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CHAPTER 1

Retinal thickness in Alzheimer's disease: a systematic review and meta-analysis

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Abstract

Retinal characteristics are increasingly recognized as biomarkers for neurodegenerative diseases. Retinal thickness measured by Optical Coherence Tomography (OCT) may reflect the presence of Alzheimer's disease (AD). We performed a meta-analysis on retinal thickness in AD and MCI patients and healthy controls (HC). We selected 25 studies with measurements of retinal thickness including 887 AD-patients, 216 MCI patients, and 864 HC that measured retinal thickness. Outcomes were peripapillary retinal nerve fiber layer (RNFL) and macular thickness. The main outcome was the standardized mean differences (SMD). We used STATA to perform the meta-analysis. Relative to HC, AD and MCI patients had lower peripapillary RNFL (SMD 0.98 (CI -1.30,-0.66, $p<0.0001$ and SMD 0.71 ((CI -1.24,-0.19, $p=0.008$). Total macular thickness was decreased in AD patients (SMD 0.88 (CI -1.12,-0.65, $p=0.000$). Retinal thickness is decreased in AD and MCI patients compared to HC. This confirms that neurodegenerative diseases may be reflected by retinal changes.

Introduction

Alzheimer's disease (AD) is the most common form of dementia. It is neuropathologically characterized by amyloid-beta (Aβ)-plaques and neurofibrillary tangles containing tau. These neuropathological changes are believed to develop 15-20 years before symptom onset. AD is diagnosed in subjects with MCI or dementia using clinical criteria combined with abnormal biomarkers for Aβ-pathology or neuronal injury[1,2]. Aβ-pathology is reflected by decreased Aβ-levels in cerebrospinal fluid (CSF) or on an amyloid positron emission tomography (Aβ -PET). Neuronal injury is reflected by either cortical atrophy on magnetic resonance imaging (MRI), hypometabolism on fluorodeoxyglucose-PET (FDG-PET) or increased tau and/or phosphorylated tau (pTau) levels in CSF[3]. These biomarkers however, are invasive, expensive or time consuming. Thus, there is an urgent need for an early, patient friendly, inexpensive AD biomarker that preferably detects AD pathology prior to severe neurodegeneration[4].

The retina is embryologically derived from the cranial part of the neural tube, similar to the brain, and therefore shares many similarities with its tissue. The retina is easily accessible and retinal neurons can be visualized through high resolution optical methods such as optical coherence tomography (OCT) visualizing thickness of retinal layers (figure 1). With OCT retinal changes are visualized both in ophthalmological disease and in neurodegenerative disease. Previous studies have shown that the retinal nerve fiber layer (RNFL) thickness and ganglion cell layer (GCL) thickness are reduced in subjects with multiple sclerosis (MS)[5], Parkinson's Disease (PD)[6] and AD[7-31].

In this study we perform a meta-analysis to assess the retinal layer thickness in AD and MCI patients and cognitively normal subjects. OCT is an optical method that accurately measures retinal layer thickness, and therefore potentially a patient friendly noninvasive method for detection of neurodegenerative diseases. We also assess the role of concomitant ophthalmological disease on retinal thickness, in particular glaucoma and the possible confounding role of age and disease severity.

Methods

Search strategy

We searched PubMed and EMBASE for studies analyzing OCT measurements in AD-patients, MCI patients and/or HC using the following search terms: "Alzheimer Disease", "senile dementia", "Mild Cognitive Impairment", "MCI", "optical coherence tomography" and "OCT" between 1990 and February 2016.

Inclusion

We included 25 studies that used NINCDS-ADRDA and/or DSMIV criteria for AD diagnosis, Petersen or Winblad criteria for MCI, and OCT to assess retinal layer thickness. Eight of these studies included an MCI group. Ten studies used first generation Time Domain (TD)-OCT and fifteen studies used Spectral Domain (SD)-OCT. Twenty-four studies performed a peripapillary RNFL protocol (of which 16 studies presented data for separate quadrants). One study performed a macular protocol only; and six studies performed both a peripapillary and macular protocol. Eight studies included neuroimaging (MRI or CT) and two studies included CSF-analysis, (table 1, characteristics of the included studies).

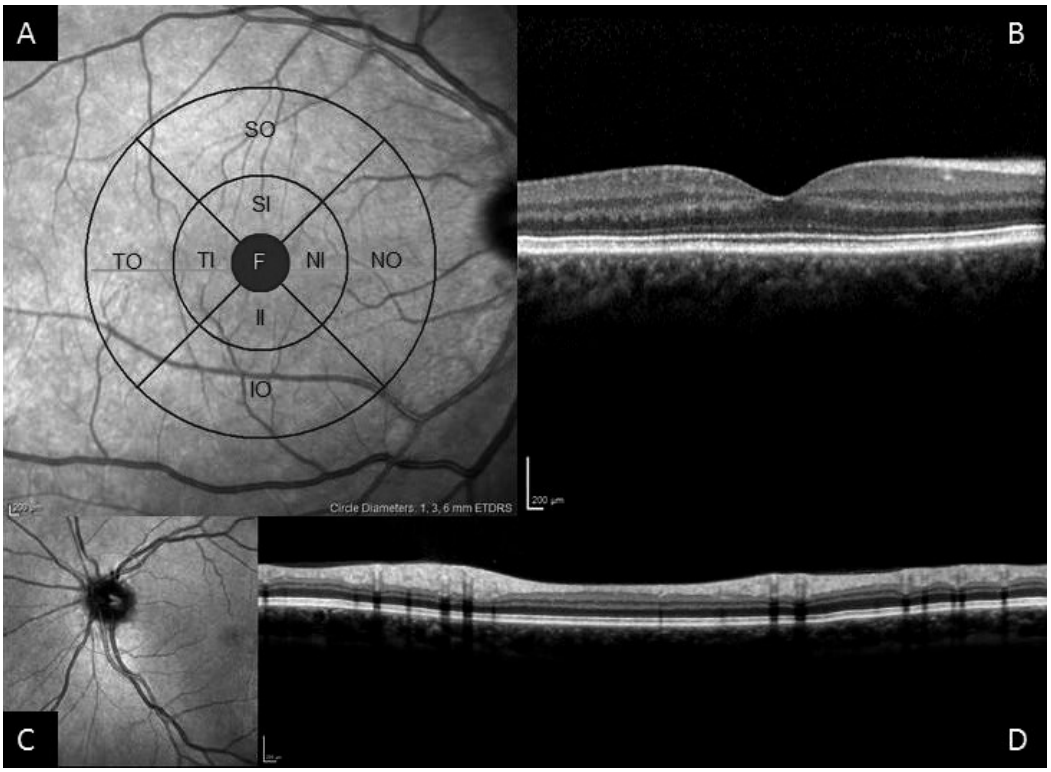


Figure 1 Optical Coherence Tomography (Heidelberg Spectralis)

