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OPTICAL COHERENCE TOMOGRAPHY AS A BIOMARKER IN AMNESTIC MILD COGNITIVE IMPAIRMENT: AN UMBRELLA REVIEW OF SYSTEMATIC REVIEWS

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ABSTRACT

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Introduction
People with mild cognitive impairment (MCI) are at a higher risk of developing Alzheimer's disease (AD), one of the most expensive diseases that lead to death and burden society. Therefore, early diagnosis is crucial to implement early and optimal AD treatment and prevent or delay disease progression. As a part of the central nervous system, the retina provides a unique and easy method for studying neurodegenerative disorders.

Purpose: The aim of this review was to screen existing systematic review results to describe the relationship between amnestic MCI and changes in the retinal layers measured with optical coherence tomography (OCT).

Methods: An umbrella review of English literature of systematic reviews was conducted on 1 October 2022 in three electronic databases (PubMed, CINAHL and MED-LINE). Studies of retinal thickness measurements by OCT in aging people with amnestic MCI were screened from the past ten years. Studies with not related OCT and Alzheimer's disease or MCI were excluded. OCTA and vessel measurements were also excluded. Data results were illustrated on tables and described narratively. In addition, the theoretical background of aMCI and retinal layers measured with OCT was collected using e-books and secondary literature sources.

Results: Seven systematic reviews met the inclusion criteria and demonstrated the link between amnestic MCI and thinning in the retinal layers, measured by optical coherence tomography (OCT). Despite the limitations in reporting of the studies, low statistical power and heterogeneity in data results, the clearest evidence of retinal thinning among patients with aMCI had observed in peripapillary retinal nerve fibre layer (pRNFL), especially in superior and inferior region, and in ganglion cell - inner plexiform layer (GC-IPL) based on included studies.

Conclusions: Though the retinal layer changes are not disease-specific for aMCI, the retina can provide a window to identify individuals at risk for AD who could benefit from early intervention. OCT could be easily used clinically with other non-invasive tests, like evaluation of functional eye movements and cognitive difficulties, as a risk indicator with multi-professional cooperation.

Keywords: optical coherence tomography, alzheimer's disease, prodromal, amnestic, mild cognitive impairment

CONTENTS

1 INTRODUCTION

Biomarkers for Alzheimer's disease (AD) have been screened widely, and the retina's non-invasive optical coherence tomography (OCT) has been proposed as one potential candidate. The retina can be called a unique "fingerprint": it is the only human tissue that allows direct visualisation of the central nervous system (CNS) and microvascular circulation. Changes in the retina have been mapped to systemic diseases, such as vascular diseases, and brain extension, such as thinning of the retinal cell layer due to neurological disorders. Thus, the retina has been considered to be a window to the CNS in terms of embryology, anatomy and physiology, also reflecting the brain changes in Alzheimer's disease in the early stage, when the only sign is a cognitive decline or even earlier before any symptoms occur. (Waduthantri, 2019.; Rodrigues-Neves et al., 2021.)

Mild cognitive impairment (MCI) is an intermediate stage between normal ageing and dementia. This condition can progress to dementia, mainly in the form of Alzheimer's disease, a progressive memory disorder with symptoms that differ from typical age-related memory problems (Petersen et al., 2017; Scheltens et al., 2021). The progression of MCI to dementia is approximately 5–17 per cent each year and increases with age and lower educational level. The prevalence of MCI in adults over the age of 60 is about 6.7 to 25.2 percent, making this impairment a significant problem, especially as we know the number of aging populations will increase in the future. (Petersen et al., 2017; World Health Organization, 2022.)

Alzheimer's disease (AD) pathology begins to develop in the brain long, up to 20 years, before clinical symptoms (Rafii, 2017). The root cause of this physical, psychological, social, and economic burden (World Health Organization, 2019) progressive memory disorder is unknown. (Sperling et al., 2011; Dubois et al., 2016.) This clinically, with neuropsychological tests, defined AD specific MCI can be called as amnestic MCI (Petersen et al., 2017). In addition to neurophysiological tests, some well-established biological biomarkers for the progression of MCI to AD exist. MCI cases positive for AD biomarkers can be defined as prodromal AD or MCI due to AD based on study diagnostic criteria consistent with the 2018 A/T/N (amyloid/tau/neuronal damage) framework. (Jack et al., 2018; Boccardi et al., 2021.) However, the main problem with biological biomarkers is that they are not always available due to their high costs. In addition, some are invasive methods and thus unpleasant for individuals. (Cohen et al., 2019.) Against this background, there is great interest

in finding other sensitive biomarkers that allow insight into the structural and functional pathophysiological changes affecting the brain.

OCT would be a non-invasive, inexpensive, and technically simple tool to carry out by a more extensive range of experts, including optometrists, thus supporting other screening methods to detect early stages of cognitive and brain changes from the retina (R. Wang, 2020). It is known that ageing affects retinal thinning (Trinh et al., 2021). Besides this, studies have shown thinning of the retinal layers in amnestic MCI, where the only sign is memory impairment (Ascaso et al., 2014; Knoll et al., 2016; Shen et al., 2014).

The aim of this umbrella review is to screen existing systematic review results to describe the relationship between amnestic mild cognitive impairment (also called prodromal AD) and changes in the retinal layers (excluding choroidal layer) measured with optical coherence tomography (OCT). The aim is to provide an overview and synthesis of existing systematic reviews on a topic review from the past ten years. The matter of interest is to screen the possibility of OCT as a biomarker to identify individuals most likely to develop Alzheimer's dementia and through it could thus give a possibility for early intervention in progression. In addition, this review is supposed to organise gathered information in clear and illustrated form with tables and figures, making clear conclusions by data-driven content analysis of selected studies. Screening of systematic reviews was selected because through it can achieve “fast” evidence in reduced timeframes (Aromataris et al., 2020) and no umbrella review on the subject was found in the preliminary data search at time being.

2 THEORETICAL BACKGROUND

When people get old, they might forget things a little bit more or have some language difficulties, but these are typical ageing problems. In normal ageing, basic activities of daily living (BADL), like eating and showering, and instrumental activities of daily living (IADL), like shopping and phone use, are stable. The first and most significant mild cognitive impairment (MCI) of Alzheimer's disease is memory loss. Short-term memory, learning new things, and executive functions (like attention control, working memory, and cognitive flexibility) become complicated. (Executive Functions: Complete Guide, n.d.) As the disease progresses, the symptom picture expands. MCI is considered a borderland or an intermediate stage between cognitive changes of ageing and very early dementia (Figure 1). In the continuum of AD, specialised nerve cells in the brain, neurons, lose the ability to communicate with one another, and eventually, these neurons die. (The National Institute on Aging, 2021a.)

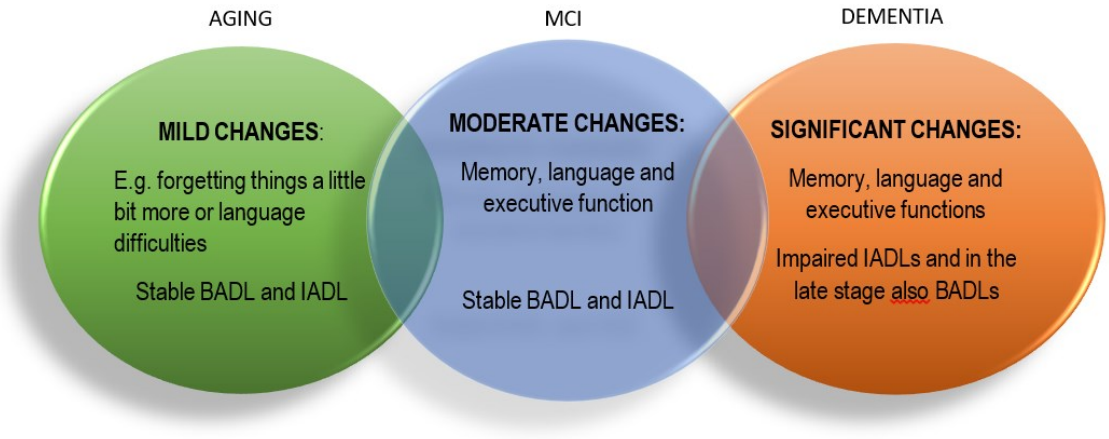


FIGURE 1. Process from normal aging through mild cognitive impairment (MCI) to dementia. BADL: Basic activities of daily living; Executive functions: basic cognitive processes such as attention control, working memory, and cognitive flexibility; IADL: Instrumental activity of daily living. Figure: Seija Säynäjäkangas.

Brain changes can already be seen in the preclinical stage of AD without significant clinical symptoms (Jack et al., 2018). However, brain changes in the next AD stage have expanded, and subtle memory, language and executive function changes become visible. This stage is called the prodromal stage of AD or mild cognitive impairment (MCI) due to AD or amnestic MCI. (Albert et al., 2011; Vermunt et al., 2019.)

Early detection of AD offers early intervention and possibilities to prevent and monitor the progression, including the intervention with disease-modifying therapy. In the field of research on AD, one goal has been to find less expensive and non-invasive methods to detect AD changes before symptoms appear and before brain cells have died (Arafa et al., 2022.) The retina has considered a window for disorders in the central nervous system (CNS) due to its embryological, anatomical and physiological extension of the brain. Optical coherence tomography (OCT) could play a role in the neurodegenerative changes in AD (London, Benhar and Schwartz, 2012).

2.1 Amnestic Mild Cognitive Impairment (aMCI) in Continuum of Alzheimer's Disease

Alzheimer's disease (AD) is a chronic brain disease that is the most common form of dementia, responsible for 60%-70% of all cases of dementia. It is estimated that over 55 million people have dementia worldwide, and almost 10 million new cases appear yearly (World Health Organization, 2022). Dementia mainly affects people older than 65 years. Under demographic ageing, dementia prevalence is expected to double by 2050, causing global challenges for healthcare and medical systems (Alzheimer's Disease International, 2020). For example, in 2019, AD was the fourth leading cause of death among people 75 years and older after ischaemic heart disease, stroke and chronic obstructive pulmonary disease (COPD) respectively (Vos et al., 2020). European countries are estimated to have nearly 19 million people with some form of dementia by 2050, which follows the global trend of doubling the cases of dementia (Alzheimer's dementia, n.d.).

Pathophysiology

In a healthy brain, neurons communicate with each other through electrical charges that travel, enabling them to form new memories, learn new things, solve problems, and move. Signals are received by dendrites of neurons, reaching the cell body, and continuing through the axon of the neuron to axon terminals which release neurotransmitters in synapses and signals are sent to other neurons. In addition, other brain cells take care of neurons, like microglia cells, which remove detrimental chemicals in the inflammation process. (Mufson et al., 2011; Petersen et al., 2014, p. 220.)

In AD, neurons lose their ability to communicate with each other due to the abnormal formation of debris. Two primary lesions in the brain appear years before AD symptoms: senile amyloid plaques and neurofibrillary tangles composed of tau protein. Also, the loss of acetylcholine is seen in the

pathologic alterations of the brain. In cell membrane has a protein amyloid precursor protein (APP), which helps the neuron grow and repair and, when used, breaks down into small pieces of peptides and, in the end, are recycled. APP is generally sectioned by alpha and gamma-secretase enzymes, forming a soluble peptide which then metabolises. (Hyman et al., 2016, pp. 107-111; McCance and Huether, 2019, pp. 520-524.)

In the case of AD, instead of alpha-secretase, beta-secretase teams up with gamma-secretase and the leftover fragment, which is not soluble, creates a monomer called amyloid beta. These monomers aggregate outside the neurons, forming clumps called 1) beta-amyloid plaques. These plaques disturb the signals between neurons. If brain cells can not signal and relay information, the brain functions like memory can be seriously impaired. It is also thought that these amyloid plaques can start an immune response and cause inflammation which might damage surrounding neurons. Amyloid plaques can also deposit around blood vessels in the brain, called amyloid angiopathy, which weakens the walls of the blood vessels and increases the risk of bleeding or rupture and blood loss. (Hyman et al., 2016, pp. 107-111; McCance and Huether, 2019, pp. 520-524.)

When neurons communicate, a signal goes from the cell body, known as soma, to the synapse to transfer the information. The signal passes through the neuron's structure composed of microtubules, stabilised by normal tau protein, preventing them from breaking apart. The microtubules play a vital role in delivering nutrients throughout the neuron. In AD, these tau proteins become defective inside the neuron and detach from the microtubules, and the structure is no longer maintained. Defective tau proteins then assemble to form filaments in the neuron called 2) neurofibrillary tangles. Without maintained structure, which also makes nutrient delivery possible, the neurons degenerate, and connections between the neurons are lost, leading to programmed cell death. When many neurons die, large-scale changes happen in the brain, including brain shrinking, sulci getting more expansive, and ventricles enlarging. (Hyman et al., 2016, pp. 107-111; McCance and Huether, 2019, pp. 520-524)

The amyloid plaque and tangle formation start from the entorhinal cortex, the middle part of the brain, spreading to the adjacent temporal and frontal regions of the brain when the disease progress (Brickwood, 2020). Tangles have been thought to develop first in the hippocampus, which is essential to memory and learning, reaching the whole brain over time. This process causes atrophy which engenders global dysfunction. The progression of the lesion corresponds with the symptoms of the disease, which begin with memory problems followed by problems of language, recognition

and incapacity to perform gestures. (Brion, 1998, pp. 165-174.) If we think development during childhood, we first learn the basic functions: continence, washing, dressing and choosing clothes. Lastly, the ability to cope with complex instrumental activities, such as the use of money, develop. In the dementia of Alzheimer's disease, the ability to function is lost in the opposite order.

The stages of tangle accumulation can divide with the Braak definition: I + II tangles are seen mainly in the early phase of medial temporal lobe structures (transentorhinal). In the intermediate stage, III + IV tangles have spread ventrally in the frontal and temporal lobe (limbic), and late phase V + VI tangles have spread widely involving the hole cortical region (isocortical). Amyloid plaques have observed at first in the entorhinal cortex, which is responsible for memory, understanding time and sense of direction and then also hippocampus is affected. (Braak and Braak, 1991.)

These two cerebral lesions, abnormal protein deposits, define AD as a unique neurodegenerative disease among the various conditions that can lead to dementia. But which comes first, plaques or tangles, are still little understood (Guzmán-Vélez et al., 2022). It has been suggested that well before the formation of senile plaques, more minor forms of amyloid beta called oligomers appear toxic to neurons disturbing their communication. These oligomers and their accumulation (plaques) are the origins of neurofibrillary tangles, which are responsible for symptoms. (Hyman et al., 2016, pp. 107-111.)

2.2 Amnestic Mild Cognitive Impairment and Prodromal Alzheimer's Disease

Alzheimer's disease can be divided into five main categories based on cognitive functions: 1) Pre-clinical stage of AD, 2) Prodromal stage of AD, also referred to mild cognitive impairment (MCI) due to AD or amnestic MCI, and 3) early, 4) middle and 5) late stages of AD dementia. In the Preclinical stage of AD, brain changes, including amyloid build-up and other nerve cell changes, may already progress, but significant clinical symptoms are not yet evident. This stage has estimated to last for years, even decades, depending on a person's age at the starting stage. (The Seven Stages of Dementia, 2019.)

2.2.1 Mild Cognitive Impairment Subtypes

MCI patients are at a higher risk of developing Alzheimer's disease and other forms of dementia (Alzheimer's Association, 2020; Panza et al., 2008). Early detection is essential. The global prevalence of MCI among community residents aged 50 years and older is greater than 15%. The MCI increases with age and decreases with educational attainment. Also, gender and region of study affect the incidence. (Bai et al., 2022.) Studies suggest that around 10% to 15% of individuals with mild cognitive impairment (MCI) go on to develop dementia each year (www.alzheimers.org.uk, n.d), and that is a lot when thinking ageing population.

MCI is classified by experts, based on practical thinking skills, in two categories (Figure 2). First is amnestic MCI (aMCI), with memory loss or impairment (amnesia) as the predominant symptom. Persons may start to forget important information that they would previously have recalled easily, such as names, places, appointments, conversations, and recent events or misplacing objects and forgetting where they are. The aMCI has seen a stronger association with AD. The aMCI can be divided into two categories depending on whether it is only memory-based problems (single-domain) or is there in addition to memory problems also other daily living problems. Amnestic MCI (aMCI), especially single domain, is generally considered as a prodromal stage of Alzheimer's disease (AD) in clinical work. Especially when evidence of the pathology or the neuronal injury is not available. (Petersen et al., 2014, pp. 217-218; Jongsiriyanyong and Limpawattana, 2018, pp. 502-504.)

The second category is non-amnestic MCI (naMCI) which affects thinking skills other than memory, like language and executive problems, including the ability to make rational decisions and challenges to judge the time and issues with visual perception. In practice, this means individuals lose their train of thought, sense of time or direction and have difficulty concentrating. (Alzheimer's Association, 2020; Petersen et al., 2014, pp. 217-218.) The naMCI may be further divided into single-multi-domain amnestic MCI. The naMCI patients are believed to be more likely to convert non-Alzheimer's disease, like frontotemporal dementia (FTD), dementia with Lewy bodies (LBD), Parkinson's disease with dementia, vascular dementia (VaD), or primary progressive aphasia. Non-amnestic MCI may also result from normal ageing and have reversible causes. (Tabert et al., 2006; Petersen et al., 2014, pp. 217-218; Jongsiriyanyong and Limpawattana, 2018, pp. 502-504.)

Either type of MCI may lead to vascular dementia (Meguro and Dodge, 2019). In a recent study, MCI subjects were subtyped based on the relationship between the AD conversion rate and its biological characteristics, such as ventricular volumes measured by magnetic resonance imaging method and APOE genotype dosage (blood test), with comparing cognitive function in each subtype. Based on study findings incorporating additional pathological information may allow more accurate prediction of the onset or progression of several neurodegenerative diseases. (Kikuchi et al., 2022.)

