Supplementary Section 1. Details of Retinal Imaging Technology for Specific Structures

1. Spectral-domain optical coherence tomography for imaging retinal neuronal and axonal layers

Optical coherence tomography (OCT) is an optical imaging technique that utilises a low-coherence light source near the infra-red spectrum to penetrate biological tissue and provides cross-sectional imaging of the retinal layered structure.\textsuperscript{S170} Spectral-domain OCT (SD-OCT) employs a spectrometer to analyse the interference spectrum data from the back-scattered light which includes the retina depth information and generate axial measurements of the retina.\textsuperscript{S35} Comparing with the earlier generation of OCT (time-domain OCT) which collected the signal as a function of time by moving a reference mirror mechanically, SD-OCT with the spectral analysis provides a higher resolution and higher speed for imaging the retinal layered structure.\textsuperscript{S35} The recent development of swept-source OCT (SS-OCT), with a longer wavelength (>1µm) than SD-OCT and utilizing a frequency-swept light source, further enhances tissue penetration into the choroid and provides a faster scanning speed.\textsuperscript{S171,S172}

Assessment of inner retinal layers in greater details is possible after the development of SD-OCT, in particular the ganglion cell layer and inner-plexiform layer, which indicate cell bodies and dendrites of retinal ganglion cells (RGCs), respectively.\textsuperscript{S173} Retinal layers (e.g. inner limiting membrane, nerve fibre layer, ganglion cell layer, inner plexiform layer and retinal pigment epithelium) are segmented automatically for different thickness and volume measurements (e.g. retinal nerve fibre layer (RNFL) thickness, ganglion cell-inner plexiform layer (GC-IPL) thickness, macular thickness and macular volume) at different locations by built-in segmentation algorithms in commercial OCT systems.
In addition to thickness measurement, built-in normative databases from healthy subjects are also provided for comparing the measured thickness or volume to age-matched data. The normative database uses a colour code to indicate the normal distribution percentiles (red: <1%, below normal limits; yellow: within 1% to 5%, suspect below normal; green: within 5%-95%, normal limits; light yellow: within 95%-99%, above normal limits; light red: >99%, above normal limits). For example, areas flagged in red indicate significant thickness reduction, compared with normative database.

2. Optical coherence tomography angiography for imaging retinal capillary networks

Optical coherence tomography-angiography (OCT-A) is based on mapping red blood cells movement over time from volumetric OCT scans. At each cross-sectional OCT image position, scan is repeated few times in order to detect and quantify the motion contrast. The degree of motion contrast is corresponding to angiographic flow, as the only expected motion in the retina is blood flow in vessels. Based on different image processing algorithms such as OCT Angiography Ratio Analysis (OCTARA), split-spectrum amplitude-decorrelation angiography (SSADA) and optical microangiography (OMAG) algorithm, OCT-angiography is able to penetrate into the retinal layers and image the various different capillary plexuses by selecting different en face slabs, thereby providing us the unique ability to reconstruct and view the retinal vasculature in a 3-dimensional fashion, as well as to visualize in isolation the individual retinal plexuses without intravenous dye injection (e.g. the superficial capillary plexus and deep capillary plexus).

It is noteworthy that the definition of “segmentation of retinal capillary plexuses” vary in different algorithms. For example, in the OCTARA, at macular region, the superficial capillary plexus default segmentation is defined as the region between the inner limiting membrane (ILM) + 2.6
μm to the inner plexiform layer (IPL)/inner nuclear layer (INL) border + 15.6 μm, while the deep capillary plexus default segmentation is defined as the region from the IPL/INL border + 15.6 μm to the IPL/INL border + 70.2 μm. In the SSASD, the superficial capillary plexus upper border is at 3 μm below ILM to the lower border at 15 μm below the IPL, while the deep capillary plexus spans from 15 μm below the IPL to 70 μm below the IPL. S176

Quantification of capillary network from OCT-A to identify early and subtle microvascular changes objectively is one of the next important milestones for the application of OCT-A into clinical practice. Currently, several quantitative OCT-A measurements (e.g. vessel density, foveal avascular zone area and circularity, fractal dimension, vessel density index) have been defined and different automated and semi-automated algorithms developed to quantify the capillary networks. S63, S64, S177 It is noted that projection artifacts from superficial blood vessels on the deeper layers (a fluctuating shadow cast by the flowing blood cells in the overlying retinal vessels projecting to the deeper layers) are common, which may lead to incorrect interpretations. S178