OCT image of the macula (A) with an overlay of the Early Treatment Diabetic Retinopathy Study (ETDRS) regions and transversal OCT image showing the macula (B). Image of optic disk (C) and a transversal OCT image through the optic disk (D). Abbreviations: F=Fovea, SI= superior inner, II= inferior inner, TI= temporal inner, NI=nasal inner, SO= superior outer, IO= inferior outer, TO= nasal inferior, NO= nasal outer.

Of the 637 records identified, 612 were excluded due to their title, topic, method or design. Others were excluded as they were abstracts, reviews, posters, communications in response to an article, or contained duplicate data. Studies with non-demented subjects or studies that use different techniques such as; RNFL thickness with Heidelberg Retinal Tomography (HRT), fundus auto-fluorescence (FAF) and electroretinography (ERG) were also excluded (figure 2, flowchart of in- and excluded articles).

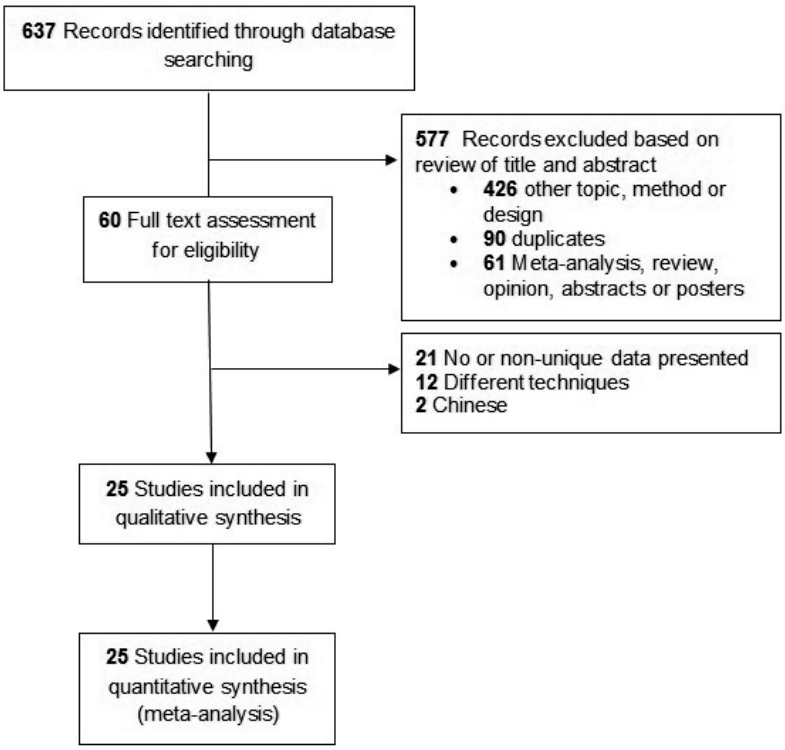


Figure 2 Flowchart of in- and excluded articles

Data extraction

We extracted mean and quadrant RNFL and macular thickness with standard deviations for AD and MCI patients and HC. In one study data were presented as boxplots[25]. Estimates of the mean and standard deviation were therefore calculated using the lower and upper quartiles, mean, and sample size following the methods described in Wan et al.[32]. A second study described RNFL thickness in bar diagrams without exact figures[27]. RNFL thickness means and standard deviations were therefore estimated with the help of the measure tool in Adobe Acrobat XI Pro (Version 11.0.0). The standard errors were calculated to standard deviations.

Outcome measures

Peripapillary RNFL thickness was presented in superior, inferior, temporal, nasal and mean quadrants. Total macular thickness was subdivided according to the ETDRS (early treatment diabetic retinopathy study) regions; fovea, inner and outer ring.

Table 1 Study Characteristics

			OCT*		Subjects			MMSE		Age	
#	Study	Year	Scanner type	Protocols used	AD	MCI	HC	AD	HC	AD	HC
1	Pillai	2016	Cirrus 4000 HD-OCT	Peripapillary RNFL	21	20	34	-	-	65.80	65.10
2	La Morgia	2016	Stratus OCT3	Peripapillary RNFL	21	-	74	18,3	-	71,20	69,10
3	Garcia	2015	OCT1000 Topcon	Peripapillary RNFL Macular thickness	23	-	28	23.3	28.2	79,30	72,30
4	Eraslan	2015	RTVue 100 Fourier-domain	Peripapillary RNFL	18	-	20	-	-	73,60	73,30
5	Güneş	2015	OPKO/OTI SD-OCT	Peripapillary RNFL	20	-	20	-	-	75,02	74,15
6	Liu	2015	Stratus OCT3	Peripapillary RNFL	67	26	39	-	-	71,35	69,70
7	Oktem	2015	Cirrus HDOCT	Peripapillary RNFL	35	35	35	18	29	75,40	70,20
8	Cheung	2015	Cirrus HDOCT	Peripapillary RNFL Macular GCL	100	41	123	-	-	73,50	65,70
9	Gao	2015	Cirrus HDOCT	Peripapillary RNFL	25	26	21	19.24	28.57	74,72	72,05
10	Bambo	2015	Cirrus HDOCT	Peripapillary RNFL	56	-	56	16.56	-	74,00	76,40
11	Larrossa	2014	Cirrus HDOCT Heidelberg Spectralis	Peripapillary RNFL Macular thickness	151	-	61	18.31	-	75,29	74,87
12	Ascaso	2014	Stratus OCT3	Peripapillary RNFL Macular thickness	18	21	41	19.31	28.78	72,10	72,90
13	Polo	2014	Cirrus HDOCT Heidelberg Spectralis	Peripapillary RNFL Macular thickness	70	-	70	15.96	-	74,15	73,98
14	Gharbiya	2014	Heidelberg Spectralis	Peripapillary RNFL	21	-	21	22.2	28.2	73,10	70,30
15	Kromer	2014	Heidelberg Spectralis	Peripapillary RNFL	22	-	22	22.59	-	75,90	64,00
16	Moreno-Ramos	2013	OCT1000 Topcon	Peripapillary RNFL	10	-	10	16.4	29.2	73,00	70,20
17	Marziani	2013	RTVue Heidelberg Spectralis	Macular thickness	21	-	21	-	-	79,30	77,00