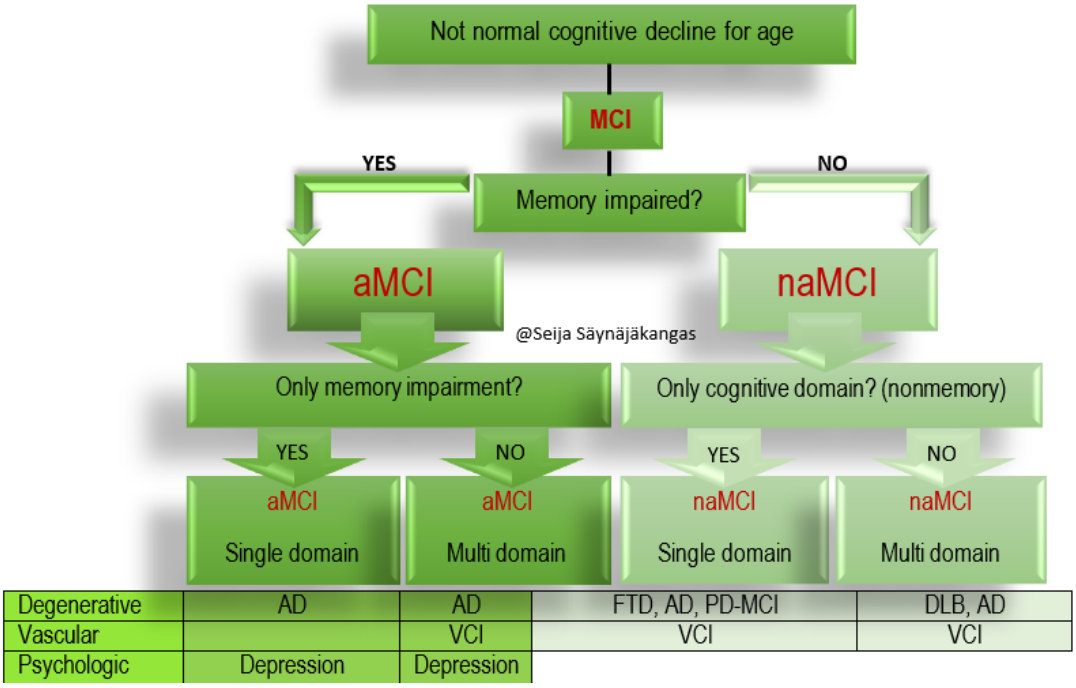


FIGURE 2. Differential diagnosis criteria for mild cognitive impairment (MCI) to amnestic disease as usually occurs. Abbreviations and Acronyms: AD = Alzheimer's disease; aMCI = amnestic MCI; DLB = dementia with Lewy bodies; FTD = frontotemporal dementia; MCI = mild cognitive impairment; naMCI = non-amnestic MCI; PD-MCI =MCI in Parkinson disease; VCI = vascular cognitive impairment. Accordingly, to the Jongsiriyanyong and Limpawattana, 2018, pp. 502-504. Figure: Seija Säynäjäkangas

2.2.2 Assessment of aMCI and Biomarkers for Prodromal AD

The categorising of MCI in clinical work starts from the subjective cognitive complaints or changes reported by the next of kin. Impairments need to be confirmed by objective cognitive measures, such as neuropsychological test batteries. (Petersen et al., 2014.) There are multiple cognitive screening guidelines suggested for testing MCI in clinical work, e.g., the mini-mental state examination (MMSE) and the Montreal Cognitive Assessment (MoCA) (Chen et al., 2021).

There is no gold standard to determine which neuropsychological test battery to use (Karantzoulis et al., 2013). Still, all significant cognitive domains (typically executive functions, attention, language, memory, and visuospatial skills) must be examined to exclude the other causes of cognitive decline. Neuropsychological testing helps clarify the patient's symptoms and distinguish between the changes in cognitive functions that occur with normal ageing. The next step is categorising MCI as an amnestic (aMCI, problems in episodic memory) or non-amnestic (naMCI, problems in cognitive domains other than memory, such as executive functions, language or visuospatial abilities) type. After non-invasive evaluation, there is still uncertainty about whether MCI is due to AD. In that phase, some help for diagnosing AD pathology is sought from imaging methods and blood tests. (Petersen et al., 2014.; Vuoksimaa et al. 2018.)

A significant correlation has been seen between measurements of total cognitive impairment and intelligence tests for adults. One study has suggested that in the areas of information processing, working memory, and perceptual aspects, cognitive deterioration in old age starts with impairment of working memory and reduced speed of information processing long before memory problems are present (Pauli et al., 2018). Including traditional screening tests for cognitive deterioration assessed by experts, digital technology has sought answers. However, before digitalisation, like smartphones and tablets, can be harnessed to home-based use for self-evaluation, among other things, test validation and technological concerns must be solved (Sabbagh, Boada and Borson, 2020). Despite that, in the light of new studies, digital cognitive biomarkers are comparable, in some cases, a better, promising tool compared with traditional paper tests to detect MCI and dementia in an early stage. (Ding, Lee and Chan, 2022; Teh, Rawtaer and Tan, 2022).

A lot of heterogeneity has been seen in the pathology of amnestic MCI. Even though the specific mechanism remains unclear, and the brain undergoes multisystem dysfunction, the cause of the disease seems to have identical types, but lesser degree, than seen changes in the brain in AD. (Jack et al., 2018.) Brain imaging studies show changes that may be associated with MCI. Shrinking of the hippocampus, which is an important area for memory (Su et al., 2021), enlargement of the brain's fluid-filled spaces or ventricles (Carlson et al., 2007), and increased glucose levels in central areas of the brain (Croteau et al., 2018; Krell-Roesch et al., 2021) have seen to be associated with MCI. NIA-AA Research Framework (Jack et al., 2018) has published the principle to approach the risk of short-term cognitive decline based on the amyloid, tau and neuronal injury biomarker profiles and cognitive stage in MCI (Figure 3).

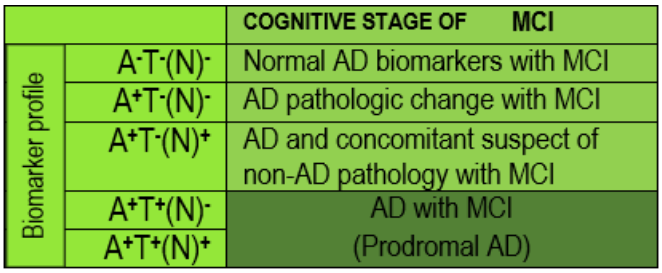


FIGURE 3. MCI due to AD in the presence of biomarker positivity and cognitive stage. Accordingly, to Jack et al., 2018 (NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease, pp. 538 and 549). Abbreviations and Acronyms: A = Amyloid (low amyloid deposition using amyloid positron emission tomography (PET), cerebrospinal fluid (CSF) amyloid or amyloid plasma levels); N = neurodegeneration or neuronal injury (cortical atrophy detected by MRI/ low glucose metabolism seen by FDG-PET or CSF total-tau levels); T = Tau (high tau deposition using tau-PET or CSF phosphorylated tau levels); (+) positive marker and (–) no marker. Figure: Seija Säynäjäkangas

The supportive biomarkers for cognitive tests of detecting MCI due to AD have been searched from biological biomarkers: the cerebrospinal fluid (CSF) markers of amyloid and tau proteins, radiological imaging covering magnetic resonance imaging (MRI) and amyloid- and fluorodeoxyglucose positron emission tomography (FDG-PET) methods for detection of neurodegeneration, which all has been found to have an association with MCI due to AD (Jack et al., 2018). According to a small clinical study, one conclusion has been using a neurodegenerative imaging marker (MRI-based hippocampal volume and 18F-FDG-PET) in addition to the cognitive marker in clinical practice to screen MCI and predict its conversion to AD (Ottoy et al., 2019).

There are no specific recommendations for imaging studies to diagnose MCI, and none of the biomarkers is as sensitive as a direct examination of tissue at autopsy. However, imaging helps identify the cause of the disease and provides information about the possible physiologic processes associated with Alzheimer's disease (Alzheimer's Association, 2020; Jack et al., 2018). On top of the fact that MRI can be used to diagnose mild cognitive impairment in patients at higher risk for Alzheimer's disease, MRI can also help identify both hippocampal atrophy and ventricular enlargement, markers of mild cognitive impairment (Apostolova et al., 2012). In addition, CSF- biomarkers, decreased levels of amyloid-beta or increased levels of tau proteins, also support their values as markers of the patient process from MCI to AD (Ma, Brettschneider and Collingwood, 2022). Testing of CSF biomarkers has been estimated to increase prognostic value in half of MCI patients (van Maurik et al., 2021).

Expensive imaging methods like MRI and PET, and for individuals, unpleasant CSF-test has driven new diagnosing methods of MCI. Laboratory tests using blood samples identify various parameter levels responsible for mild cognitive impairment (Pereira, Simões do Couto and de Mendonça, 2006) and blood markers on which amyloid-beta and tau proteins can be determined from the blood (Chen et al., 2019). A rapid, non-invasive, highly quantitative, and low-cost peptidome technology has developed as a new serum biomarker (BLOTCHIP®-MALDI-TOF/MS analysis) for MCI and AD (Abe et al., 2020). MCI and AD patients have been found to have increased oxygen saturation levels, indicating that retinal oxygen metabolism may be affected in patients with MCI and thus provide one supporting method for diagnosing MCI (Olafsdottir et al., 2018). The miRNA, a sample gathered from blood plasma serum, has also been suggested as a promising fluid biomarker among MCI patients to identify the early stages of AD (Ogonowski et al., 2022).

In some cases, AD may begin with visual disturbances, including reading difficulties, blurred vision, and complaints of poor vision. Such patients may have normal routine eye examination findings, including normal visual acuity and fundus. However, in patients with AD, optic nerve degeneration and retinal cell loss, particularly loss of ganglion cells and their axons, is evident, as well as decreased levels of acetylcholine, which is crucial for the proper function of retinal cells. These dysfunctions explain, at least in part, the reason for the visual disturbances seen in patients with early AD. (Krasodomska et al., 2010.)

It has been proposed to diagnose visual abnormalities in AD with examinations that measure the bioelectrical activity of retinal ganglion cells and the optic nerve (Krasodomska et al., 2010). Some studies have demonstrated impairment in eye movements (saccades and fixations) and reading problems in individuals with mild cognitive impairment (MCI). In addition, reading problems increase in severity as AD progresses. (Hannonen et al., 2022; Fernández et al., 2013.)

2.3 Treatment, Risk and Protective Factors

Now, there is no curative drug or treatment for AD. The purpose of the existing drugs is to ease the current symptoms or delay the progression of the disease. Real work should be done in prevention because the damages to the nervous system already exist and are difficult to fix with drugs. Different medicines have their targets in the brain tissue, and the medication selection depends on the disease phase and the needs or obstacles of AD patients (National Institute on Aging, 2021b;

www.kaypahoito.fi, n.d.) A new randomised-control trial is starting with the drug Metformin, which has been used in the treatment of diabetes for a long time, including customised lifestyle changes, investigating possible ways to prevent cognitive decline in elderly adults at risk of dementia (Imperial College London et al., 2022).

The most strongly associated risk factors for dementia are ageing, a family history of Alzheimer's, and the risk of cardiovascular disease. In addition, the conditions like blood pressure (Gaussoin et al., 2021), the effects of anticholinergic medications (Weigand et al., 2020, pp. 2301-2302), depression (Kim, 2019, pp. 211-216), hormonal changes (Gleason et al., 2015) or even vitamin-B levels (Olaso-Gonzalez et al., 2021, pp-77-82) can influence the progression of dementia. There has also been a connection between low parathyroid hormone levels and cognitive impairment (Sardella et al., 2020) and connection between hyperinsulinemia in type 2 diabetes mellitus and MCI (Bashir and Yarube, 2022).

In addition, anxiety, physical illness like an infection or severe constipation, and sight or hearing loss have been a cause of dementia (www.alzheimers.org.uk, n.d.). The recent report has identified 12 risk factors for dementia which might prevent or delay up to 40% of dementias when treated: low education and social contact, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, excessive alcohol consumption, traumatic brain injury, and air pollution (Livingston et al., 2020; Marioni et al., 2012.)

Health-promoting lifestyles, such as regular exercise or physical activity, not smoking, avoiding excess weight, using brain activity and treating underlying diseases well, can reduce the risk of Alzheimer's disease (National Institute on Aging, 2020). A large randomised controlled trial (FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability database) found that active participation was associated with better developmental trajectories in the full neuropsychological test battery (NTB) and all cognitive subdomains. Furthermore, improving lifestyles was related to the advancement of NTB's overall and executive functions (Finnish Institute for Health and Welfare, n.d.). Multi-domain lifestyle changes are beneficial for cognitive functioning, but future interventions must be sufficiently intensive and supporting commitment is essential. (Ngandu et al., 2021.)

Other risk factors have been found, like sleep difficulties (Naismith and Mowszowski, 2018) and stress (Trammell et al., 2020) which management should also pay attention to. The recognition of

AD in the earliest possible stage could lead to secondary prevention by controlling health factors meaning that after correcting these medical and other conditions, a person might stay stable and ageing with normal ageing progression (Gauthier et al., 2006, p 1262-1263). The earlier a patient at risk is found, the better the chances are of preventing neurological changes in the brain.

2.4 Optical coherence Tomography

Retinal changes can be visualised both in ophthalmological disease and in neurodegenerative disease. Optical coherence tomography (OCT) is a medical imaging technique widely used by ophthalmologists and optometrists to obtain high microscopic resolution images of the anterior segment and retina, identifying diseases and their progression. OCT imaging has two different resolutions: axial resolution in the depth direction and lateral resolution in the surface plane, as in a microscope. OCT can produce high-resolution images, typically 20–5 µm. The light beam is directed at the tissue surface, and a small portion of the light reflected is collected, allowing the image to be created. (Aumann et al., 2019, pp.59-67.)

Many light-reflecting areas will have more interference than those that do not. However, the light beyond a short coherence length does not interfere. This reflectance profile is called an A-scan. A cross-sectional tomography (B-scan) 3D map can be obtained laterally, combining a series of these axial depth scans (A-scan). In addition, C-scans (Enface) are obtained with OCT, which corresponds to the coronal part. The C-scan image can also be called a "phase fundus image", which is like a fundus camera image, but without colour. Image parameters and types of scans have illustrated in Figure 4. (Aumann et al., 2019, pp.59-67.)

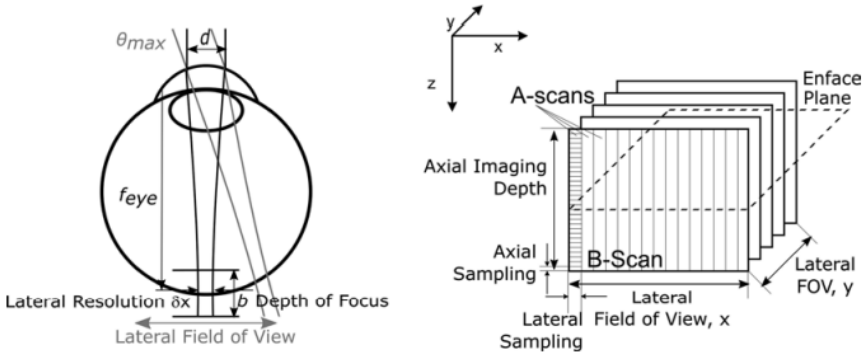


FIGURE 4. Image parameters and scan types. The left is shown lateral image parameters of retinal OCT depending on the focusing of the probing beam by the human eye. The right is illustrated a schematic of sampling an OCT volume: A-scan, B-scan and C-scan (Enface). FOV= field of view. (Aumann et al., 2019, p.67.)

OCT imaging is limited to 1–2 mm below the biological tissue surface. There is no requirement for special patient and sample preparation. It is also important to note that without ionising radiation, it is eye-safe, using ear infrared light, so eye damage is not likely. In addition, OCT enables, with a high resolution, to identify of retinal changes that are not detectable by ophthalmic examination. (Aumann et al., 2019, pp.59-67; American Academy of Ophthalmology, 2005.)

The OCT is a low-coherence interferometric technique where the basic principle is to measure the travel time of light echoes through the tissue. This is done by creating an interference pattern between the light propagating in the sample arm and the light propagating in the reference arm of the Michelson interferometer (Davis et al., 2008, p. 3905-3906). Because of the interferometric measurement method, the axial resolution is determined by the light source, not the focusing optics. Therefore, it overcomes the limitations of optical focusing due to the eye's limited pupil size. In addition, in traditional imaging, scattered light adds background noise, obscuring the image. However, in OCT, interferometry's technique records the optical path length of all received photons, allowing most dissipative photons to be rejected before detection. As a result, the technology gives instant and direct tissue morphology imaging and is now widely available. (Schmidt-Erfurth et al., 2018, pp.1-2; Aumann et al., 2019, pp.59-61.)

The first version of OCT used time-domain (TD) interferometry technology. Still, in the '90s, TD OCT was replaced by Fourier-domain (FD), also called frequency-domain, OCT system including two main variations, spectral-domain OCT (SD-OCT) and swept-source OCT (SS-OCT). FD OCT can achieve much higher sensitivity and imaging speed than TD-OCT. However, these two FD OCT techniques differ due to the mechanism used to measure interferences corresponding to different frequencies. (Aumann et al., 2019, pp.61-68; Insight Ophtalmology, 2022a.; Kalkman, 2017.)