18	Kirbas	2013	OCT1000 Topcon	Peripapillary RNFL	40	-	40	18-25	-	69,30	68,90
19	Moschos	2012	Stratus OCT3	Peripapillary RNFL	30	-	30	-	-	71,77	-
20	Kesler	2011	Stratus OCT3	Peripapillary RNFL	30	24	24	23.6	-	73,70	70,90
21	Lu	2010	Stratus OCT3	Peripapillary RNFL	22	-	22	-	-	73,00	68,00
22	Paquet	2007	Stratus OCT3	Peripapillary RNFL	26	23	15	19.8	28.9	78,53	75,50
23	Berisha	2007	Stratus OCT3	Peripapillary RNFL	9	-	8	23.8	29.5	74,30	74,30
24	Iseri	2006	Stratus OCT3	Peripapillary RNFL Macular thickness	14	-	15	18.5	29.4	70,10	65,10
25	Parisi	2001	Stratus OCT3	Peripapillary RNFL	17	-	14	16.38	23	70,37	-
					887	216	864				

*First generation (Time domain) OCT-scanner is the Stratus OCT3 and second generation (Spectral Domain) OCT-scanners are the Cirrus HDOCT, Heidelberg Spectralis, OPKO/OTI , OCT1000 Topcon and RTVue.

Study quality rating

The QUADAS-tool was used to assess the methodological quality for each study by two authors (JdH and FvB) (supplementary table 1)[33]. Glaucoma is an important potential confounder as it is a neurodegenerative disease of the retina resulting in RNFL loss. We therefore reviewed whether glaucoma was assessed by; a) medical history, b) intra-ocular pressure, c) bio microscopy, d) fundus photographs and/or e) functional assessment in the form of visual field defects in order to generate a glaucoma exclusion score. All studies used ophthalmological history and intraocular pressure for the exclusion of glaucoma. However, this may not detect all cases, in particular normal tension glaucoma. Therefore, we totaled the number of additional assessments performed for exclusion of glaucoma; a) posterior segment bio microscopy, b) fundus photographs and/or c) functional assessment (visual fields). The higher the resulting glaucoma exclusion score, the more stringent the exclusion criteria for glaucoma were met (supplementary table 2).

Statistical analysis

We used random-effects models for the meta-analysis with a main outcome measure of Cohen's d (SMD). Heterogeneity was assessed by χ^2 test, and Egger's regression test was used to test funnel plot asymmetry. A funnel plot was generated to assess publication bias

and was statistically tested with Begg's and Egger's tests. We used STATA (StataCorp, Texas, Version 14.0) for all analyses, with the metan command to create forest plots, the metabias command for funnel plot and the metareg command to perform meta regression. Both univariate and multivariate meta-regression were used to assess whether study characteristics were associated with the SMD. Meta regression was carried out with the SMD as a dependent variable. Independent variables were; OCT type (Time Domain (TD) vs. Spectral Domain (SD)), mean study Mini Mental State Examination (MMSE) in the AD group, study glaucoma exclusion score and mean study age. We performed subgroup analysis for first and second generation OCT scanner type (TD-OCT and SD-OCT respectively) and for the four (superior, inferior, nasal and temporal) peripapillary quadrants.

Results

Peripapillary retinal nerve fiber layer thickness

Mean peripapillary RNFL was described in 24 studies including 887 AD patients and 864 HC. RNFL thickness was lower in AD vs HC (SMD-0.98 (CI -1.30, -0.66, p=0.000), which corresponds to an absolute decrease of 9.70 μm (CI -10.76,-8.6, p=0.000) (figure 3A). Figure 3B and 3C show a larger effect for the TD than the SD scanner type, with effect estimates of respectively -1.38 (CI -1.91,-0.86, p=0.000) and -0.70 (CI -1.07,-0.33, p=0.000).

Table 2 shows the differences between AD and HC for the mean peripapillary RNFL thickness and in the four quadrants in 20 studies. The superior and inferior quadrant are thinner than the nasal and temporal quadrant. Eight studies measured peripapillary RNFL thickness including a MCI group consisting of 322 AD patients, 216 MCI patients and 367 HC and measured peripapillary RNFL thickness. RNFL thickness of the MCI group was between the RNFL thickness of AD patients and HC, with a standardized mean difference of -0.71 (CI -1.24,-0.19, p=0.008) compared to controls and of -0.43 (CI -0.73,-0.13, p=0.005) in comparison with AD patients.

Table 2 Peripapillary RNFL in all quadrants (n=20 studies)

Peripapillary RNFL	Mean	Superior	Inferior	Nasal	Temporal
AD vs. HC	-0.95	-0.99	-0.81	-0.57	-0.42
	[-1.29,-0.61]	[-1.34,-0.65]	[-1.13,-0.49]	[-0.83,-0.30]	[-0.63,-0.20]

Standardized mean differences of peripapillary RNFL between study groups in all quadrants.
All P < .000.

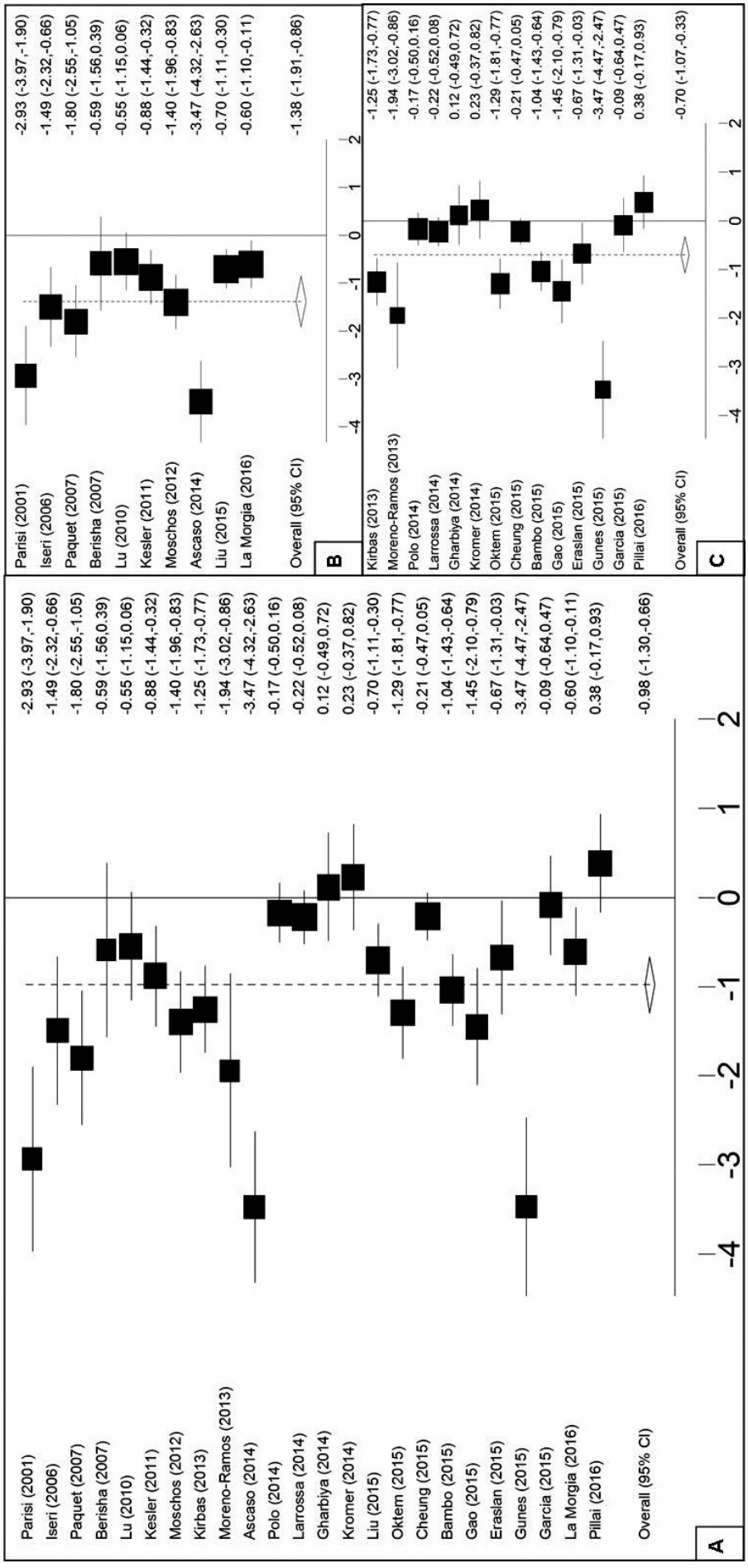


Figure 3 Mean peripapillary RNFL in AD and HC

Forest plots of standardized mean peripapillary retinal nerve fiber layer (RNFL) in A) all studies (n=24), B) studies with Time Domain (TD)-OCT scanners (n=10) and C) Spectral Domain (SD)-OCT studies (n=14).

Macular thickness

Seven studies described macular thickness of 302 AD patients in total and 241 HC, showing significant thinning in the fovea, inner ring and outer ring. Effect estimates are displayed in these three macular regions showing the largest effect on the outer ring -0.88 (CI -1.12, -0.65, p=0.000), followed by the inner ring -0.77 (CI-0.96,-0.59) p=0.000) and fovea (-0.37 (CI -0.65,-0.09), p=0.010) (figure 4).

Meta regression

Meta regression shows that OCT-type, mean study MMSE score, glaucoma exclusion score and mean study age is not associated with the SMD in the AD group compared to HC.

Publication bias

The funnel plot is relatively asymmetrical and indicates publication bias (Supplementary figure 1).