SD-OCT is based on measuring the interference spectrum in space with a spectrometer, meaning that different frequencies of light are shined simultaneously on the sample and then spatially separated the frequencies using a spectrometer. SS-OCT measures the interference spectrum during scanning the wavelength of a laser source that can be quickly tuned in time. In other words, the technique uses a laser that "sweeps" through different frequencies over time to record interference as a function of frequency or colour. SS-OCT is the technique of choice when faster and deeper imaging is required, such as in cardiovascular and dermatological applications, where both applications require more in-depth imaging. In addition, SD-OCT can provide wide-field retinal imaging

without loss of axial image resolution, and it is lower in cost than SS-OCT, enabling wider availability. (Aumann et al., 2019, pp.61-68; Insight Ophtalmology, 2022a.; Bille, 2019.)

2.5 Retinal Tissue and Optical Coherence Tomography Measurements

2.5.1 Retinal Layers

The retina consists of ten distinct retinal layers (Figure 5.). From innermost layer to outermost layer: (1) Inner limiting membrane, (2) Retinal nerve fibre layer (RNFL), (3) Ganglion cell (GC) layer, (4) Inner plexiform layer (IPL), (5) Inner nuclear layer (INL), (6) Outer plexiform layer (OPL), (7) Outer nuclear layer (ONL), (8) External limiting membrane (ELM), (9) Photoreceptor layer (PRL) and (10) Retinal pigment epithelium (RPE). Outer layers, respectively, are Bruch's membrane (BM), choriocapillaris and choroidal stroma, including blood vessels. (McCance and Huether, 2019, pp. 488-489; Lumbroso and Marco, 2015, pp. 11-10.) In this study, the research targets are the innermost macular layers of RNFL and GCL and peripapillary RNFL.

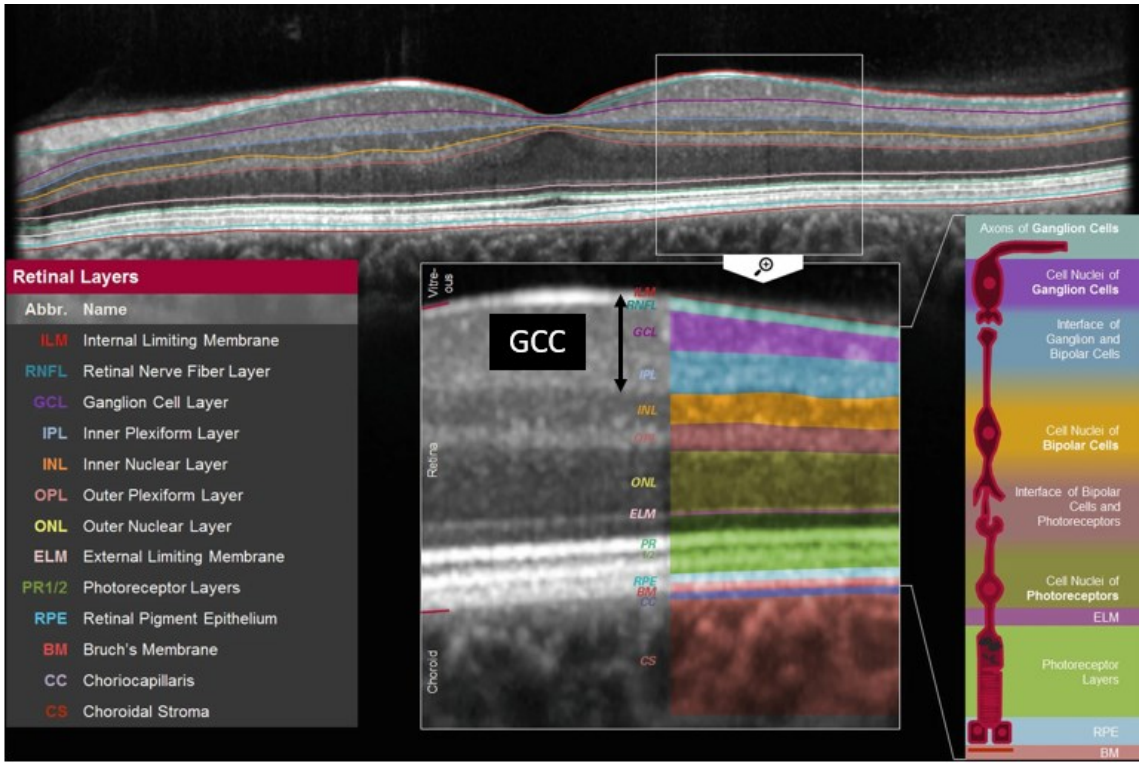


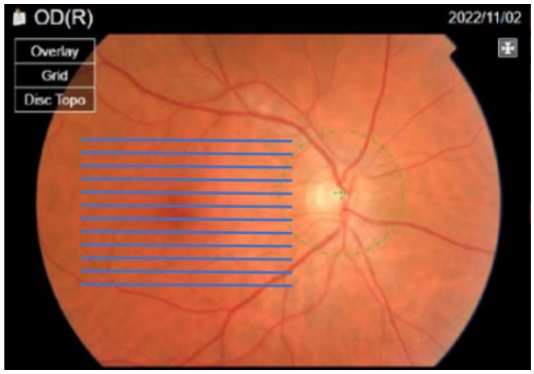
FIGURE 5. Retinal layers with OCT B-scan. Ganglion cell complex (GCC, black arrow) consist of the retinal nerve fibre layer (axons) (RNFL), ganglion cell layer (body) (GCL) and inner plexiform layer (dendrites) (IPL). GCC added by Seija Säynäjäkangas. (Aumann et al., 2019, p.74)

2.5.2 OCT Parameters and Output of Scan Types

An OCT can provide many different outputs: raster (line) scan, three-dimensional (3D) scan, radial line scan, thickness map from specific layers of the retina, retinal nerve fibre layer (RNFL) scan and macula single line scan. Algorithms created for different OCT types allow comparing measurements with normative values, thus giving an understanding that values are within normal limits. Outcomes of retinal layer thickness vary depending on technique or type of OCT. The next illustrated scan types and retinal layer outcomes give an overall picture of the subjects (Lumbroso and Rispoli, 2014.)

The raster (line) scan (Figure 6.A) describes the pattern of scan lines used by a given test. For example, it can have a horizontal or vertical grid. The distance between the scan lines can be varied, and if lines are too far apart, there is a greater chance of missing the retinal damage. Some machines have raster patterns closer together at the fovea and farther apart from the fovea being scanned. (Insight Ophtalmology, 2022b.; Lumbroso and Rispoli, 2014.)

The radial line scanning (Figure 6.B) directs the OCT beam radially, producing images displayed as a "radar-like" circular diagram. These images have the highest accuracy when the probe is inserted into a small diameter lumen. The advantage of a radial line scan is that it provides a larger area of the macula than a single line scan. In contrast, the disadvantage is that potential lesions may be missed in the parafoveal area, where the distance between scan lines is more remarkable. There are available 6-, 12- (Figure 6.B) and 24 -line radial scans. (Insight Ophtalmology, 2022b.; Lumbroso and Rispoli, 2014.)

A. 

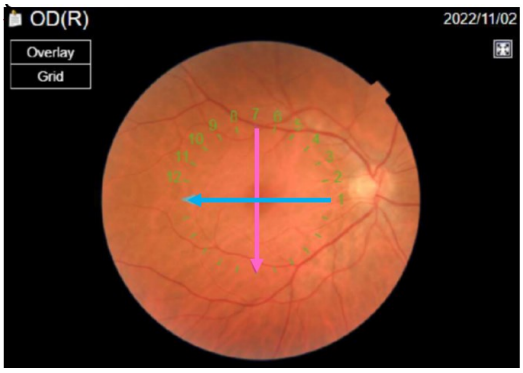
B. 

FIGURE 6. Scan types: Raster scan (A), Radial scan (B). Figures modified and measured with Topcon Maestro2 by Seija Säynäjäkangas.

Macular thickness

The retinal thickness maps (Figure 7.A) can provide quantitative data that provide colour maps of a specific region of interest. Total macular thickness consists of the inner limiting membrane (ILM) to retinal pigment epithelium (RPE). Warm colours indicate increased retinal thickness, and cooler colours represent thinner areas. ETDRS (Early Treatment Diabetic Retinopathy Study) grid (Figure 7.B) measures total macular thickness: The central field is a central circle with a diameter of 1 mm. The inner ring consists of four subfields surrounding a central circle, and the diameter of this inner circle is 3 mm. The outer ring consists of four subfields surrounding the inner ring, and the diameter of the outer circle is 6 mm. Areas are illustrated in Figure 7.C. (Mazzarella & Cole, 2015.)

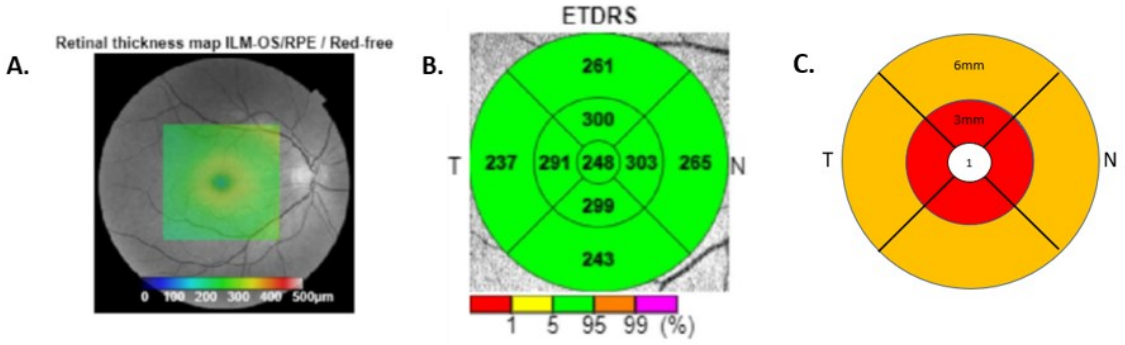


FIGURE 7. **A.** Retinal thickness map (in microns) in a colour map: cooler colours indicate thinner areas. The caption of the colours is below of the map. **B.** Retinal thickness map with EDTRS grip including the hole thickness of retina consisting of ILM-RPE; Colour values: retinal thickness compared with normative database. The caption of the colours is below of the map: Green indicates normative values compared to database, yellow indicate thinner than fifth percentile and red thinner than first percentile. In **C.** EDTRS grip areas (central 1mm, white colour; Inner ring 3mm; red colour and the outer ring 6mm; orange colour. Figures Seija Säynäjäkangas (A. and B.: Topcon Maestro2).

Volume scan

A 3D scan (e.g., volume scan, cube scan and box scan) consists of several B-scans, where each B-scan includes multiple A-scans in a 6mm square grid. Thus, a series of horizontal and vertical raster scans create cube images. Volume scans allow a larger retinal area to be scanned without the patient changing fixation. This is ideal when screening out anomalies or creating an overall impression of an area of interest. (Insight Ophtalmology, 2022b.; Lumbroso and Rispoli, 2014.)

Macular Nerve Fibre Layer, Ganglion Cell Layer, and Inner Plexiform Layer

OCT imaging techniques can create thickness maps from specific layers necessary for evaluating retinal ganglion cell and axon loss. One of these is the three innermost retinal layer complex, ganglion cell complex (GCC), consisting of the nerve fibre layer (NFL), the ganglion cell layer (GCL), and the inner plexiform layer (IPL). The ganglion cell (GC) layer contains cell bodies, nucleus, the inner plexiform layer (IPL) contains cell dendrites and synapses with amacrine and bipolar cells, and the nerve fibre layer (NFL) contains axons of ganglion cell nuclei. (Strehaianu et al., 2017.) The GCC has decreased significantly among AD patients compared to healthy age- and sex-matched individuals (Farzinvash et al., 202, pp. 679-881).

The ganglion cell – inner plexiform (GC-IPL) layer thickness can separate to detect ganglion cell loss from the macular region. However, the GCL is easier to measure with the IPL because the boundary between the GCL and the IPL is detectable only in the nearest foveal part due to similar reflectivity. The AD pathology has seen first to affect to the IPL, followed by the GCL and, lastly, the NFL. (Strehaianu et al., 2017.)

Peripapillary RNFL

The RNFL scan is a circular scan focusing on the optic nerve head, which is affected significantly in glaucoma. It can be used to describe the shape of the optic nerve head and assess the thickness of the RNFL and the axons of GCs. The scan of the thickness profile of the RNFL can be impressed with NSTIN (nasal, superior, temporal, inferior, nasal) or TSNIT map (temporal, superior, nasal, inferior, temporal). The report of different layer thicknesses is illustrated by the glaucoma report in Figure 8, which corresponds to similar measurements used in MCI retinal layer thickness measurements in this review. (Insight Ophthalmology, 2022b.) A significant thinning in RNFL and GCL has been observed between probable AD patients and healthy controls (HC) (López-de-Eguileta et al., 2020).

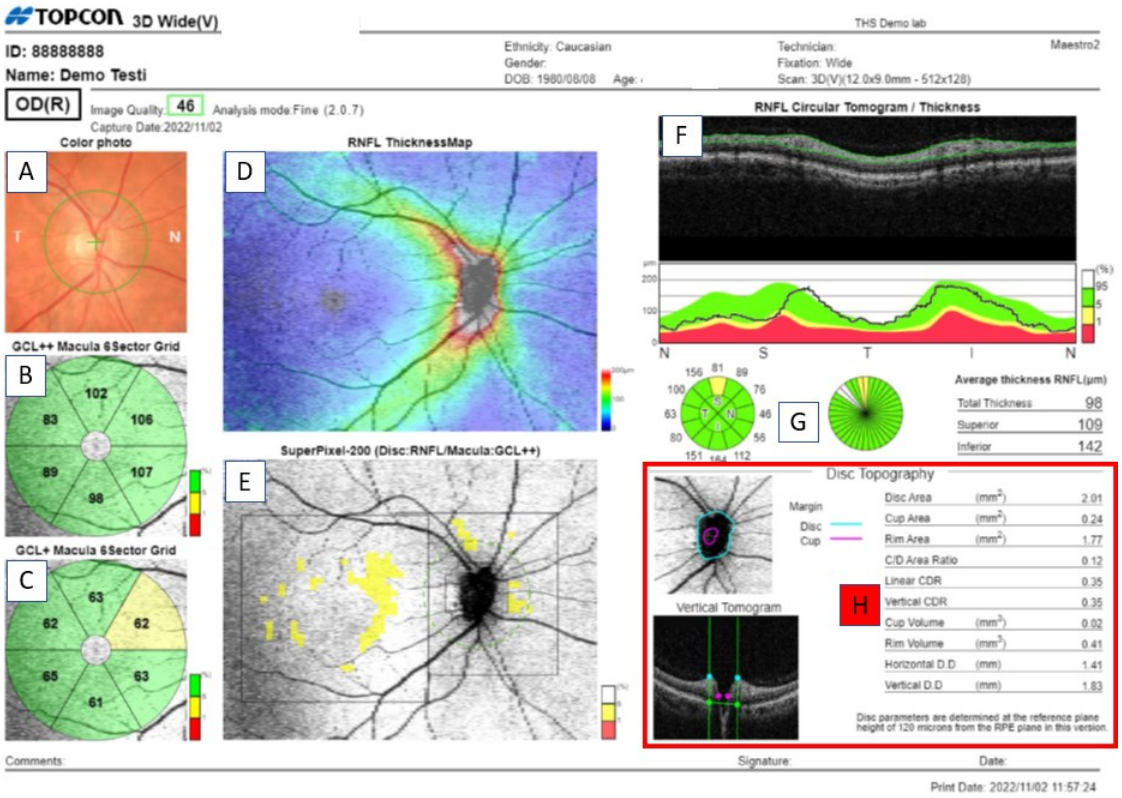


FIGURE 8. OCT (Maestro2) results of different macular layers of the right eye of a healthy 52 years-old female. **A.** Colour fundus photo of optic nerve head (ONH) region. **B.** GCL++ = Thickness of Ganglion cell complex (GCC) consisting of RNFL, GCL and IPL. **C.** GCL+ = Thickness of ganglion cell -inner plexiform layer (GC-IPL). Six sectors colour values in A and B (in microns): thickness of tissue in interest compared with normative database where the caption of the colours is at right of the maps. Green indicates normative values compared to database, yellow indicate thinner than fifth percentile and red thinner than first percentile. **D.** Thickness map (in microns and illustrated by colours) of RNFL both in macular and optic nerve region: cooler colours indicate thinner areas (caption of colours in right side). **E.** RNFL thickness in optic disc (right box) and macular GCC (left box) in a colour map: yellow or red if a pixel is low of fifth or first percentile, respectively (caption of colours in right side). **F.** Circumpapillary (peripapillary) RNFL with coloured thickness map and **G.** sectorial thickness with average thickness of total, superior and inner region. H. Related more to glaucoma report with several outcomes (see in photo). Figure Seija Säynäjäkangas.

2.5.3 Factors Affecting the OCT Measurements of Retinal Layers

Many studies have reported significant thinning among AD patients in the overall peripapillary RNFL (Jindahra et al., 2020). In addition, most studies have shown significant thinning in the superior and inferior quadrants of the RNFL in AD (Bambo et al., 2014; Liu et al., 2015), whereas some studies found thinning only in the superior quadrant (Kirbas et al., 2013; Jindahra et al., 2020). The marked loss of RNFL in the superior and inferior regions may be due to the more significant number of neurons in these regions. A possible explanation for the dominant defect of the superior RNFL

is that the axons of the upper retina anatomically project into a smaller lobe in the occipital lobe (the cyneal gyrus) in the primary visual cortex. A higher density of senile plaques and neurofibrillary tangles accumulates in this region. (Liu et al., 2015.)