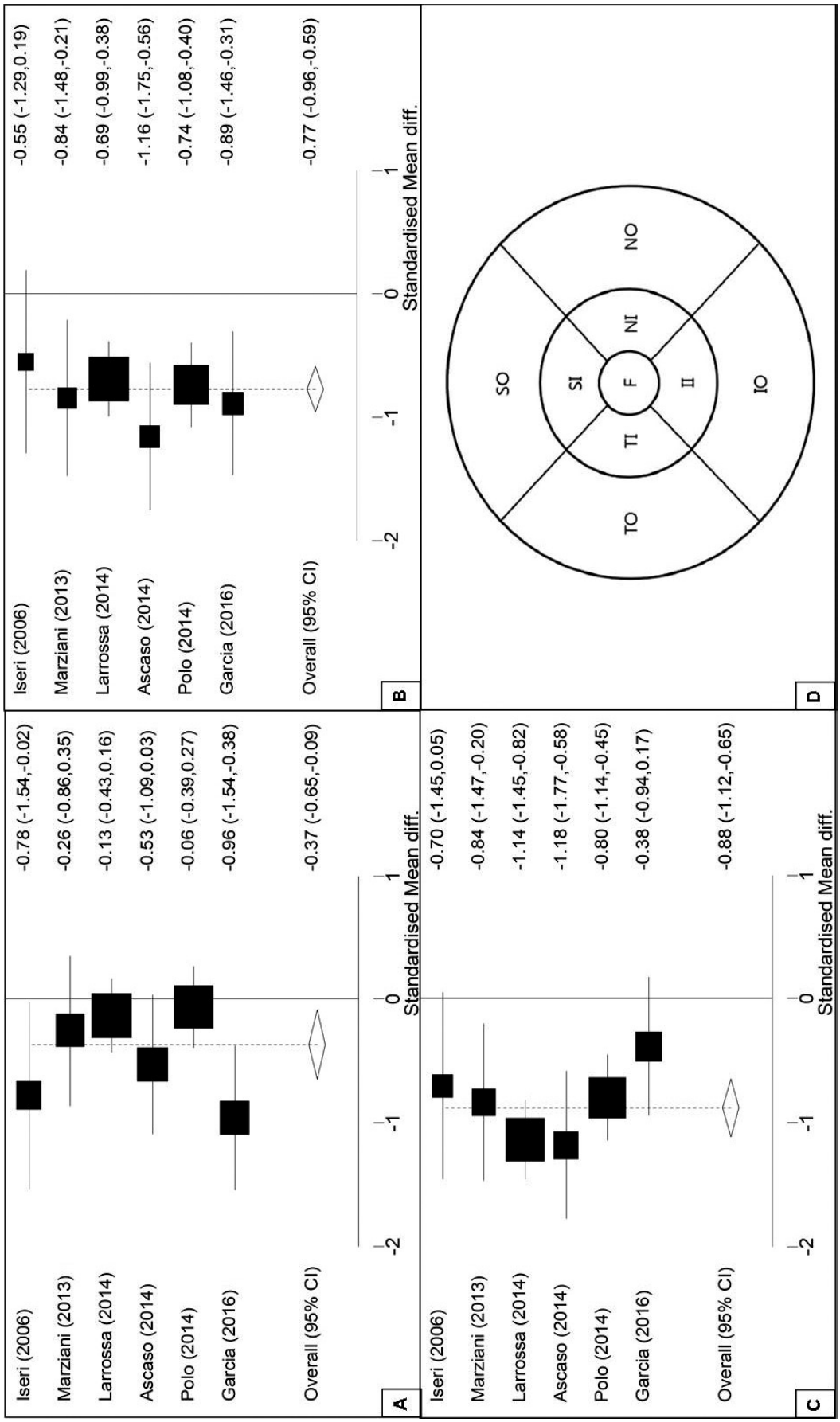


Figure 4 Total macular thickness in AD and HC

Forest plots of standardized mean macular thickness, in the A) fovea, B) inner ring and (C) outer ring. Panel D shows the ETDRS regions of the macula (inner and outer ring subdivided in four quadrants).

Discussion

We performed a systematic review and comprehensive meta-analysis to assess differences in retinal layer thickness between AD and MCI patients and HC. We show that both mean peripapillary RNFL and macular thickness decreased in AD patients compared to HC. The difference in thickness is more apparent with TD scanners than the now widely used SD-OCT. This presents an interesting finding, since the resolution (5μm vs. 10μm) and acquisition time of the currently used SD-OCT are superior to TD-OCT and currently used by most clinicians. However, fewer artefacts and significantly higher retinal thickness in SD-OCT with higher resolution compared to TD-OCT was reported before and this may be an explanation for these differences[34].

The MCI group was in between AD and HC. As the differences are small, however application of retinal thickness measurements as a diagnostic biomarker in the individual patient is challenging.We found peripapillary RNFL thickness to be lower in the superior and inferior quadrants than in nasal and temporal quadrants. This may be related to the fact that the superior and inferior quadrants contain more neurons and therefore neurodegeneration is expected to be most prominent. Similarly we would expect a more prominent change in the thicker GCL in the inner ring of the macula. In contrast, macular thickness displays the most prominent decrease in the outer ring, which may reflect RNFL loss in the periphery.

Retinal thinning is not only associated with AD but also with glaucoma. Glaucoma is a chronic, age-related and neurodegenerative disease affecting the RNFL, and hypothesized to share a common pathophysiology (neuro-inflammation, lower Aβ in CSF[35] and vitreous humor[36], and retinal ganglion cell death[37]). In addition the prevalence of glaucoma is increased in AD patients; 25.9 %, compared to 1-5.2% in the normal population[38-40]. The reverse correlation is less distinct as some population studies of glaucoma patients show a higher risk of AD[41], while others reported no association[42,43]. Possibly, AD is a risk factor for glaucoma, or AD and glaucoma share a pathophysiological process with retinal neurodegeneration as final common pathway. Two recent studies of Eraslan et al. and Cesareo et al. measuring RNFL with OCT, visual field defects with Frequency Doubling Technology (FDT) and optic nerve head morphology with Heidelberg Retinal Tomography (HRT), showed similar patterns of RNFL thinning, visual field loss and optic nerve head morphology in AD and normal tension glaucoma (NTG)[10,44]. Consequently, it seems very challenging to discriminate retinal changes due to AD from retinal changes due to glaucoma. Therefore stressing the need to account for glaucoma as a contributor to retinal thickness decrease.

The strengths of our meta-analysis are the inclusion of a large number of AD and MCI patient cohorts and HC, as well as assessment of both peripapillary and macular thinning. In addition we addressed, scanner difference and the influence of glaucoma as a possible confounder. Amongst limitations are; the studies used showed heterogeneity in the meta-regression that could not be attributed to scanner type, MMSE and/or age. Another limitation is that AD-diagnosis in the included studies was based on clinical criteria without the support of biomarkers. The National Institute on Ageing-Alzheimer's Association (NIA-AA) criteria suggest incorporating the use of biomarkers reflecting AD-pathology for an accurate diagnosis[2]. In this respect it is important to realize that several amyloid PET studies showed that around 20% of clinically diagnosed AD patients have a normal amyloid PET scan, leading to a change in clinical diagnosis[45]. A third limitation is that we did not have sufficient data to compare retinal thickness in other neurodegenerative diseases. We found only one study with data on Parkinson's disease (PD) and dementia with Lewy Bodies (DLB), showing retinal thinning in PD and DLB. A fourth limitation is revealed by the funnel plot asymmetry and statistical tests, indicating publication bias, with an overrepresentation of smaller positive studies. Study results may thus be an overestimation of the true effect.

Segmentation software recently became available to section retinal layers for assessment of change in individual retinal layers. With this method, a loss of GCL was demonstrated in patients with diabetes mellitus type II (DMII) for example, without signs of vasculopathy, in the inner ring, reflecting neuro-retinal degeneration[46]. A recent study of Garcia et al. used segmentation analysis in AD and mainly showed a contribution of inner retinal layers; ganglion cell layer (GCL), retinal nerve fiber layer (RNFL) and inner plexiform layer (IPL)[43]. Interestingly, they found a decrease in macular thickness while peripapillary thickness was unchanged, suggesting macular before peripapillary degeneration. In contrast, an increase of inner plexiform layer (IPL) thickness was reported in a recent study of Snyder et al. in preclinical AD[47]. Future research may use segmentation to identify the alterations of specific retinal layers in AD and its preclinical and prodromal stages.

As shown before and in this meta-analysis, group differences in RNFL and macular thickness are small, limiting clinical application as a biomarker. When comparing these group differences with widely used MRI-biomarkers, however, retinal neurodegeneration shows a comparable group difference to visual rating scores such as medial temporal lobe atrophy (MTA) (1.1-1.79 SD)[48-50]. In order to assess the diagnostic value of OCT, comparison with the current gold standard, NIA-AA criteria based diagnosis with the use of biomarkers (e.g. amyloid PET, CSF and/or FDG-PET) is necessary to determine sensitivity and specificity of OCT.

Conclusion

We found that the peripapillary RNFL and macular thickness are significantly decreased in AD patients compared to HC. In addition, we took glaucoma into account as a potential confounder that possibly overestimated the effect of AD on retinal thickness in the described studies. As of yet OCT cannot yet be applied as a diagnostic biomarker for AD in clinical practice. Future research should focus on OCT measurements in a well described cohort of preclinical, prodromal (i.e. MCI) and demented AD patients and subjects with information on amyloid status (positive or negative). Segmentation of individual retinal layers may provide insight into the pathophysiology of retinal neurodegeneration in AD. Correlating OCT measurements with other biomarkers of neuronal injury (i.e. hippocampal atrophy on MRI, hypo-metabolism on FDG-PET, or increased CSF tau and pTau levels) may give new insight in OCT measurements as biomarker of neurodegeneration.

References

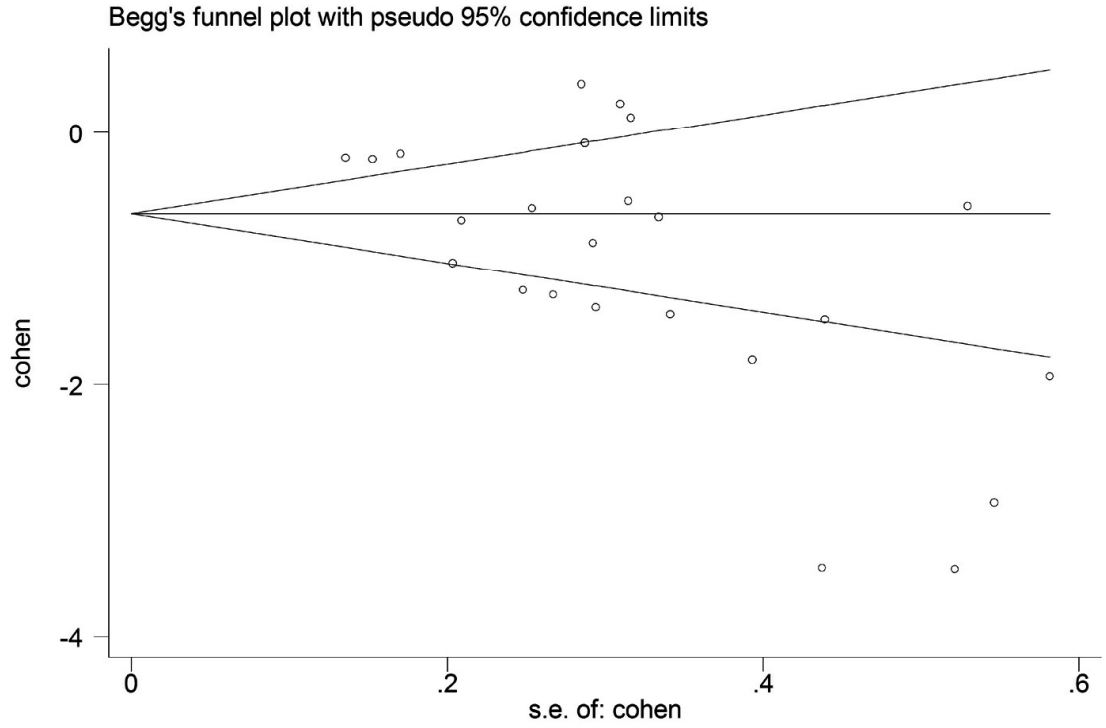
1. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):280-292.
2. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia.* 2011;7(3):263-269.
3. Jack CR, Holtzman DM. Biomarker modeling of alzheimer's disease. *Neuron.* 2013;80(6):1347-1358.
4. Reardon S. Antibody drugs for Alzheimer's show glimmers of promise. *Nature.* 2015;523(7562):509-510.
5. Petzold A, de Boer JF, Schippling S, et al. Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis. *The Lancet Neurology.* 2010;9(9):921-932.
6. Yu JG, Feng YF, Xiang Y, et al. Retinal nerve fiber layer thickness changes in Parkinson disease: a meta-analysis. *PLoS One.* 2014;9(1):e85718.
7. 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. *American journal of Alzheimer's disease and other dementias.* 2016.
8. La Morgia C, Ross-Cisneros FN, Koronyo Y, et al. Melanopsin retinal ganglion cell loss in Alzheimer's disease. *Annals of neurology.* 2015.
9. Salobrar-Garcia E, Hoyas I, Leal M, et al. Analysis of Retinal Peripapillary Segmentation in Early Alzheimer's Disease Patients. *BioMed research international.* 2015;2015:636548-636548.
10. Eraslan M, Çerman E, Çekiç O, et al. Neurodegeneration in ocular and central nervous systems: optical coherence tomography study in normal-tension glaucoma and Alzheimer disease. *Turkish journal of medical sciences.* 2015;45(5):1106-1114.
11. Güneş A, Demirci S, Tök L, Tök Ö, Demirci S. Evaluation of retinal nerve fiber layer thickness in Alzheimer disease using spectral-domain optical coherence tomography. *Turkish journal of medical sciences.* 2015;45(5):1094-1097.
12. Liu D, Zhang L, Li Z, et al. Thinner changes of the retinal nerve fiber layer in patients with mild cognitive impairment and Alzheimer's disease. *BMC Neurology.* 2015;15(1):1-5.
13. Oktem EO, Derle E, Kibaroglu S, Oktem C, Akkoyun I, Can U. The relationship between the degree of cognitive impairment and retinal nerve fiber layer thickness. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology.* 2015.
14. Cheung CY-l, 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. *Journal of Alzheimer's disease : JAD.* 2015;45(1):45-56.
15. Gao L, Liu Y, Li X, Bai Q, Liu P. Abnormal retinal nerve fiber layer thickness and macula lutea in patients with mild cognitive impairment and Alzheimer's disease. *Archives of Gerontology and Geriatrics.* 2015;60(1):162-167.