Different studies have shown that the macular GCL-IPL thickness has been significantly reduced in all six sectors (superior, superior nasal, inferior nasal, inferior, inferior temporal and superior temporal) in AD patients compared with normal controls. Patients with MCI have also reported significantly reduced GC-IPL thicknesses compared with controls. Against that background has been suggested that the sensitivity of macular GCL-IPL measurements is higher than that of peri-papillary RNFL measurements for distinguishing patients with AD from controls. (Jindahra et al., 2020.) Furthermore, it is known that the macula contains more than 50% of total RGCs. Thus, thinning of the macular GC-IPL could be more sensitive to AD pathologic features than RNFL thinning. Also, the GC-IPL thickness is less influenced by individual variation when compared with RNFL thickness. (Mwanza et al., 2011.)

The cell bodies and dendrites of RGCs are mainly located in the GC-IPL in the macular region. At the same time, the axons of RGCs converge in the RNFL of the peripapillary area and exit the retina via the optic nerve. Therefore, thinner macular GC-IPL and peripapillary RNFL show fewer RGCs. There has been found that thinner RNFL and GCL are associated with lower grey matter density in the visual cortex. Thinning of GCL has also been associated with lower grey matter density of the thalamus. Against that background has been suggested that retinal thinning measured with OCT may be specifically related to changes in the visual pathway rather than with overall changes in the brain, meaning the window to understand the basics of visual symptoms in elderly patients, patients with Alzheimer's disease. (Mutlu et al., 2018.)

In other words, the retinal ganglion cells, the cells responsible for combining and relaying visual information to the brain directly via the optic nerve, share similar properties to brain neurons. AD pathological features thus co-occur in both the brain and the retina, leading to thinning of the retinal neuronal layers. Fewer RGCs in AD is consistent with the hypothesis that the pathological cascade in AD affects both the cranial nervous system and retinal RGCs, leading to loss of RGCs over time. Consistent with this hypothesis, previous electroretinography analyses suggest that RGCs are directly involved in AD, and fewer RGCs in AD patients may partially explain the ocular manifestation. (Banitt et al., 2013.)

In summary, the OCT makes it possible to measure the thickness and volume of the macula. Peripapillary RNFL thickness is considered to reflect axons, allowing quantification of axonal loss. On the other hand, macular thickness and volume are supposed to reflect retinal neurons, which in turn provides for quantifying neuronal loss. This is because the macular area contains mostly bodies of retinal neurons and glial cells, and the nerve fibres are around the macula and collected in peripapillary region.

Confounders in Retinal Layer Measurements

Confounders in OCT measurements include e.g. age-related macular degeneration (AMD) (Salehi et al., 2022), severe hypertension (Lee et al., 2019; Lim et al., 2019) and severe diabetes mellitus (Ng et al., 2016). Also, glaucoma is one of the main confounders in retinal measurements. A glaucoma is a group of many conditions sharing a final common pathway characterised by accelerated death of retinal ganglion cells and their retinal nerve fibre layer (RNFL) axons corresponding optic nerve head anatomical changes. (Banitt et al., 2013; Kim et al., 2022.) AMD shares similar environmental risk factors with AD, such as smoking, hypertension, hypercholesterolemia, atherosclerosis, obesity, and unhealthy diet, as well as similar cellular pathology associated with increased oxidative stress and inflammation. However, AMD and AD's genetic background appears to differ (Kaarniranta et al., 2011.)

AD pathology features have been found in visual pathways, including the lateral geniculate nucleus and superior colliculus (Ascaso et al., 2014). Consistent with this hypothesis, RNFL and GCL thickness changes and neuronal abnormalities are also associated with non-AD dementias (Živković et al., 2017) and other neurodegenerative diseases, including Multiple Sclerosis (Longoni et al., 2022), Neuromyelitis Optica (Fu et al., 2021), Parkinson disease (Yu et al., 2014) and brain atrophy (Ong et al., 2015). It is also important to remember that RNFL and macular thickness generally decreases with age. Thus age-matched controls are essential for the analysis of retinal layers (Trinh et al., 2021).

3 PURPOSE AND OBJECTIVES OF THE THESIS

Purpose: The aim of this umbrella review was to screen existing systematic review results to describe the association between amnestic mild cognitive impairment (also called prodromal AD) and changes in the retinal layers measured with optical coherence tomography (OCT).

Objective: As a study objective of this review was to raise awareness of AD, its pathophysiology, and especially earlier stages of AD. In addition, the objective was to reach more profound knowledge about OCT as a technical tool and identify retinal structures affected in the early stage of AD. The objective of development phase was to gather evidence of association between ageing amnestic MCI patients and changes in the retinal layer thicknesses measured with optical coherence tomography (OCT) compared with healthy ageing controls. In addition, this umbrella review was supposed to organise gathered information in clear and illustrated form, making clear conclusions by data-driven content analysis of selected studies.

3.1 Summary of Data extraction and synthesis

This thesis was written between July 2022 and December 2022. At first, the background information on MCI and prodromal AD and OCT, including retinal layers, were collected from PubMed and associated journals, websites, and guidelines from international and domestic platforms. In searches was used search words such as optical coherence tomography, Alzheimer's disease, mild cognitive impairment, and retinal layers. Then, after theoretical background gathering, the evidence-based articles based on systemic reviews of the present subject were conducted from three databases: PubMed, CHINAHL and MEDLINE using keywords "(optical coherence tomography OR OCT Tomography) AND (Alzheimer's disease OR AD OR Alzheimer) AND (mild cognitive impairment OR amnestic OR prodromal OR mild neurocognitive disorder)" formed by medical subject headings (MeSH).

The results of the systematic reviews were performed and gathered on the tables as they were stated in the studies. The synthesis of included studies was performed narratively and qualitatively. However, to clarify the results, percentage values of significant findings were calculated if an appropriate database was available for calculations in selected studies and performed on tables. In

data extraction and synthesis was followed The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), and Quality Assessment of Systematic Reviews and Meta-Analyses tool (NIH, 2009). A selection and quality evaluation of the studies were evaluated by two authors (SS, SH). The primary purpose of this coverage review was to describe and map the body of literature based on characteristics and factors according to the review objective, questions, and inclusion criteria. The findings of the selected studies were classified in a clear and compact format, considering all retinal layer measurements and their combinations told in the chosen studies. The conclusions were compiled in a precise and reliable format through background information and the results of analysed studies.

4 IMPLEMENTATION OF THE THESIS

The implementation of the thesis included forming a research question, defining the selection criteria for the studies, information search process, selection, and quality assessment of the studies, and analysing the data.

4.1 Umbrella Review as a Research Method

The umbrella review provides an overview and synthesis of existing systematic reviews related to a specific topic or question. It is a review of previously published systematic reviews or meta-analyses. Key points with umbrella review are to ensure that umbrella review is needed, clearly defining the variables of interest, estimate joint effect size, report heterogeneity and potential bias, report transparent results and acknowledge limitations. The aim of the umbrella review is to build on the comprehensive domain of existing systematic reviews by combining evidence from all relevant reviews to produce a single report that summarizes the current knowledge on the topic and presents the summary in a clearly illustrated form. Examining the evidence using umbrella evaluation allows one to assess and consider whether reviews dealing with similar evaluation questions independently observe similar results and arrive at similar conclusions. (Aromataris et al., 2020; Fusar-Poli and Radua, 2018.)

Studies were evaluated narratively and qualitatively following the statistical performance like stated in the selected studies. To clarify the results, percentage values of significant findings were calculated if an appropriate database was available for calculations in selected studies. The findings of the selected studies were classified in a clear and compact format, considering all retinal layer measurements and their combinations told in the chosen studies. The conclusions were compiled in a precise format through background information and the results of analysed studies.

In this overview was used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist, which contains 27 reporting items. The overview of systemic reviews help screen and synthesise the evidence. Among other things, umbrella reviews help determine whether a systematic literature review is warranted. (Prisma-statement.org, n.d.)

4.2 Research Questions (PICO)

The research question was formulated using the Population, Phenomenon of Interest, Context, and Outcome (PICO) framework:

P (population) = Amnestic MCI patients
I (Intervention) = Using of OCT
C (Comparison) = Healthy controls
O (Outcome) = Changes in retinal layer(s) thickness

Research question: What is the evidence of association between amnestic MCI patients (Population) and changes in the retinal layer thicknesses (Outcome) measured with optical coherence tomography (OCT) (Intervention) compared with healthy controls (Comparison)?

4.3 Criteria for the Selection of Studies

The umbrella review was conducted to assess the most substantial evidence of the connection between OCT retinal layer thickness measurements and MCI (amnestic or prodromal) among older people compared with healthy controls. The framework of PICO was supplemented with the limitation of study design complementing PICO into PICOS to identify the key elements of the research question in the review. The search terms had to be in the title or the abstract. The systematic review articles selected were written in English and published in the past ten years before October 1, 2022. They all had to relate to the connection between OCT and prodromal AD or MCI due to AD or amnestic MCI, including healthy controls. Three articles were considered in the first phase of the search, while 44 articles did not meet the selection criteria. The second data search revealed six articles meeting the requirements, while ten were excluded. Finally, seven papers were included based on inclusion and exclusion criteria after removing duplicates.

Inclusion criteria: Only systematic reviews with full text availability concerning retinal layer measurements with OCT and Alzheimer's disease with prodromal stage or mild cognitive impairment (MCI) due to AD, amnestic MCI or just MCI were included. In addition, only systematic reviews comparing results with healthy controls were included (Table 1).

Table 1. Inclusion criteria for the umbrella review defined with the PICOS framework.

P (Population)	Studies that investigate people over 50 with a diagnosis of MCI due to AD (Prodromal AD, amnestic MCI, MCI)
I (Phenomenom of Interest)	Studies measurements were performed with any type of OCT
C (Comparison)	Studies which included the comparison with healthy controls and age older than 50

O (Outcome)	Studies which included retinal layers thickness measurements
S (Study design)	Systematic reviews

Exclusion criteria: Studies unrelated to retinal layer measurements with the connection of AD or mild cognitive impairment compared with healthy controls were excluded. In addition, studies concerning only vascular or other forms of dementia than AD and optical coherence tomography angiography (OCTA) as a measuring tool were excluded. Thus also choroidal layer measurements were excluded. Studies carried out in animal models were also excluded (Table 2).

Table 2. Exclusion criteria for scoping review defined with PICOS framework

P (Population)	Studies considering other dementia forms than AD among investigated people, did not evaluate people with MCI or prodromal AD or were not human studies.
I (Phenomenom of Interest)	Studies where retinal layer measurements were performed with OCTA.
C (Comparison)	Studies without comparison with healthy controls
O (Outcome)	Studies without retinal layers thickness measurements or measurements of choroidal layer
S (Study design)	Studies other than systematic reviews

4.4 Data Search Process, Selection and Assessment

A preliminary coverage search was conducted in PubMed at the end of August 2022 with the keywords "optical coherence tomography" AND "mild cognitive impairment" without any filters. Thus, to determine how many studies could be found and evaluate requirements for keywords and filters for the primary data search process. In that phase, the method by which can be gathered comprehensive data and reach the overview of the subject was clarified. Based on that background was ended to select only the most substantial evidence, systematic reviews of a topic. That phase also helped to finalise the review question.

4.4.1 Information Sources and Data Search Methods

This thesis was written between July 2022 and December 2022. At first, the background information on MCI and prodromal AD and OCT, including retinal layers, were collected from PubMed and

associated journals, websites, and guidelines from international and domestic platforms. In searches was used search words such as optical coherence tomography, Alzheimer's disease, mild cognitive impairment, and retinal layers. Then, after theoretical background gathering, the evidence-based articles based on systemic reviews of the present subject were conducted on October 1, 2022, using three online databases, PubMed, CINAHL and MEDLINE.

Keywords were chosen using medical subject headings (MeSH) tools. The search was refined in Pubmed and in EBSCOhost, which included both CINAHL and MEDLINE databases, using the following keywords: "(optical coherence tomography OR OCT Tomography) AND (Alzheimer's disease OR AD OR Alzheimer) AND (prodromal OR mild cognitive impairment OR amnestic OR mild neurocognitive disorder)".

4.4.2 Data Selection

The English literature search was first limited to PubMed and EBSCOhost reviews, including both CINAHL and Medline databases, including abstracts published in the past ten years before October 1 in peer-reviewed journals. The results of the application of the relevant Boolean operators and article selection process is depicted in the flow chart (Figure 9). Studies that fulfilled the inclusion criteria were selected by two authors. The search was limited to identifying systematic reviews of the associations between retinal layer thickness changes measured with OCT and prodromal AD or amnestic AD or MCI due to Alzheimer's disease compared to controls using refined keywords. Thirty-three review studies were found in PubMed search and 13 EBSCOhost (CINAHL n=0, Medline n=13) databases.

To reduce the chance of missing relevant review articles, a new search was done for systematic reviews in CHINAHL using the keywords in the review search. Systemic review -choice was not possible in the MEDLINE database search. This search found one more (CHINAHL n=1) review about the subject. After 47 review studies were identified in a systematic search of three online databases, 13 duplicate studies were removed, and 34 remaining studies were screened based on title with author and publish date information. 23 Studies not related to AD and OCT or studies handling only OCTA and vascular measurements were excluded. Studies included based on titles were then assessed by abstracts, and eight studies were excluded based that they were not related

to the association between prodromal (or MCI due AD) and OCT measurements or were not systematic reviews dealing with measures. In the last phase of screening, the remaining three studies were screened for eligibility, and all met the inclusion criteria. The selection process for the three included studies is illustrated in Figure 9 using blue coloured boxes.

Because of the few numbers of studies in the first literature search, an additional search was made in PubMed to identify the systematic reviews. However, other limitations remain the same as in the first literature search: abstracts were published in the past ten years before October 1 in peer-reviewed journals and refined with previously used keywords. Sixteen studies were identified, and six remain after the title (n=8) and abstract (n=2) based exclusion. After removing duplicates (n=2), four studies were screened for eligibility by full-text review, and all met the inclusion criteria. The selection process for the additional search for six studies is illustrated in Figure 9 using green-coloured boxes. Finally, seven systematic reviews, three from the first (blue boxes) data search and four from the second (green boxes) data search, were included for this umbrella review (orange box in Figure 9).

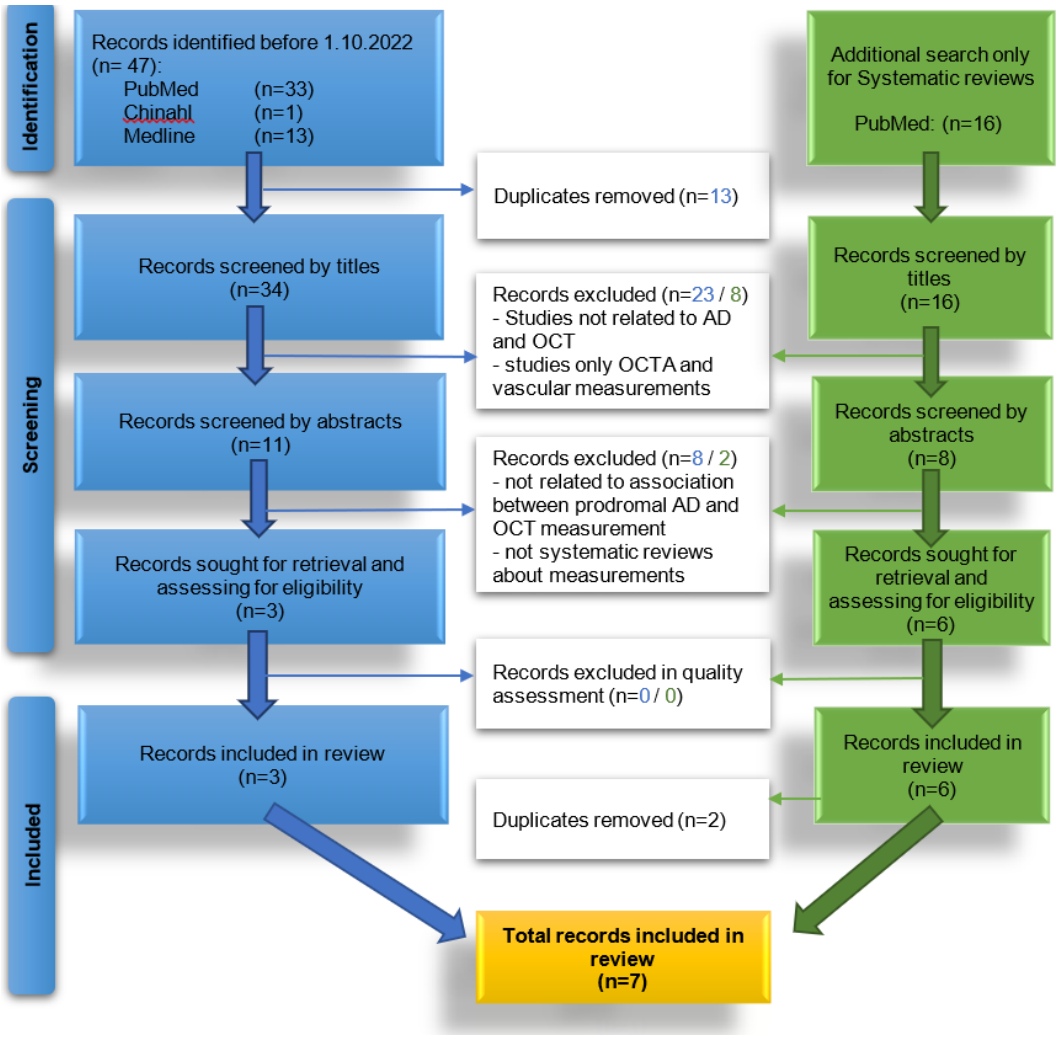


FIGURE. 9. A PRISMA flow chart of the selection of included articles

4.4.3 Quality Assessment of the Studies

Seven large population-based systematic reviews were selected by inclusion-exclusion criteria for this scoping review and are performed in Table 3. All seven studies were published in pre-review journals and written in English. Studies were fully read and thoroughly revised. In this review, the critical appraisal of the sources evidence (also called assessing the risk of bias or assessing the methodological quality) was done with the Risk of Bias in Systematic Reviews tool to assess review quality by two authors. The main purpose of this review was to describe and map the body of evidence and get an overview of the subject based on the characteristics and factors detailed by the review objective, question, and inclusion criteria (Peters et al., 2022).