16. Bambo MP, Garcia-Martin E, Gutierrez-Ruiz F, et al. Analysis of optic disc color changes in Alzheimer's disease: a potential new biomarker. *Clinical Neurology and Neurosurgery.* 2015;132:68-73.
17. Larrosa JM, Garcia-Martin E, Bambo MP, et al. Potential new diagnostic tool for Alzheimer's disease using a linear discriminant function for Fourier domain optical coherence tomography. *Investigative ophthalmology & visual science.* 2014;55(5):3043-3051.
18. Ascaso FJ, Cruz N, Modrego PJ, et al. Retinal alterations in mild cognitive impairment and Alzheimer's disease: an optical coherence tomography study. *Journal of neurology.* 2014;261(8):1522-1530.
19. 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 (Basingstoke).* 2014;28(6):680-690.
20. M G, A T, F P, et al. Choroidal thinning as a new finding in Alzheimer's Disease: Evidence from enhanced depth imaging spectral domain optical coherence tomography. *Journal of Alzheimer's Disease.* 2014;40(4):907-917.
21. Kromer R, Serbecic N, Hausner L, Froelich L, Aboul-Enein F, Beutelspacher SC. Detection of Retinal Nerve Fiber Layer Defects in Alzheimer's Disease Using SD-OCT. *Frontiers in psychiatry.* 2014;5:22-22.
22. Moreno-Ramos T, Benito-Leon J, Villarejo A, Bermejo-Pareja F. Retinal nerve fiber layer thinning in dementia associated with Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease. *Journal of Alzheimer's disease : JAD.* 2013;34(3):659-664.
23. Marziani E, Pomati S, Ramolfo P, et al. Evaluation of retinal nerve fiber layer and ganglion cell layer thickness in Alzheimer's disease using spectral-domain optical coherence tomography. *Investigative ophthalmology & visual science.* 2013;54(9):5953-5958.
24. Kirbas S, Turkyilmaz K, Anlar O, Tufekci A, Durmus M. Retinal Nerve Fiber Layer Thickness in Patients With Alzheimer Disease. *Journal of Neuro-Ophthalmology.* 2012:1-1.
25. Moschos MM, Markopoulos I, Chatziralli I, et al. Structural and functional impairment of the retina and optic nerve in Alzheimer's disease. *Current Alzheimer research.* 2012;9(7):782-788.
26. Kesler A, Vakhapova V, Korczyn AD, Naftaliev E, Neudorfer M. Retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. *Clinical Neurology and Neurosurgery.* 2011;113(7):523-526.
27. Lu Y, Li Z, Zhang X, et al. Retinal nerve fiber layer structure abnormalities in early Alzheimer's disease: Evidence in optical coherence tomography. *Neuroscience Letters.* 2010;480(1):69-72.
28. Paquet C, Boissonnot M, Roger F, et al. Abnormal retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. *Neuroscience Letters.* 2007;420(2):97-99.
29. Berisha F, Feke GT, Trempe CL, McMeel JW, Schepens CL. Retinal abnormalities in early Alzheimer's disease. *Investigative Ophthalmology and Visual Science.* 2007;48(5):2285-2289.
30. Iseri PK, Altinas O, Tokay T, Yuksel N. Relationship between cognitive impairment and retinal morphological and visual functional abnormalities in Alzheimer disease. *Journal of neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society.* 2006;26(1):18-24.
31. Parisi V, Restuccia R, Fattapposta F, Mina C, Bucci MG, Pierelli F. Morphological and functional retinal impairment in Alzheimer's disease patients. *Clinical Neurophysiology.* 2001;112(10):1860-1867.

32. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol.* 2014;14:135.
33. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol.* 2003;3:25.
34. Forte R, Cennamo GL, Finelli ML, de Crecchio G. Comparison of time domain Stratus OCT and spectral domain SLO/OCT for assessment of macular thickness and volume. *Eye (Lond).* 2009;23(11):2071-2078.
35. Bouwman FH, Schoonenboom NS, Verwey NA, et al. CSF biomarker levels in early and late onset Alzheimer's disease. *Neurobiol Aging.* 2009;30(12):1895-1901.
36. Yoneda S, Hara H, Hirata A, Fukushima M, Inomata Y, Tanihara H. Vitreous fluid levels of beta-amyloid((1-42)) and tau in patients with retinal diseases. *Jpn J Ophthalmol.* 2005;49(2):106-108.
37. Sadun AA, Bassi CJ. Optic nerve damage in Alzheimer's disease. *Ophthalmology.* 1990;97(1):9-17.
38. de Voogd S, Ikram MK, Wolfs RC, Jansonius NM, Hofman A, de Jong PT. Incidence of open-angle glaucoma in a general elderly population: the Rotterdam Study. *Ophthalmology.* 2005;112(9):1487-1493.
39. Wolfs RC, Borger PH, Ramrattan RS, et al. Changing views on open-angle glaucoma: definitions and prevalences--The Rotterdam Study. *Investigative ophthalmology & visual science.* 2000;41(11):3309-3321.
40. Bayer AU, Ferrari F, Erb C. High occurrence rate of glaucoma among patients with Alzheimer's disease. *European neurology.* 2002;47(3):165-168.
41. Lin IC, Wang YH, Wang TJ, et al. Glaucoma, Alzheimer's disease, and Parkinson's disease: an 8-year population-based follow-up study. *PLoS One.* 2014;9(9):e108938.
42. Ou Y, Grossman DS, Lee PP, Sloan FA. Glaucoma, Alzheimer disease and other dementia: a longitudinal analysis. *Ophthalmic epidemiology.* 2012;19(5):285-292.
43. Keenan TDL, Goldacre R, Goldacre MJ. Associations between primary open angle glaucoma, Alzheimer's disease and vascular dementia: record linkage study. *The British journal of ophthalmology.* 2015;99(4):524-527.
44. Cesareo M, Martucci A, Ciuffoletti E, et al. Association Between Alzheimer's Disease and Glaucoma: A Study Based on Heidelberg Retinal Tomography and Frequency Doubling Technology Perimetry. *Frontiers in neuroscience.* 2015;9:479-479.
45. Ossenkoppele R, Jansen WJ, Rabinovici GD, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *JAMA.* 2015;313(19):1939-1949.
46. van Dijk HW, Verbraak FD, Kok PH, et al. Early neurodegeneration in the retina of type 2 diabetic patients. *Investigative ophthalmology & visual science.* 2012;53(6):2715-2719.
47. Snyder PJ, Johnson LN, Lim YY, et al. Nonvascular retinal imaging markers of preclinical Alzheimer's disease. *Alzheimer's & dementia (Amsterdam, Netherlands).* 2016;4:169-178.
48. Lehmann M, Koedam EL, Barnes J, et al. Visual ratings of atrophy in MCI: prediction of conversion and relationship with CSF biomarkers. *Neurobiology of aging.* 2013;34(1):73-82.

49. Clerx L, Visser PJ, Verhey F, Aalten P. New MRI markers for Alzheimer's disease: a meta-analysis of diffusion tensor imaging and a comparison with medial temporal lobe measurements. *Journal of Alzheimer's disease : JAD.* 2012;29(2):405-429.
50. van de Pol LA, Hensel A, van der Flier WM, et al. Hippocampal atrophy on MRI in frontotemporal lobar degeneration and Alzheimer's disease. *Journal of neurology, neurosurgery, and psychiatry.* 2006;77(4):439-442.

Supplementary material



Supplementary figure 1: Funnel plot

Supplementary Table 1

	Author	Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
1	Pillai	2016	1	1	1	9	1	1	1	1	1	0	1	1	8	8	**10**
2	La Morgia	2016	1	1	1	9	9	1	1	1	1	0	1	1	8	8	**9**
3	Garcia	2015	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**9**
4	Eraslan	2015	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**9**
5	Güneş	2015	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**9**
6	Liu	2015	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**9**
7	Oktem	2015	1	1	1	9	1	1	1	1	1	0	1	1	8	8	**10**
8	Cheung	2015	1	1	1	9	1	1	1	1	1	0	1	1	8	8	**10**
9	Gao	2015	1	1	1	9	1	1	1	1	1	0	1	1	8	8	**9**
10	Bambo	2015	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**9**
11	Larrossa	2014	1	1	1	9	9	1	1	1	1	0	1	1	8	8	**10**
12	Ascaso	2014	1	1	1	1	1	1	1	1	1	0	1	1	8	8	**11**
13	Polo	2014	1	1	1	9	9	1	1	1	1	0	1	1	8	8	**9**
14	Gharbiya	2014	1	1	1	9	1	1	1	1	1	0	1	1	8	8	**9**
15	Kromer	2014	1	1	1	9	9	1	1	1	1	0	1	1	8	8	**9**
16	Moreno-Ramos	2013	1	1	1	9	1	1	1	1	1	0	1	1	8	8	**10**
17	Marziani	2013	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**9**
18	Kirbas	2013	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**9**
19	Moschos	2012	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**9**
20	Kesler	2011	1	1	1	9	1	1	1	1	1	0	1	1	8	8	**10**
21	Lu	2010	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**9**
22	Paquet	2007	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**10**
23	Berisha	2007	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**9**
24	Iseri	2006	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**9**
25	Parisi	2001	1	1	1	9	0	1	1	1	1	0	1	1	8	8	**9**

QUADAS-tool scores for the included studies. 1=yes, 0=no, 8= non-applicable 9= unclear.

Supplementary Table 2

	Study	Bio microscopy	Fundus photos	Functional testing (visual fields)	Total
1	Pillai	0	0	0	0
2	La Morgia	0	0	0	0
3	Garcia	1	0	0	1
4	Eraslan	1	0	0	1
5	Güneş	1	0	0	1
6	Liu	1	0	0	1
7	Oktem	1	0	0	1
8	Cheung	1	0	1	2
9	Gao	1	0	0	1
10	Bambo	1	1	0	2
11	Larrossa	1	0	1	2
12	Ascaso	1	0	0	1
13	Polo	1	0	1	2
14	Gharbiya	1	1	0	2
15	Kromer	1	0	1	2
16	Moreno-Ramos	0	0	0	0
17	Marziani	1	0	1	2
18	Kirbas	1	0	0	1
19	Moschos	1	0	1	2
20	Kesler	1	1	0	2
21	Lu	0	0	0	0
22	Paquet	1	1	0	2
23	Berisha	1	0	0	1
24	Iseri	0	0	0	0
25	Parisi	1	0	0	1

Glaucoma exclusion scores for the included studies (1=yes, 0=no).