Studies were identified by authors, title, year, and place of publication. The number of studies, databases used in selected systemic reviews and numbers of the patient with the status of Alzheimer's disease (AD) and mild cognitive impairment (MCI) due to AD and healthy controls (HC) were to point out the extent of selected studies giving an overall picture from the connection between retinal layer thicknesses and amnestic MCI in population-based studies. A number of patients impressed by the status in Table 3 were valid based on MCI compared to healthy controls if identified in texts or tables of the review. If there was no separation between AD vs HC and MCI vs HC, the study's total number of AD, MCI and HC were included in Table 3.

TABLE. 3. Studies selected for overview

Authors	Year	Study	Journal	Included Studies, Databases	Data search period	Patients Status (Total number in study) measuring retinal layer changes
Chan et al.	2019	Spectral-Domain OCT Measurements in Alzheimer's Disease: A Systematic Review and Meta-analysis	Ophthalmology	30 (cross-sectional studies) PubMed and Excerpta Medica Database	Published until December 31, 2017	AD (n=1257) MCI (n=305) HC (n=1460)
den Haan et al.	2017	Retinal Thickness in Alzheimer's Disease: A Systematic Review and Meta-analysis	Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring	25 (cross-sectional studies) PubMed and EMBASE	Published between 1990 and February 2016	AD (n=887) MCI (n=216) HC (n=864)
Ge et al.	2021	Retinal Biomarkers in Alzheimer's Disease and Mild Cognitive Impairment: A Systematic Review and meta-analysis	Ageing Research Reviews	126 (cross-sectional studies, studies with longitudinal design) PubMed, EMBASE, Scopus, and Web of Science	Published until January 15, 2021	96/126 Studies measured only AD (n=5144) vs HC (n=6668) 49/126 Studies measured only MCI (n=2777) vs HC (n=5076)

Mejia-Vergara, Restrepo-Jimenez and Pelak.	2020	Optical Coherence Tomography in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis	Frontiers in Neurology	15 (14 Prospective and 1 Retrospective Cross-sectional studies) PubMed, EMBASE, and Latindex	Published between 1 January 2000 and 31 July 2019	MCI (n=386) HC (n=557)
Noah A., Almghairbi D., Moppett I.	2020	Optical Coherence Tomography in Mild Cognitive Impairment: Systematic Review and Meta-analysis	Clinical neurology and neurosurgery	26 (cohort and case-control studies) Medline, EMBASE, PubMed, Scopus, CINAHL, Cochrane, PsycINFO, Web of Science and TRIP	Published between 1995 and March 2019 for MCI	MCI (n=841) HC (n=1405)
Song et al.	2021	Optical Coherence Tomography in Patients with Alzheimer's Disease: What Can It Tell Us?	Eye and Brain	71 (cross-sectional studies, case-control studies, retrospective cohort and prospective studies) PubMed	Data search time is not known. Studies included between 2001-2020	AD (n=2350) MCI (n=793) HC (n=2902)
Thomson et al.	2015	A Systematic Review and Meta-analysis of Retinal Nerve Fibre Layer Change in Dementia, using Optical Coherence Tomography	Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring	17 (original studies, not reviews and case studies) Medline, EMBASE, Web of Knowledge, Scopus, and Google Scholar	Published until September 2014	MCI (n=214 eyes) HC (n=421 eyes)

Six articles were systematic reviews (Chan et al.,2019; den Haan et al., 2017; Ge et al., 2021; Mejia-Vergara et al., 2020; Noah, Almghairbi and Moppett, 2020; Thomson et al., 2015) with some meta-analysis of the results when examining the relationship of OCT measurements and retinal layer thicknesses in MCI patients and controls. Song et al. (2021) was systematic review without

meta-analysis, where statistical calculations of included studies were in descriptive form to determine baseline characteristics of the studies included. In addition, all systematic reviews included only relevant, original, and peer reviewed studies and narrative synthesis to display the results.

The selected studies were published between 2015 and 2021 giving a broad-spectrum data of retinal layer measurements in era of AD and amnestic MCI compared to healthy controls (HC). Data search period varied in selected studies from past (no limited date) to 15th of January 2021 and included from 214 to 2777 mild cognitive impairment (MCI) patients and at least 421 healthy controls (HC). It was notable that selected papers included a lot of same studies (cross-sectional studies, case-control studies, retrospective cohort or prospective) for their systematic review.

Thomson et al. (2015) and den Haan et al. (2017) used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, and Chan et al. and Noah et al. QUADAS-2 tool (Whiting, 2011) to assess the quality and risk of bias of their included articles. Mejia et al. used the Robvis tool, and Ge et al. used the Joanna Briggs Institute (JBI) Critical Appraisal tool for quality and risk of bias assessment. Song et al. (2021), which had no meta-analysis, did not mention any quality assessment tool. All others, except Thomson et al. (2015) den Haan et al. (2017) and Song et al. (2021), used Advised Protocol for OCT Study Terminology and Elements (APOSTEL) recommendations (Cruz-Herranz et al., 2016) for reporting OCT results.

Background information from studies

The included articles are performed from now on in chronological order (1. -7.) on this chapter and in results chapter.

1. Thomson et al. (2015) focused on their study to peripapillary RNFL measurements including seventeen studies with AD, MCI and HC (healthy controls) measured with either TD- or SD-OCT. They identified five studies with the result of mean or overall total thickness among amnestic MCI (n =135) patients vs HC (n=299). An average age range was between 69.3-79.6 years for MCI patients and 64-75.5 years for HC. In four of five aMCI vs HC studies were used TD-OCT. Inclusion criteria for AD and MCI patients was used NINCDS-ADRDA -criteria. Other confounding eye pathologies (glaucoma and diabetic retinopathy) were excluded in their selected articles.

2. den Haan et al. (2017) concentrated to evaluate peripapillary RNFL (pRNFL) and macular thickness among AD, MCI and HC through twenty-five papers. Eight of their selected papers included measurements among aMCI patients (n= 217) and HC (n= 332) measured with either TD- or SD-OCT. The average age of participants in their articles ranged from 65.8-79.3 years for MCI and 64 -77 years for HC. They demonstrated the disagreement of pRNFL thickness between TD-OCT and SD-OCT. Four studies had used TD-OCT and four SD-OCT. Diagnostic criteria for AD was approved NINCDS-ADRDA and/or DSM-IV and for aMCI patients conventional Petersen (or Winblad) criteria. They also assessed the role of glaucoma as a confounder influencing retinal thinning.

3. Chan et al. (2019) identified thirty eligible studies, involving MCI patients (n=305), controls (n=1460), also AD patients (n=1257), all of which were cross-sectional studies. They did not specify the average age in articles, but mentioned that the mean ages of AD patients, MCI patients, and control groups did not differ significantly in any studies. Study included studies between MCI and HC in macular ganglion-cell inner plexiform layer (GC-IPL) thickness, total macular thickness (TMT), peripapillary RNFL (pRNFL) thickness and total macular volume. After closer look, nine articles were identified with 292 aMCI patients and 440 HCs. Their selected articles consisted only SD-OCT measurements. For diagnostic criteria in AD was allowed DSM-5 and/or NINCDS-ADRDA and in MCI Petersen's criteria.

4. Noah A., Almghairbi D., Moppett I. (2020, Jun) Twenty-six studies (841 MCI vs 1405 HC) were identified on retinal layer thickness in people with MCI compared to controls. Age range was on average between 68.2-78.7 years in studies. There was significant heterogeneity in the included studies for all retinal layers investigated including retinal nerve fibre layer (RNFL), ganglion cell inner plexiform layer (GC-IPL), total macular thickness (TMT) and total macular volume (TMV). Meta-analysis of mean pRNFL changes was performed on 17 studies with 622 MCI case compared to 1154 healthy controls. All included articles did not specify the type of MCI. Thus, they performed subgroup analysis of studies which used similar criteria for amnestic MCI. Also, OCT type subgroup analysis was performed. Five diagnostic criteria appeared in their included studies: Petersen, Winblad, Albert, NIA-ADC UDC battery and MMSE.

5. In Mejia-Vergara, Restrepo-Jimenez and Pelak (2020, Oct) identified 15 articles (386 MCI/ 557 HC) of which 6 did not specified amnestic MCI. In nine studies (240 MCI/ 384 HC) was performed the type of aMCI. Participants age for MCI varied between 68.2-79 years and for HC between 65-75.5 year in studies. The most studies used SD-OCT (11 of 15 studies), and the rest

used TD-OCT. Subgroup analysis was done to articles with SD-OCT. Outcomes of retinal tissues included pRNFL, GC-IPL, total macular volume and total macular thickness. Four diagnostic criteria appeared in their included studies: Petersen, NINCDS-ADRDA, NIA-AA and DSM-IV.

6. Song et al. (2021, Jan) included 71 studies of which eighteen evaluate measurements among MCI patients (n=596) and HCs (1149) using any domain OCT. The average baseline age for patients for MCI was 71.5 years and HC 70.6. The outcomes of their study included pRNFL, GC-IPL, total macular volume (TMV) and total macular thickness (TMT). Diagnostic criteria used in their selected studies varied a lot: Cognitive tests (MMSE or MoCA), neuropsychologiacal tests (DSM-IV or NINCDS-ADRDA), neuroimaging tests (MRI, CT or PET) and immunohistopathological staining (amyloid and tau).

7. The study of **Ge et al.** (2021, May) was the largest of all included studies for this scoping review. It included 126 articles of which 49 concerned the measurements of MCI patients (n=2777) and cognitive normal controls (n=5076). The included studies were performed widely across continents, in Europe (44.4 %), in Asia (25.4 %), in North America (23.8 %), in Oceania (4.9%), and in South America (1.6%). The average age of participants in their articles ranged from 59.1–78.9 years. In the study, retinal thickness measurements with OCT were categorised in subgroups: Preclinical vs cognitive normal (CN), MCI vs CN, AD vs MCI and AD vs CN. Under estimation of this review only subgroup MCI vs CN was considered based on relation to this study objective. They did subgroup analyses on pRNFL, GC-IPL, total macular thickness (TMT), and total macular volume (TMV). Diagnostic criteria used in their selected studies were clinical, such as NINCDS-ADRDA and Petersen's criteria, but not biological biomarkers (like brain imaging and CSF biomarkers).

After critical evaluation of the studies, all seven studies were included in the review to meet reliability and credibility criteria. All studies had flaws and weaknesses. In the six selected studies that included meta-analyses, the weaknesses could be considered non-critical. The study of Song et al (2021) differed from other studies and had the most weaknesses, but because of comprehensive list of included studies, it was included to this overview. All specifications regarding quality assessment aspects are summarized in Table 4.

Table 4. Quality Assessment of Included Systematic Reviews.

Study no	Based on a focused question /Question is adequately formulated and described using PICO	Eligibility criteria for included and excluded studies predefined and specified	Literature search strategy with comprehensive and systematic approach (at least two databases or additional search)	Dual review for determining which studies to include and exclude	Quality appraisal for internal validity	Included studies were listed along with important characteristics and results of each study	Publication bias assessed	Heterogeneity assessed if meta-analysis done
1	Y/N	Y	Y	NS	Y	Y	Y	Y
2	Y/N	Y	Y	NS	Y	Y	Y	Y
3	Y/N	Y	Y	Y	Y	NS	Y	Y
4	Y/N	Y	Y	Y	Y	Y	Y	Y
5	Y/N	Y	Y	Y	Y	Y	Y	Y
6	Y/N	x	Y	NS	N	Y	N	N
7	Y/N	Y	Y	Y	Y	NS	Y	Y

Item adequately addressed: Y = Yes; N = No; x = cannot determine/unclear; NS = not stated/not open access; G= Good; F = Fair; P = Poor.

5 RESULTS

Study results contained variable aspects regarding retinal layer measurements. Numbers and outcomes of included articles have collected on tables: Macular ganglion cell inner plexiform layer abbreviated **GC-IPL** (Table 5.), macular ganglion cell complex thickness abbreviated **GCC** (Table 6.), total macular volume abbreviated **TMV** (Table 7.), total macular thickness abbreviated **TMT** (Table 8.), macular retinal nerve fibre layer thickness abbreviated **mRNFL** (Table 9.) and peripapillary RNFL thickness abbreviated **pRNFL** on (Table 10.). The articles are in chronological order (1. -7.) in result -tables thus illustrating the interest of tissue measurement over selected studies and time.

From each article was searched retinal measurements of amnestic MCI (**aMCI**) patients compared to controls. Also not specified MCI types (abbreviated MCI) were reviewed and considered. If the amount of aMCI or MCI patients and control group was not clearly in the text, the author of this umbrella review extracted the data from the relevant studies, if data was available. The summary of the results is illustrated on Table 11 and instructions for interpretation of the table outcomes are given in legend or caption.

The amount of percentage number of significant findings among amnestic MCI (and in the absence of information, MCI) patients was calculated, if data was clearly available and could be accessed. By seeking of significant and non-significant findings the overall picture about the findings was easier to illustrate, especially because the meta-analysis was not available for all measurements. If selected systematic review included meta-analysis of any tissue findings, the results were gathered into the tables based on the outcomes of the studies. From meta-analysis was taken only standardized mean difference (SMD) results to the tables, but both SMD and weighted mean difference (WMD) was mentioned in the text (Andrade, 2020). Minus value favours thinning among MCI patients and plus value among controls. P-value tells statistical significance of the meta-analysis (Tanha, Mohammadi and Janani, 2017) and I^2/% the heterogeneity among included studies (Sedgwick, 2015; Siebert, 2018). Statistical concepts are explained in the abbreviations chapter at the end of this review.

5.1 Ganglion Cell - Inner Plexiform Layer (GC-IPL)

The study findings of Ganglion cell inner plexiform layer (GC-IPL) have illustrated in Table 5. The earliest studies **1. Thomson et al.** (2015) and **2. den Haan et al.** (2017) did not identify any results of macular GC-IPL measurements and MCI. **3. Chan et al.** (2019) showed in their results, in four (MCI 147, HC 239) of thirty studies, that the GC-IPL generally was thinner in patients with MCI. GC-IPL mean SMD was -0.57 (-1.38 to 0.24) and p-value 0.17 with lot of heterogeneity (I^2 91%). When they did meta-analysis by weighted mean difference (WMD -10.19, from -20.42 to 0.05) using same scale, they found thinning becoming significant (p=0.05). However, in a subgroup (performed subgroup analyses according to the types of OCT model and the method of eye selection i.e., single-eye or paired-eyes dataset) analysis including studies with a single-eye dataset, the difference in GC-IPL thickness in patients with MCI became statistically significant (SMD, -0.95; 95% CI, -1.79 to -0.10; P= 0.03). So, the difference of macular GC-IPL thickness in MCI patients was statistically significant ($P < 0.05$) only among studies with a single-eye dataset, but not among studies with a paired-eyes dataset. Four studies Chan et al. reported, were carefully reviewed to identify MCI patient numbers and significance of outcomes. Two (MCI 109, HC 188) of four studies reported about significantly thinner GC-IPL among MCI participants and rest two (MCI 38, HC 54) reported non-significant differences among MCI compared to controls. In summary, 74.1% of the macular GCL-IPL demonstrated significant thinning among MCI patients compared with controls.

4. Noah A., Almghairbi D., Moppett I. (2020) reported that eight of their twenty-six included studies evaluate GC-IPL centered on fovea in MCI (n= 169) compared to controls (n=287). After accurate search and calculations, was found three studies of 85 MCI (165 HC) patients with significant difference and five studies of 84 MCI (122 HC) patients without significant difference. In summary 50.3% of MCI patients had statistically reduced thickness in their GC-IPL. Only four of eight studies had numerical values. As a result of the limited number of studies with data, they could not perform meta-analysis on GC-IPL thickness in MCI compared to controls. They reported that six studies looked at regional GC-IPL thickness and three (MCI 46, HC 71) of them did not find significant reduction in thickness of regional (quadrants or sectors) GC-IPL, while other three (MCI 85, HC 165) reported the reductions as follows; superior quadrant (MCI 24, HC 21), superior and inferonasal sectors (MCI 20, HC 21), and superior nasal, inferior and inferotemporal sectors (MCI 41, HC 123).

5. Mejia-Vergara, Restrepo-Jimenez and Pelak (2020) reported five studies (MCI 130, HC 245) of fifteen included articles, which measured the GCL-IPL thickness using SD-OCT. Meta-analysis showed medium effect size (SMD −0.47; −2.36 to 1.40) without statistically significant result (P = 0.619) and with large heterogeneity (I^2 97.9%). Two of the five studies reported significant thinning of the GCL-IPL in MCI patients compared with controls (MCI 65, HC 144) and the other three studies did not show significant difference between the two groups (MCI 65: HC 101). In summary, 50.0% of the macular GCL-IPL complexes measured demonstrated significant thinning in MCI compared with controls.

6. Song et al. (2021) had not any meta-analysis, but all studies were performed in table. Eight of seventy-one studies included measurements of GC-IPL and MCI patients (211) compared to controls (452). In five studies, thinning of GC-IPL was significant in 140 MCI patients and not significant among 71 MCI patients. In summary, 66.4% of all MCI patients with GC-IPL layer measurements had reported significant changes.

7. Ge et al. (2021) reported eight of 126 studies with GC-IPL measurements. The results were performed clearly in the with forest plot (eyeball graphic demonstration), with large sample size (MCI 433: HC 944), but small effect size (SMD = -0.187) showing statistically significant result (P = 0.038) and not significant heterogeneity (I^2 41%). The GC-IPL were found to be thinner in meta-analysis among MCI patients compared to HC, but the percentage value of significant thinning in MCI patients was not possible to calculate because the lack of information about included studies.

TABLE 5. Macular Ganglion cell – inner plexiform layer (GC-IPL) study findings.

	Study number	Sample size MCI/HC, %	SMD (95% CI)	P-value	I^2/%
3.	4	147/239, 74.1% (aMCI)	-0.57 (-1.38 to 0.24)/ se -0.95 (-1.79 to -0.10)	0.17 0.03	91
4.	8	169/287, 50.3% (aMCI)	-	-	-
5.	5	130/245, 50.0% (MCI)	-0.47 (−2.36, 1.40)	0.619	97.9
6.	8	211/452, 66.4% (aMCI)	-	-	-
7.	8	433/944, -	-0.19	0.038	41

Studies 1 and 2 had no results. Abbreviations: % = the amount of MCI patients with significant changes; MCI = mild cognitive impairment; HC = healthy controls; aMCI = amnestic mild cognitive impairment; se=single eye.

5.2 Ganglion Cell Complex (GCC)

The study findings of ganglion cell complex (GCC) have illustrated in Table 6. **1. Thomson et al.** (2015), **2. den Haan et al**. (2017), **3. Chan et al.** (2019) and **5. Mejia-Vergara, Restrepo-Jimenez and Pelak** (2020) did not identify any study or articles examining the ganglion cell complex (GCC) thickness in patients with MCI.

4. Noah A., Almghairbi D., Moppett I. (2020) argued in their article significant reduction in the macular ganglion cell complex thickness in the MCI group, but only one of their twenty-six included studies identified ganglion cell complex measurements. The access to this study was limited and the percentage value of MCI patients with significance changes was not able to calculate and the basic of the claim about significance was not able to confirm.

6. Song et al. (2021) showed in their data table four studies involving with ganglion cell complex (GCC) measurements, but only one was conducting with MCI patients. After closer investigation of this one article, it focused only to analyse retinal vessels and no data of MCI patients with GCC - measurements was found.

7. Ge et al. (2021) had five of 126 articles handling measurements of macular ganglion cell complex (mGCC) thickness. A meta-analysis showed significant decrease of GCC thickness in MCI patients (n=187) compared to controls (n=200) with medium effect size (SMD -0.597), which showed high statistical significance ($P < 0.001$). In their report was not seen any heterogeneity (0%). Their study did not include the details of selected 5 studies, thus the percentage value of MCI patients with significance changes was not able to calculate.

TABLE 6. Macular Ganglion Cell Complex Thickness (mGCC, consisting of RNFL and GC-IPL) study findings.

	Study number	sample size MCI/HC,	SMD (95% CI)	P-value	I^2/%
7.	5	187/200, -	-0.597	< 0.001	0

Studies 1 - 6 had no results. Abbreviations: MCI = mild cognitive impairment; HC = healthy controls.

5.3 Total Macular Volume (TMV)

The study findings of total macular volume (TMV) have illustrated in Table 7. **1. Thomson et al**. (2015) and **2. den Haan et al** (2017) did not identify any study or articles examining the total macular volume (TMV). **3. Chan et al** (2019) identified seven studies of thirty about macular volume with small effect size between MCI patients and controls: SMD -0.21 (-0.67 to 0.25) p=0.37, WMD -0.10 (-0.31 to 0.11) p=0.36 with heterogeneity (I^2) of 61%. After closer reading of seven studies (aMCI 77, HC 85), eventually five studies included macular volume measurements with MCI (n=120) and controls (n=168). Two studies (MCI 54, HC 87) had found significant reduction in macular volume and three studies (MCI 68, HC 81) with no significant findings. Based on these details 44.3% in MCI patients had seen significant reduction in macular volume.

4. Noah A., Almghairbi D., Moppett I. (2020) identified four studies (MCI 85, HC 113) comparing mean macular volume from both eyes. There was no significant difference in macular volume between participants with MCI (n=59) and controls (n=92) in three studies. One selected study showed the macular volume was statistically reduced in the MCI (n=26) compared to control group (n=21). Unfortunately, they were not able to do meta-analysis of macular volume because the lack of studies. In summary of four study findings, 30.6% of MCI patients had statistically significantly reduce in macular volume.

5. Mejia-Vergara, Restrepo-Jimenez and Pelak (2020) identified six studies (MCI 149, HC 189) of fifteen the results of macular volume. Half (MCI 83, HC 67) of the six studies, had a significant reduced in macular volume among aMCI compared with controls, and other half did not find differences (MCI 66: Controls 122). Thus, 55.7% of all aMCI patients that had their macular volume measured had a statistically significant reduction in volume compared with controls. To meta-analysis was approved only three studies (MCI 69, HC 91) with high pooled effect size (SMD -1.12; −3.51 to 1.27) and statistical significance (p = 0.36) but with high heterogeneity (I2 = 97.3%).

6. Song et al. (2021) identified 10 studies of total 71 studies measuring macular volume based on their details of selected articles. After closer analysing five of ten studies compared macular volume in MCI (n=124) and controls (n=192). In their study was not any meta-analysis of the results. After individual screening of these five articles 42% among MCI patients (n=52) had significant finding in macular volume decrease.

7. Ge et al. (2021) identified five of 126 articles comparing macular volume changes in MCI patients (285) and controls (n=515) giving small effect size (SMD -0.266) and statistically significant result (p-value 0.079) showing no significant reduction. Heterogeneity (I2) was 52%. Their study did not include the details of selected 5 studies, thus the percentage value of MCI patients with significance changes was not able to calculate.

TABLE 7. Total Macular Volume (TMV) study findings.

	Study number	sample size aMCI/HC, %	SMD (95% CI)	P-value	I^2/%
3.	5	122/168, 44.3% (aMCI)	-0.21 (-0.67 to 0.25);	0.37	61
4.	4	85/116, 30.6% (aMCI)	-	-	-
5.	3	69/91, 37.7% (aMCI)	−1.12 (−3.51 to 1.27)	0.36	97.3
	6	149/189, 55.7% (MCI)	-	-	-
6.	5	124/192, 42% (aMCI)	-	-	-
7.	7	285/515, -	-0.27	0.079	52

Studies 1 and 2 had no results. Abbreviations: % = the amount of MCI patients with significant changes; MCI = mild cognitive impairment; HC = healthy controls; aMCI = amnestic mild cognitive impairment.

5.4 Total Macular Thickness (TMT)

The study findings of total macular thickness (TMT) have illustrated in Table 8. There were not any results from **1. Thomson et al.** (2015) of TMT and **2. den Haan et al.** (2017) identified only 1 study with MCI vs HC and result was also opposite to other studies telling increasing of total macular thickness (TMT) instead of decreasing. **3. Chan et al**. (2019) did not compare the macular thickness between MCI patients and controls because only two studies were eligible. They included 68 MCI and 74 HC with no significance in thinning

4. Noah A., Almghairbi D., Moppett I. (2020) found five studies of macular thickness in MCI patients (MCI 134, HC 202) from their twenty-six included studies. Three found no statistically significant difference in macular thickness between MCI (n=80) participants and controls (n=106). In one study had reported a statistically significant reduction in macular thickness (MCI 33, HC 25) and an another showed a statistically significant increase in macular inner ring thickness in participants

with MCI (n=21) compared to controls (n= 41). based on those findings, 24.6% of aMCI patients had significant thinning. A meta-analysis was performed for four studies of mean foveal thickness in MCI (101 participants) vs controls (147). Analysis showed a lot of heterogeneity (I2 79 %). The SMD for the four studies was 0.05 (-0.54 to 0.63) being small effect size and statistically significant result ($p < 0.01$), meaning that fovea was thinner among controls.

5. Mejia-Vergara, Restrepo-Jimenez and Pelak (2020) had six of total 15 studies in their report including macular thickness measurements. The one of the articles mentioned “macular thickness” and “macular cube” meaning same thing, but any data about macular thickness did not find. One of remaining five studies got opposite results than in general: macular thickness in aMCI patients (n=21) was significantly greater than in control (n=41) group. Possible reason they performed to increase of macular thickness was that in aMCI patients, the swollen RGCs and Müller cells can be greatly enlarged, thickening the macular area in this early stage of degeneration. Swollen neurons, also known as ballooning neurons, are one of the pathological hallmarks of many neurodegenerative diseases, including AD (Ascaso et al., 2014). Into meta-analysis Mejia-Vergara, Restrepo-Jimenez and Pelak (2020) included only three studies (MCI 78, HC 85). They got, as a result of these three studies, large effect size (SMD =−1.39; −2.32, to −0.47) with lower macular thicknesses in MCI patients, results was also statistically significant (p=0.001), but with lot of heterogeneity (I^2 85.3%). In summary, when including also two studies (excluded from meta-analysis) with statistically significant difference (values not reported), 65% (n=80) of total MCI (123) patients had significant decreasing of macular thickness.

6. Song et al. (2021) identified five studies with 113 MCI patients and 170 controls. Study did not perform any meta-analysis. Two studies of five showed significant thinning of macular thickness in MCI (n=48) vs controls (n=82) and non-significant change in remaining three studies (MCI 65, controls 88). Based on these numbers, 42.5% of MCI patients had significant thinning of macular thickness. **7. Ge et al.** (2021) performed through seven of 126 articles that the total macula was thinner in MCI (n=417) compared to controls (n=662), however being poorly applicable mainly due to clinical reasons of the selected studies. Their results performed greater reduction in total macular thickness (TMT) after meta-analysis (SMD = -0.302, $p < 0.001$) with some heterogeneity (I2=43%). They reported significant thinning in total macular thickness in superior inner, inferior inner, superior outer and temporal outer sectors. Their study did not include the details of selected seven studies, thus the percentage value of MCI patients with significance changes was not able to calculate.

TABLE 8. Total Macular Thickness (TMT) study findings.

	Study number	sample size MCI/HC, %	SMD (95% CI)	P-value	I^2/%
3.	-	68/74, no thinning	-	-	-
4.	4 5	101/147 134/172, 24.6% (aMCI)	0.05 (-0.54 to 0.63)	<0.01	79
5.	3 5	78/85 123/147, 65% (MCI)	-1.39 (−2.32 to -0.47) -	0.001 -	85.3 -
6.	5	113/170, 42.5% (aMCI)	-	-	-
7.	7	417/662, -	-0.302	<0.001	43

Studies 1 and 2 had no results. Abbreviations: % = the amount of MCI patients with significant changes; MCI = mild cognitive impairment; HC = healthy controls; aMCI = amnestic mild cognitive impairment.

5.5 Retinal Nerve Fibre Layer (RNFL)

Macular RNFL (Table 9)

Only **7. Ge et al.** (2021) performed studies where macular RNFL thickness was evaluated. They conducted 3 studies including 261 MCI patients and 495 healthy controls of macular RNFL measurements. Details for author for closer look of articles was not available, thus calculation of the percentage amount of MCI patients observed with RNFL thinning was not possible. They performed meta-analysis where standardized mean difference (SMD) was -0.304 showing not so practically significant effect size of macular RNFL thinning, with statistically high significance ($p < 0.001$) and homogeneity (I^2, 0%).

TABLE 9. Macular Retinal Nerve Fiber Layer Thickness (mRNFL) study findings.

	Study number	sample size MCI/HC	SMD (95% CI)	P-value	I^2/%
7.	3	261/495	-0.304	< 0.001	0

Studies 1 -6 had no results. Abbreviations: MCI = mild cognitive impairment; HC = healthy controls.

Peripapillary RNFL (Table 10)

1. Thomson et al. (2015) identified five studies including 135 MCI subjects (214 eyes) and 299 controls (421 eyes), demonstrating a significant reduction in the overall mean peripapillary RNFL thickness in patients with MCI (WMD 28.23; -14.00 to -2.45; p= 0.005). There were four studies including 88 MCI subjects (168 eyes) and 132 controls (391 eyes) for the mean RNFL thickness by quadrant, showing significant reduction in all four quadrants; superior, inferior, temporal and nasal. There was significant heterogeneity (I^2 96%) between the studies. In **2. den Haan et al** (2017) eight selected studies peripapillary RNFL thickness of the MCI group (n= 217) was between the pRNFL thickness of AD patients and HC (n=332), with practically applicable significant thinning (SMD -0.71: -1.24 to -0.19) showing also statistically significant result (P=0.008) compared to controls. Six of all of eight studies showed significant thinning in MCI patients (n=155) meaning 71.4% of total number (n=217). They found peripapillary RNFL thickness to be lower in the superior and inferior quadrants than in nasal and temporal quadrants. The reason for vertical decrease may be related, according to the authors, to the fact that the superior and inferior quadrants contain more neurons, and therefore, neurodegeneration is expected to be most prominent.

3. Chan et al. (2019) informed in their article about six studies that examined the difference of the peripapillary RNFL (pRNFL) thickness between MCI patients and controls. After closer look of studies, seven studies (MCI 207, HC 358) identified peripapillary measurements. Peripapillary RNFL mean thickness showed limited applications for practical with small effect size (SMD -0.25: -0.68 to 0.18) being statistically significant (P= 0.25) finding, also in weighted evaluation (WMD -2.39: -6.34 to 1.57; P=0.24). This conclusion appeared in all quadrants, where only the superior peripapillary region showed some thinning (SMD: -0.10; -0.34 to 0.15; P=0.44 / WMD: -1.98; -6.43 to 2.47; P=0.38) of RNFL among MCI patients. Thinning in other regions, nasal (SMD 0.32: -0.24 to 0.88; P=0.26 / WMD 2.64: 1.80-3.49; P= <0.00001), inferior (SMD 0.12: -0.17 to 0.41; P=0.42 / WMD 2.13: -3.04 to 7.30; P=0.42) and temporal (SMD 0.24: -0.66 to 1.14; P=0.60 / WMD -0.51: -5.52 to 4.50; P=0.84), could not authenticate statistically. Heterogeneity was significant in mean (80%), nasal (85%) and temporal (94%) thickness results, but in inferior (37%) and superior part (15%) showed more same kind of results between studies. The conclusion was that results revealed a trend of pRNFL thinning in MCI patients, but the magnitude was not statistically significant. In summary of seven studies, 43.5% (90 of 207 MCI) of aMCI patients had seen significant thinning pRNFL.

4. Noah A., Almghairbi D., Moppett I. (2020) reported twenty studies of twenty-six investigating mean pRNFL thickness in MCI (n=697) vs. controls (n=1226). There was statistically significant reduction in the mean pRNFL thickness in MCI compared to controls in nine studies (MCI 257, HC 294) and without significant reduction in eleven studies (MCI 440, HC 932). In summary of that result, 36.9% of MCI patients had statistically significant difference compared to controls. In meta-analysis, which was performed on seventeen studies after exclusion of three unsuitable studies and regardless of OCT type, mean pRNFL was significantly thinner in MCI (n=622) compared to controls (n=1154) although significant heterogeneity was observed (Higgins I^2, 82 %). The effect size (SMD) in meta-analysis was below 0.5 being -0.42 (- 0.68 to -0.16) with high significance (P=0.002). This difference was not significant when analysing studies using only SD-OCTs.

5. In Mejia-Vergara, Restrepo-Jimenez and Pelak (2020) review was identified 12 (MCI 307, HC 475) articles. Seven demonstrated significant pRNFL thinning in MCI (n=181) compared with controls (n=255) for either average pRNFL (4 of 12) or localized thinning in the superior (1 of 12) or inferior quadrants (2 of 12) or both. All five studies that used TD-OCT, and two studies using SD-OCT to measure pRNFL, showed a significant difference. Of the remaining five (MCI 126, HC 220) studies using SD-OCT, did not show significant difference in pRNFL. In summary, 59% (MCI 181) of the MCI subjects (n=307) with measurement of pRNFL had significant thinning compared with controls. The problem with their included studies was after closer looking, that not all of them had specified the type of aMCI. When considering only number of aMCI (240) compared to controls (384), 63.3% of aMCI had significant reduction in mean value of pRNFL. Seven studies (MCI 307, HC 475) was included to meta-analysis, which showed medium effect size (SMD -0.4; -1.40 to 0.43) of pRNFL thickness with statistically significant result (p-value 0.298) and high heterogeneity (I2 = 94.8%).

6. Song et al. (2021) had in seventeen studies of seventy-one measurements of peripapillary RNFL with 578 MCI patients without specified type and 1014 controls. In twelve studies had reported significant thinning with 334 MCI patients and remaining 5 studies did not report significant changes including 273 MCI patients. In summary, 55% MCI patients had significant decrease of pRNFL thickness. When concerning only articles with clear amnestic MCI specification, 8 (MCI 333, HC 593) articles was found where half of them demonstrated thinning among 28.8% (MCI 96) participants. **7. Ge et al** (2021) included twenty-one studies (MCI 1194, HC 2260) of total 126 articles performing thinner peripapillary RNFL in MCI compared to controls with SMD = -0.324, $p < 0.001$ and heterogeneity 74%. Especially superior and temporal quadrants of pRNFL showed significant

thinning in MCI compared to controls. Percentage value of MCI patients with significant findings was not able to calculate because the lack of twenty-one article details.

TABLE 10. Peripapillary retinal nerve fibre layer (pRNFL) thickness study findings.

	Study number	Sample size aMCI/HC, %	SMD (95% CI)	P-value	I^2/%
1.	5	135/299, 65.2% (aMCI)	thinning in all quadrants	-	-
2.	8	217/332, 71.4% (aMCI)	m -0.71 (-1.24 to -0.19) superior and inferior	0.008	-
3.	7	207/358, 43.5% (aMCI)	m -0.25 (-0.68 to 0.18) I 0.12 (-0.17 to 0.41) S -0.10 (-0.34 to 0.15) N 0.32 (-0.24 to 0.88) T 0.24 (-0.66 to 1.14)	0.25 0.42 0.44 0.26 0.60	80 37 15 85 94
4.	12 17 13 8 20 17	479/986 (MCI + SD-OCT) 622/1154 (MCI + any OCT) 540/1036 (aMCI + any OCT) 397/868 (aMCI + SD-OCT) 697/1226, 36.9% (MCI) 629/1138, 32.4% (aMCI)	m -0.22 (-0.46 to 0.03) m -0.42 (- 0.68 to -0.16) m -0.54 (-0.82 to-0.26) m -0.32 (-0.58 to -0.06)	<0.01 0.002 0.0001 <0.01	72 82 81 70
5.	7 12 9	190/304, 33.7% (MCI) 307/475, 59% (MCI) 240/384, 63.3% (aMCI)	m −0.4 (−1.40 to 0.43) superior and inferior	0.298	94.8
6.	17 8	578/1014, 51% (MCI) 333/593, 28.8% (aMCI)	superior		
7.	21	1194/2260	m -0.324 superior and temporal	< 0.001	74

Abbreviations: % = the amount of MCI patients with significant changes; MCI = mild cognitive impairment; HC = healthy controls; aMCI = amnestic mild cognitive impairment; m = mean value; ISNT = inferior, superior, nasal, temporal.

5.6 Summary of the Results

In this section systematic reviews have mentioned only with numbers as follow: 1. Thomson et al. (2015); 2. den Haan et al. (2017); 3. Chan et al. (2019); 4. Noah A., Almghairbi D., Moppett I. (2020, Jun); 5. Mejia-Vergara, Restrepo-Jimenez and Pelak (2020, Oct); 6. Song et al. (2021, Jan); 7. Ge et al. (2021, May). Summary of the mean results of meta-analysis has been collected and highlighted with different colours depending on significance for practical application (effect size) on table 11 if data has been available. Also, the percentage values of the amnestic MCI patients, who had been observed thinning, was calculated with available data details, and illustrated on same table. MCI without mention of amnestic form was performed, only if amnestic type was not clearly informed. Statistical significance of meta-analysis has illustrated with P-value (P) and heterogeneity of the results with Higgins's index (I^2) as stated in selected studies.

Two oldest (1. and 2.) systematic reviews did not identified any GC-IPL measurements. Remaining five (3.-7.) studies screened the GC-IPL layer, and all of them found in over 50% of amnestic MCI patients with significant thinning vs controls. Three (3., 5 and 7.) had done meta-analysis, where the most extensive sample size study (7.) showed the most minor size effect meaning limited practical applications with statistical significance and low heterogeneity giving thus quite reliable result. Two other meta-analyses (3. and 5.) found medium size effect. Another got a statistical significance result among aMCI patients (3.). But in other there was not a statistical significance result when the type of MCI was not specified (5.). Both had high heterogeneity in the meta-analysis. Interesting finding was that high effect size with statistical significance was observed when only single-eye subgroup analysis was done (3.). When considering the study number, sample size and heterogeneity of the studies, the trend of GC-IPL thinning was observed in MCI patients showing a little over small size effect in 63.6% of aMCI patients on average.

Only one study (7.) identified GCC -measurements, and their meta-analysis showed a significant decrease in GCC thickness in MCI patients vs controls. Percentage value of thinning observed among aMCI patients was not able to demonstrate because of the lack of study data details. In summary, the medium effect size with high statistical significance was reported. Five (3. - 7.) studies reported macular volume measurements. Three (3., 5., and 7.) of them did a meta-analysis of macular volume with some decrease in MCI patients vs controls. Two (3. and 7.) of meta-analysis with some heterogeneity showed a small effect size with five or more included studies. At the same time, one (5.) reported a high effect size, but with quite small number of studies and with high

heterogeneity. The reduction in macular volume was on average in 38.7% of aMCI patients. When all MCI studies was considered, on average in 42.1% of all MCI patients had macular volume decreasing. Based on all macular volume results in the table and when considering the study number, sample size and heterogeneity of the studies, a macular volume decrease was observed, but with less than medium effect size meaning the limitation of practical applications.

Same five (3.- 7.) studies had identified macular thickness measurements. In the earliest study (3.) was not observed thinning favouring MCI patients. In two (4. and 6.) studies decrease was observed on average in 33.6% of aMCI patients. When all MCI patients was considering (4., 5. and 6.), 44% of MCI patients had observed thinning in total macular thickness and as a note, these studies had included nearly same amount of MCI patients and controls. Three (4., 5. and 7.) did meta-analysis. Two (4. and 7.) of them showed small effect size with significant heterogeneity (4.) and low heterogeneity (7.). In summary total macular thickness was decreased, but effect size was small with variable heterogeneity. Only one (7.) reported measurements of macular RNFL thickness, showing not so practically significant effect size being statistically high significance result with homogeneity.

All studies reported pRNFL measurements, of which all except one (1.) had done also meta-analysis. Sample sizes of all retinal layer measurements were largest in the pRNFL across the systemic reviews being the most believable for analysis. All meta-analyses included seven or more individual articles. The mean value of effect size, when effect on different quadrants was considered, showed nearly medium (from small to high) effect size with statistical significance and significant heterogeneity. Based on database of reviews, on average in 50.8% of aMCI patients was reported thinning of pRNFL and almost the same (48.5%) was among total number of MCI patients. Mainly thinning was observed in superior part and secondly both in superior and inferior region. One study (4.) had done subgroup analysis based on measurements both with aMCI and MCI with any domain OCT and using only SD-OCT. These findings showed higher effect size when measurements were done with any type of OCT when compared to SD-OCT measurements. As previously mentioned, TD-OCT has lower sensitivity than SD-OCT.

TABLE 11. Summary of the mean results of retinal layer findings in MCI or amnestic MCI based on available database of seven systematic reviews.

	GC-IPL	GCC	Macular Volume	Macular thickness	Macular RNFL	Peripapillary RNFL
1.	(-)	(-)	(-)	(-)	(-)	Lower in all parts **65.2%** (aMCI)
2.	(-)	(-)	(-)	(-)	(-)	Lower in sup & inf **71.4%** (aMCI) P=0.008
3.	Generally thinner **74.1%** (aMCI) P =0.17, I^2 91%	(-)	Generally thinner **44.3%** (aMCI) P =0.37, I^2 61%	(-)	(-)	Generally thinner **43.5%** (aMCI) P =0.25, I^2 80%
4.	**50.3%** (aMCI)	(-)	30.6% (aMCI)	**24.6%** (aMCI) P= 0.01, I^2 79%	(-)	**32.4%** (aMCI) P <0.01, I^2 70%
5.	50% (MCI) P =0.619, I^2 97.9%	(-)	**37.7%** (aMCI) P =0.36, I^2 97.3%	65% (MCI) P =0.001, I^2 85.3%	(-)	Lower in sup & Inf **63.3%** (aMCI) P =0.298, I^2 94.8%
6.	**66.4%** (aMCI)	(-)	**42%** (aMCI)	**42.5%** (aMCI)	(-)	Lower in Sup. **28.8%** (aMCI)
7.	P=0.038, I^2 41%	P <0.001, I^2 0%	P =0.079, I^2 52%	P <0.001, I^2 43%	P<0.001, I^2 0%	P <0.001, I^2 74%

Results have arranged into the table in chronological order: 1. Thomson et al. (2015); 2. den Haan et al. (2017); 3. Chan et al. (2019); 4. Noah et al. (2020, Jun); 5. Mejia et al. (2020, Oct); 6. Song et al. (2021, Jan); 7. Ge et al. (2021, May). Abbreviations: GC-IPL = ganglion cell -inner plexiform layer; GCC = ganglion cell complex; RNFL = retinal nerve fibre layer; (-) = no data available; **%-value** = **per cent value of MCI patients in studies with significant thinning** (MCI = type not specified; **aMCI**= amnestic specified participants); **Statistically significant result: P<0.5**; **I^2 = Heterogeneity of the results.**

Colours on table = Effect size: Statistical Power of study results where practical significance has performed with Standardized Mean Difference (SMD); Effect size from ≤0.2 (limited practical applications) to ≥0.8 (high statistical power of results) favour thinning among MCI patients. Green colour = thinning favour controls.

Interpretation of table colours:

Effect size	Small ≤ 0.2	0.21-0.39	Medium 0.4-0.6	0.61-0.79	High ≥0.8

6 DISCUSSION AND CONCLUSIONS

The primary purpose of the master's Thesis was to increase the author's knowledge and deepen her understanding of the topics related to the Thesis and give tools to her working life. The aim of the Umbrella review was to achieve “fast” evidence in reduced timeframes and build on the comprehensive domain of existing systematic reviews by combining evidence from relevant reviews to produce a single report that summarizes the current knowledge on the topic.

The purpose of this Thesis was to raise awareness of one of the most common neurodegenerative diseases among the ever-growing ageing population, Alzheimer's disease (AD), and its effects on vision and the eye. The main purpose was to increase knowledge of OCT as a tool for detecting AD in the early stage. Especially in the phase when memory problems are increased more than normal ageing, meaning amnestic mild cognitive impairment (aMCI). The purpose was also to get an overall picture of the MCI's effects on vision when considering older patients in the examination of vision.

A representative of the business world has been Topcon Healthcare Solutions and their country manager, who has enabled the use of the OCT device Maestro2 to get figures to illustrate the retinal tissue in research phase. In the development phase an information of the research phase and data analysis of the systematic reviews are synthesized concerning of the effects of MCI on the layers of the retina detected by OCT and evaluating the gaps of the reviews. An article of this thesis will be published on the page of Finnish Association of Vision and Eyecare, NÄE ry.

Discussion

OCT technology is nowadays at the level where a more detailed assessment of retinal layers is possible. Retinal layers reflect the brain changes being a window to the central nervous system (CNS). People worldwide are living longer, and because of this, the number, and the proportion of older people in the world's population are increasing. Older people have many common health problems and are more likely to have multiple co-morbidities as they age, including dementia, the seventh leading cause of death among all diseases among the elderly worldwide. (World Health Organization, 2022).

The retina, a unique "fingerprint" produced by the OCT technique, is the only human tissue that allows direct visualisation into systemic diseases, such as vascular diseases, and brain extension, such as thinning of the retinal cell layer due to neurological disorders. Retinal ganglion cells (RGC) have similar features to the cerebral neurons, and thus is assumed that AD pathology affects both the RGS and brain neurons. If cerebral neurons are lost, retinal ganglion cell loss is also seen over time.

The results of the seven systematic reviews selected for this review seemed partly inconsistent. The results were characterized by heterogeneity and low practical significance. That is perhaps due to differences in study design (cross-sectional studies, case-control studies, retrospective cohort, and prospective studies), OCT device used (TD- and SD-OCT), inclusion and exclusion criteria, and differences in the implementation of diagnostic criteria for MCI. Still, despite the differences between studies, the primary outcome is that there is evidence of the association between retinal thinning already in the MCI phase and especially in amnestic MCI, showing thinning of certain layers falling between patients with AD and healthy controls.

Based on the study findings of systematic reviews and when considering the study number, sample size and heterogeneity of the studies, the most evident changes were observed in ganglion cell – inner plexiform layer (GC-IPL) and peripapillary RNFL. Studies showed that macular GC-IPL and peripapillary RNFL are generally thinner in MCI patients compared to controls. Retinal ganglion cells (RGC), including cell bodies and dendrites, are located mainly in the GC-IPL at the macular area. Still, the axons of RGCs are at the highest level in the peripapillary RNFL (pRNFL) region.

Against previous background, thinner GC-IPL and pRNFL indicate decreased RGCs in MCI. Mention of the opposite result, the increasing macular GC-IPL thickness (Chan et al., 2019) was thought to be caused by neuronal swelling and activation of perifoveal Müller glial cells with consequent hypertrophy (https://fyra.io (n.d.). This condition may occur in the early stages of retinal neurodegeneration, leading to an increase in macular GC-IPL thickness that may offset the magnitude of neuronal thinning. Ge et al. (2021) supported this assumption by stating that the retina is thicker in the earlier stages (preclinical stage) due to inflammation and thinner in the advanced stages. These assumptions are supported by the longitudinal study of Kreeke et al. (2020), where thinning of any retinal layers had not been observed in the preclinical stage of AD.

The most widely investigated retinal layer, peripapillary RNFL, gave quite a clear outcome of axonal loss, especially in the superior and inferior region, thus reflecting the loss of ganglion cells of the macular region. It is known that in the superior and inferior parts of the optic nerve head, the ganglion cell axons are at the highest amount, which is why the loss of axons is expected to be most significant in these regions. According to Ge et al. (2021), thinning happens diffusely, affecting all pRNFL areas, but the superior quadrant has the most significant effect size.

The effects of diagnostic criteria

Although results did not reach general statistical power, thinning of retinal layers was observed among MCI patients and, more precisely, among aMCI patients. The lack of statistical power of systematic reviews can partly be explained by the small number of eligible studies selected for systematic reviews. Also, broad criteria for MCI definition may influence the results. These reasons are probably also the cause for the significant heterogeneity of the meta-analysis done in reviews.

Closer screening of systematic reviews showed that a limited number of studies had investigated MCI patients with OCT measurement differences, indicating an increased risk of AD development. Thus, systematic reviews included a lot of the same studies, with each other, in their evaluations and meta-analysis. The limited number of studies cannot reach statistical power; more longitudinal studies with biological biomarkers and, at the same time, retinal changes with OCT are needed. Only that way would we find out if OCT measurements could be used as a surrogate biomarker of aMCI and AD.

Close examination of the studies in the selected systematic reviews showed that, although most included patients were amnestic MCI type, several different diagnostic criteria for MCI were used, and the specification of MCI type may have been missing. It was confusing to note that when some systematic reviews brought up details of MCI type from their selected articles, others who used the same papers in their meta-analysis did not specify the MCI criteria used in their chosen documents so clearly. Furthermore, systematic reviews showed variability in cognitive tests in many studies, which might confound the results.

The question is, which test reflects the best prodromal AD, the AD-specific MCI? It is proposed (Vuoksimaa et al., 2018) that impairment of at least two memory tests could primarily improve to predict of prodromal AD. One main limitation observed across the studies was that AD or MCI

diagnostic was based on clinical criteria without the support of biomarkers (Amyloid, tau, neuronal injury). It is reported that only two-thirds of amnestic MCI patients have Alzheimer's pathology, diagnosed e.g., by NINCDS-ADRDA (Dubois et al., 2016), giving doubt about the absolute amount of amnestic MCI patients in systematic reviews. Some systemic reviews took clearly under consideration the type of MCI and used as an inclusion criterion to select studies with only amnestic MCI (aMCI), which is generally considered a prodromal stage of Alzheimer's disease (AD) (Petersen et al., 2014, pp. 217-218; Jongsiriyanyong and Limpawattana, 2018, pp. 502-504).

It is proposed that the definition of MCI influences the effects found for outcome measures, thus being an essential factor in clinical trials. Although a change in cognition would be the most clinically relevant outcome, at least three times larger sample sizes are required to demonstrate effects or statistical power than estimates based on biomarkers. (Bertens et al., 2017.) Some measurements in aMCI and controls were relatively small, thus giving doubt about the statistical power of the results, even though outcomes showed power in effect size.

OCT-type and its influence

A possible source of bias is the different types and models of OCT devices used across the studies. Two different generations of OCT technology have been used in the articles analysed in this review: Time-domain OCT (TD-OCT) and Spectral-domain OCT (SD-OCT) (also known as Fourier domain). SD-OCT is the more recent technology and shows considerable improvements over TD-OCT in every aspect of image acquisition, processing, and analysis. Now, both technologies are used in the field. Studies using both two generations of technology cannot be directly compared.

In studies where both devices were under consideration (Thomson et al., 2015; den Haan et al., 2017; Noah et al., 2020; Mejia et al., 2020), the SD-OCT technique showed less difference in retinal thickness measurements. Also, results appear to be more consistent between MCI and controls, with a small but significant loss of retinal ganglion cells and degeneration and loss of RGC axons in peripapillary RNFL than with TD-OCT. Fewer artefacts and significantly greater retinal thickness in SD-OCT at a higher resolution than TD-OCT may explain these differences. Nevertheless, thinning, especially in GC-IPL and pRNFL region, was detected on any OCT machine, whether TD-OCT or SD-OCT. All systematic reviews alleviated that in the future, longitudinal studies will need to focus on only one type of OCT technique measurements.

Other diseases excluded, is it reality in ageing population?

It should be noted that the retina is not an isolated entity but a composite of the whole visual pathway. The association between poor vision and the increased risk of AD or dementia (Shang et al., 2021) could also be explained by the anterior segment, optic nerve, or visual cortex abnormalities, as well as eye-movements disorders. All systematic reviews included on this overview excluded participants with ophthalmic or systemic chronic diseases. However, these diseases are shared among the ageing population. Therefore, ideal biomarkers should be applied to apparently healthy subjects and those with multiple co-morbidities.

A close review of the exclusion criteria of potential confounders of OCT measurements revealed that the presence of conditions associated with macular thinning, such as glaucoma, age-related macular degeneration, severe hypertension, and severe diabetes mellitus, were consistently excluded. Still, more subtle confounders, such as axial length or refractive error consideration in general, were missing. These factors have been reported to affect significantly, e.g., the retinal nerve fibre layer thickness, and it should be considered in any measurements or outcomes related to retinal layer thickness measurements (Kausar et al., 2018).

One question is whether average data values for the thickness of retinal layers with different ethnic and age groups can be combined. Ethnicity did not appear to be under consideration, but age matching between groups occurred in studies in this review. Age-matched trials are essential, because it is known that the retinal layer is thinner while people are ageing.

Publication bias and knowledge gabs of studies

Song et al. (2021) had a variety of implementations of included articles. They performed, e.g., results from macular thickness changes, but under precise evaluation of their included studies, some misleading results were observed. They had included, e.g. article by Ascaso et al. (2014) showing significant thinning in macular RNFL among MCI patients, but that study performed only peripapillary RNFL measurements. That study did not include any meta-analysis for helping results interpretation. A considerable problem for the author was to find the right results because of the different meanings or names of the targets in articles. E.g. abbreviation mRNFL, meant by Song et al. (2021) "mean" RNFL when in Ge et al. (2021) and Mejia-Vergara et al. (2020), it denoted "macular" RNFL.

Against that background, the study without any meta-analysis (Song et al., 2021) gave the lowest reability.

There was some confusion between studies. There seemed to have differences in the interpretation of the same (e.g. case-control) study. For example, when one paper claimed that, e.g. a particular study had specified MCI as an amnestic form, the other said that MCI had not been defined as an amnestic form. That led to doubt about the reliability of the studies. Thus, this thesis writer ended up checking all little studies included in systematic reviews, if data details (Authors, title, published year) were clearly informed in text, tables, or references. That caused extra work for the writer and was time-consuming, but simultaneously showed how important it is to evaluate the studies thoroughly to screen the reliability. After a profound evaluation of small articles, it was possible to improve the reliability of this thesis.

Differences in exclusion criteria, study design, OCT type and number of studies, meta-analysis of studies can mislead the result and thus give also large heterogeneity. It is also possible that heterogeneity is due to the stage of MCI, thus giving variable results of retina degeneration in different stage among individuals. In addition, differences between different retinal tissues, like the degree of degeneration in ganglion cells and their axons, may influence on results. A noticeable pitfall is the small number of the study subjects included in systematic reviews as well as variability in diagnostic criteria.

Other markers of risk at AD patients

It is known that Alzheimer's effects also on vision, and thus some other tests could be included in future trials. For example, visual acuity and depression are found to be linked with each other in middle and older adults (Medscape, n.d.). Moreover, even mild visual deficits may be associated with depression. Thus, the evaluation of vision routinely among the ageing population is essential, mainly because it is known that depression and mild cognitive impairment can be linked together (Rock et al., 2013.)

It is also demonstrated an impairment in eye movements (saccades and fixations) with reading problems in individuals with mild cognitive impairment (MCI). In addition, reading problems increase in severity as AD progresses. (Hannonen et al., 2022; Fernández et al., 2013.) Against these facts, optometrist should be aware of influences of AD to vision. An alarming sign is if patients subjectively

feel that they see poorly or have vision problems, but according to vision tests done by an optometrist, there is no problem. These causes might be cause of neurodegenerative disease, Alzheimer's disease.

In summary

This umbrella review highlights the potential of retinal biomarkers for the diagnosis, prognosis, and risk assessment of amnestic AD. But more valuable would be the evaluation of OCT measurements with other non-invasive diagnosis assessments, like cognitive tests and eye-tracking movement tests in a routine visit. More efforts are needed to identify and validate the biomarkers before their ultimate applications in clinical practice. A combination of different imaging modalities and blood tests might help improve the biomarker performance and accelerate the clinical application of retinal markers with OCT for neurodegenerative disorders in general and specifically for AD. Still, they are expensive, worse, and less often feasible with routine visits.

Further exploration of OCT as a screening tool in prodromal neurodegenerative changes is warranted, especially in larger cohorts of amnestic MCI patients. In addition, longitudinal studies with a broad range of tests are needed to expand the knowledge of which combination of tests is reliable enough for screening patients at risk of AD in the early phase. It is also important to find out sensitive enough non-invasive biomarkers to detect risk patients before neurons die, which is irreversible, once lost, always lost. Then, in early intervention, the risk patients could be educated about risk factors and how the disease could slow down, stay stable, or even prevent it. They also may benefit the available treatments so that nothing irreversible happens.

OCT has been widely used in ophthalmology as a tool for detecting and managing retinal and ocular diseases. The ability to image retinal layer structure in 3D and non-invasively in seconds would make it an accessible and affordable tool for detecting at-risk AD patients. A prominent Northern Finland Birth Cohort Eye Study (Pitkänen et al., 2021) already found a statistically significant correlation between the subjects at age 46 with RNFL thinning and cognitive decline. Another study (Kim et al., 2022) done in 430 Korean community-dwelling individuals, observed the connection between cognitive impairment and e.g thinning of macular RNFL. These findings indicate the need for clinically easy to use biomarkers, which detect as early as possible the retinal changes.

Another Finnish study used baseline data from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). As a result, they suggested combining demographic data, vascular risk factors, cognitive performance, APOE genotype, and brain MRI measures can help identify Aβ positivity. Detecting amyloid positivity could reduce invasive and costly assessments during the screening process in clinical trials. (Pekkala et al., 2020.).

The actual diagnostic and prognostic value of SD-OCT measurements in AD may lie in their integration with other clinical and imaging biomarkers. For example, retinal vessel morphologic features, brain magnetic resonance imaging biomarkers, and neuropsychological tests. As optometrists use OCT more widely in Finland in their clinical work and can thus be the first person to detect abnormal retinal changes without any other confounding disease, the knowledge about signs of decreased cognition would be suitable also for them. Eye movement disorders, in saccadic and pursuit movements (Hannonen et al., 2022) in MCI patients, are also essential to know in the optometric field in Finland.

Close cooperation with other specialists in geriatric would be patient-centered care. The care of ageing people is nowadays fragmented, and the new division of Finland into new welfare areas brings challenges to the treatment of an ageing population. What would be the smoothest treatment path? I could see that a large senior population would benefit from their consultation room in health centers, where experts from different fields would work together. For example, an optometrist with a master's degree could also work together with an ophthalmologist.

It is known that the chance of multiple co-morbidities increases when people age. Thus, there can be several confounders when evaluating inner retinal measurements with OCT and misleading the interpretation of results. Furthermore, confounders can cover up a significant illness that requires treatment or its precursors, such as Alzheimer's. Therefore, the big question is how to find at-risk patients with ophthalmic and systematic diseases (multiple co-morbidities), which are very common among the ageing population.

It is also known that the progression of cognitive decline can be prevented or slowed down with multidomain lifestyle intervention. A Finnish FINGER study investigated the efficacy of a multidomain lifestyle intervention such as dietary guidance, physical activity, cognitive training, and management of cardiovascular risk factors. The control group received general health advice. As a result, they improved more in all studied cognitive domains: executive function, processing speed,

and complex memory tasks. Furthermore, the intervention was beneficial regardless of genetic risk or baseline risk factor levels. (Strandberg et al., 2017). Thus, early detection allows early intervention and prevention of cognitive impairment.

Recent research suggests that identifying APOE ε4, the leading genetic risk factor for Alzheimer's disease, would be helpful in clinical trials for MCI patients. MCI patients without the APOE ε4 allele with progressive brain atrophy should be excluded from clinical trials because they may progress to neurodegenerative diseases other than AD. (Kikuchi et al., 2022.)

Retinal structural, vascular, and electrophysiological biomarkers have great potential in diagnosing, prognosis, and risk assessment of MCI due to AD. Therefore, these biomarkers should be developed in the future, especially in the accuracy of diagnostic tests and longitudinal studies. (Ge et al., 2021.) For example, a histopathological study has found a loss of melanopsin in retinal ganglion cells (mRGC) with Alzheimer's pathology (La Morgia et al., 2015). So melanopsin could be included in the future MCI at-risk evaluation research battery.

The know-how increases, and the results given by OCT can be interpreted even better with the help of advanced algorithms. As the population ages, it can be thought that the prevalence of possible neurodegenerative diseases will also become more common. Alzheimer's disease is the most common neurodegenerative disease, which causes dementia. Therefore, it would be suitable for every optometrist to be aware of the visual disturbances of this disease and the characteristic features that affect vision and eye function.

Vision and visual acuity are crucial for the functioning of an ageing individual both at home and in social life. To get proper and available treatment, an early possible detection of the disease is crucial. OCT would be an excellent tool due to its generality, affordability, and non-invasiveness if specific retina layers can be reliably shown to be thinning even before brain degeneration has progressed too far. In addition, the optician may be the first person who can notice through anamnesis, eye examination and examination of the eyes' health that vision problems are related to something other than an eye or systematic disease.

In the future, professional competence in Finland will probably be divided into two different profiles: knowledgeable developers in the field and patient-facing people. A large amount of data processing is required in the background of the optometrist's work so that the information about the patient,

symptoms, measurements, and treatment options is selected and organized into a format that can be used in client situations. For example, anamnesis is very important when dealing with an ageing person. With the information provided by it and the OCT, it is possible to delve even better into the patient's problems and conduct examinations to exclude other diseases or problems and possibly detect the possibility of neurodegenerative disease.

Conclusions

The main purpose of this umbrella review was to increase knowledge of OCT as a tool for detecting Alzheimer disease (AD) in the early stage. Especially in the phase when memory problems are increased more than normal ageing, meaning amnestic mild cognitive impairment (aMCI), also identified as prodromal AD. By screening systematic reviews, some evidence of GC-IPL and pRNFL thinning was observed.

Several studies demonstrated unique differences in retinal structure in patients with MCI compared to healthy controls. OCT appears to have diagnostic utility in MCI, especially in peripapillary RNFL and GC-IPL layer measurements. However, there is a lack of statistical power, perhaps due to the small number of eligible studies and their small sample sizes with the broad definitions of MCI for which there are multiple subtypes (e.g., amnestic and non-amnestic MCI). Studies including only amnestic MCI are more relevant to the study of AD. To decrease the chance of bias and increase the statistical power of reviews, MCI due to AD should confirm clearly with cognitive tests and brain imaging or CFS -tests, along with more extensive studies with longitudinal data, like prospective cohort studies.

Though the retinal layer changes are not disease-specific for aMCI or prodromal Alzheimer's disease (AD), the retina can provide a window to identify individuals at risk for AD who may then benefit from further investigations, including brain imaging, CSF-tests and detailed neuropsychological assessments and developing treatments. OCT could be easily used clinically with other non-invasive tests, like evaluation of functional eye movements and cognitive difficulties, as a risk indicator with multi-professional cooperation.

7 REVIEW OF THE RELIABILITY AND ETHICALITY OF THE THESIS

This umbrella review has been written by one author, but with the help of a mentor (specialist in neurology) to delimit the subject and ensured that studies in the data selection phase are critically evaluated, and relevant studies are not overlooked. Some help was obtained from an information specialist in the Oulu University of Applied Sciences library at the beginning of the written process. Her support ensured the relevance and comprehensiveness of key search terms based on the research question.

Some limitations can be observed due to the exclusion criteria and software use. Articles without full text were excluded due to limit access, and these may have included evidence, which could have given more knowledge about the subject. Another limitation of this study was that it was not possible to use any meta-analytical software of included systematic review results. However, meta-analysis of the results of systematic reviews is not the purpose of the umbrella review, but the collection of results and their clear presentation as presented in systematic reviews, as well as the analysis of the reliability of the results, differences, and future needs. Nevertheless, an overview of the topic was achieved, which is the purpose of the umbrella study.

Making an umbrella review as a thesis has developed my skills in identifying, evaluating, and synthesizing research results. It has also taught me to read various scientific texts more critically and interpret extensive systemic review results. While evaluating multiple studies, I have noticed how important it is to illustrate information with tables and figures to clarify the topic and outcomes and help the reader to get inside the subject. I have tried to bring the same manner to my thesis. The final work has been instructive and shows that I can work independently, be self-directed and tolerate a lot of pressure.

This umbrella review has been done by the guidelines approved by Oulu University of Applied Sciences. The instructions follow responsible research (RCR) and procedures by preventing research fraud in all disciplines in Finland. These guidelines were prepared and published in 2012 by the Finnish National Board on Research Integrity (TENK) in cooperation with the Finnish research community. The Research Ethics Advisory Board (TENK) is an expert body of the Ministry of Education and Culture, which the Ministry appoints based on a proposal from the scientific community.

(Finnish Research Integrity Board, n.d.). A separate Institutional Review Boards' approval was not sought since an umbrella review does not belong to the studies requiring IRB approval.

8 TIMETABLE AND BUDGET

The Thesis was initially started in the spring of 2022 with the planning of the Thesis, after the subject validation. Some literature search was conducted in July getting an overall picture about the number of studies relevant to this topic. The main writing of the final Thesis began on August. It was continued throughout the fall and finalized in December of 2022.

This Thesis was conducted purely as a part of a Master´s Degree program in Clinical Optometry studies. Neither financial support nor funders or sponsors were included as part of the Thesis.

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ABBREVATIONS

APOSTEL = Advised Protocol for OCT Study Terminology and Elements with 9-point checklist: study protocol, acquisition device, acquisition settings, scanning protocol, funduscopic imaging, postacquisition data selection, postacquisition analysis, nomenclature and abbreviations, and statistical approach.

Cytoskeleton = A microscopic network of protein filaments and tubules in the cytoplasm of many living cells, giving them shape and coherence.

Confidence interval (CI) = In statistics refers to the probability that a population parameter falls between a set of values a certain number of times. Analysts often use confidence intervals that contain either 95% or 99% of the expected observations. A 95% confidence level means that 95 times out of 100 estimates fall between the upper and lower values defined by the confidence interval. SMD and WMD is usually marked as 95% Confidence Interval (CI). (Bevans, 2020.)

Heterogeneity = In systematic reviews is often used meta-analysis for combining of the results and to help clinical decision-making if the results of multiple studies are diverse and conflicting. Sometimes among studies occurs excessive variability and that is called heterogeneity. The opposite of heterogeneity is homogeneity meaning that all studies show the same effect. There are different types of heterogeneity: Clinical (differences in participants, interventions or outcomes), methodological (differences in study design, risk of bias) and statistical (variation in intervention effects or results). Statistical heterogeneity comes into the picture when individual trials have results that are not consistent with each other. Heterogeneity can be assessed using the eyeball test (graphical method, forest plot method) or more formally with statistical tests, such as the Cochran's Q test or Higgins's index of heterogeneity I^2. A rough guide to interpretation of Higgins's I^2 is as follows: 0% to 40% - might not be important; 30% to 60% - moderate heterogeneity; 50% to 90% - substantial heterogeneity and 75% to 100% - considerable heterogeneity. It has been proposed also that the adjectives low, moderate and high be assigned to I^2 values of 25%, 50% and 75%. Generally, significant heterogeneity is present if the I2 is 50% or more. (Sedgwick, 2015; Siebert, 2018.)

Microtubules = a microscopic tubular structure present in numbers in the cytoplasm of cells, sometimes aggregating to form more complex structures

P-value = Research authors propose a hypothesis (the full name is the null hypothesis), which can be a statement that suggests that nothing interesting is happening, such as that there is no difference between the observed data and what was expected, or that there is no difference between two groups. Clearly stated it is zero (0) point. The authors then calculated the probability (p-value) of the collected data that the null hypothesis was true. If the P-value is too small, they have every reason to doubt the accuracy of the null hypothesis. Then they reject the null hypothesis and accept the alternative hypothesis. The p-value reflects the strength of the evidence against the null hypothesis. Generally, a threshold value of 0.05 is used as the P-value. If the P-value is larger than 0.05, can be said that the evidence against the null hypothesis is not strong enough and we cannot reject the null hypothesis. If P-value is lower than 0.05, can be assumed that the evidence against the null hypothesis is strong enough, so we reject the null hypothesis and accept the alternative hypothesis, which implies heterogeneity meaning that P-value is generally considered statistically significant. In other words, the lower the P-value is, the greater the statistical significance of the observed difference is. The P-value is a statistical measure which is used to determine the likelihood that an observed outcome is the result of change. (Tanha, Mohammadi and Janani, 2017.)

Standard deviation (SD) = When the SD is large, it is because the values of individual patients are spread widely, which means a wider margin of error, so the sample mean may not accurately represent the population mean. When the sample size is small, there is a higher probability that the sample does not represent the population well, which in turn makes the value of the mean questionable. In brief, when the sample size is large and when the SD associated with the mean is small, the mean is expected to be more precise and is assigned a higher weight when averaging results across studies in meta-analysis. (National Library of Medicine, 2006.)

Standardized mean Difference (SMD) = Pools many studies together and compares 1 group to another group. Is used also in meta-analysis, when trial assess the same outcome answering the same research question, but have measured differently, including using different scales/units. SMD standardize the results, based on standard deviation, so that they are comparable. SMD is only a statistical value, not a unit of measurement like e.g. age is. SMD of 0 means that there is no difference between intervention and control groups, and a negative SMD means that the experimental group has a lower mean score than the control group (this is when the numerator of the SMD is

calculated as experimental minus control and the negative sign is kept). If the 95% CI of the SMD includes 0, the SMD is not "statistically significant". SMD is calculated by equation of MD/SD. In meta-analysis studies comparing MCI to controls, negative value of SMD means it favours retinal thinning among MCI patients. Positive value indicates that control group has retinal thinning. Generally accepted values, negative or positive, of SMD effect sizes are small (≤ 0.2), medium (≤ 0.5) and large (≤ 0.8), where large effect size means that the research result has practical significance, while a small effect size means limited practical applications. (Andrade, 2020.)

Weighted Mean Difference (WMD) = Used in meta-analysis and compares the mean value of two groups, pooling many studies together and compares 1 group to another group. All studies answer the same research question and are measured in the same unit. Certain studies will have more weight than others, because they are better studies for their study design (randomized or not), sample size (large or small) and variability in results. WMD is calculated by equation: weighted mean of control group (WM1) - weighted mean of intervention group (WM2) or mean difference (MD) x weight value in one study and then calculating together all studies WM. (Andrade, 2020.)