3. Enhanced depth imaging OCT for imaging choroidal vasculature

The choroid is the posterior part of the eyeball, which is sandwiched between the retina and the sclera, and is one of the most vascularized structures in the human body. Although SD-OCT can image the layered retina in details, imaging the choroid with SD-OCT is impeded by poor signal penetration beyond the heavily pigmented retinal pigment epithelium. S179 With the introduction of enhanced depth imaging (EDI) technique of SD-OCT, the visualization of choroidal scleral interface is enhanced and imaging of choroidal vasculature has become possible. S179 SS-OCT with a loner wavelength than SD-OCT, reducing the scatter reflection of the retinal pigment epithelium, also enables a better imaging of choroidal vasculature. S171, S172 The thickness and volume of the
choroid at different regions (e.g. subfovea, macula, peripapillary) can be subsequently measured by computer software.\textsuperscript{S104,S180} It is noteworthy that choroidal thickness is associated with several physiological variables (e.g. age, axial length of eyeball, intraocular pressure) in normal individuals.\textsuperscript{S181} Choroidal vascularity index, defined as the ratio of vascular area to the total choroidal area, is recently proposed to quantify choroidal vascular alterations in a more reliable manner as it has lesser variability and influence by these factors.\textsuperscript{S182}

4. Retinal vasculature analysis with retinal photography for imaging and quantifying retinal vasculature

The optical design of retinal photography with fundus camera is based on the principle of monocular indirect ophthalmoscopy, with the pupil used as both an entrance and exit for the fundus camera's illuminating and imaging light rays. With advancements in digital retinal photography and image processing technologies, quantitative retinal vasculature analysis from retinal photographs can be performed with computer software and standardized photographic protocols. Retinal Analysis (RA; University of Wisconsin, Madison, WI) and Integrative Vessel Analysis (IVAN; University of Wisconsin, Madison; WI) were widely used for measuring retinal arteriolar caliber and retinal venular caliber from retinal photographs in numerous large population-based studies.\textsuperscript{S183,S184} Retinal vessels, coursing through a specified area of a standardized grid (0.5–1.0 disc diameter from the disc margin), are measured. The revised Knudtson-Parr-Hubbard formula is widely used to summarize the retinal arteriolar and venular calibers of the large six arterioles and venules as central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) respectively.\textsuperscript{S185} Subsequently, newer retinal geometric branching parameters were defined to quantify the optimal state of retinal vasculature in recent computer software systems (e.g. SIVA
(Singapore I Vessel Assessment) software\textsuperscript{S103,S186} and VAMPIRE software (Vascular Assessment and Measurement Platform for Images of the REtina))\textsuperscript{S61} measured from a wider measured area, based on Murray’s principle that the branching pattern of vascular networks develops to minimize the energy required to maintain efficient blood flow.\textsuperscript{S53} It is noted that the current retinal vasculature analysis software tools are mainly semi-automated, and require manual adjustment and assessment usually by trained technicians to maximise the accuracy of the measurements.

5. Dynamic vessel analyzer for measuring the flicker-induced vasodilatory response

The principle of dynamic vessel analyzer (DVA) is based on dynamic reaction of retinal vessels to flickering light which stimulates activity of the neural retina and leads to retinal vessel dilation influenced by neurovascular coupling. In order to generate flickering light during DVA imaging, an optoelectric shutter is inserted in a retinal camera to produce a bright-to-dark contrast ratio of at least 25:1.\textsuperscript{S187} In each imaging cycle, retinal arteriolar and venular diameters are firstly measured in a certain time period for baseline measurement, followed by a stimulation with flickering light of the same wavelength for another time period, and then a non-flicker period. The responses to flickering light can be represented as an average increase in the retinal arteriolar and venular diameters during several cycles, and defined as the percentage increase relative to the baseline diameter size.\textsuperscript{S84}

6. Retinal oximetry for measuring retinal vessel oxygen saturation

Retinal oximeter, composed of an optical adapter and an image splitter fitted to a fundus camera, measures retinal vessel oxygen saturation based on acquisition of two images of the same area of the retinal fundus at two different wavelengths of light simultaneously. One of the two wavelengths
is sensitive to oxygen saturation (isosbestic wavelength of 570nm), i.e. the light absorbance changes with the oxygen saturation, while the other is insensitive to oxygen saturation (non-isosbestic wavelength of 600nm) and is used to calibrate the light intensity. The oxygen saturation can therefore be estimated by comparing light absorption at oxygen sensitive wavelengths for assessing retinal oxygen metabolism. Nevertheless, the choroid may have a considerable role in oxygenating the inner retina under some circumstances (e.g. 100% oxygen breathing), but this is not accounted for in the current estimation of haemoglobin oxygen saturation.

7. Ultra-wide field retinal photography for imaging the retinal periphery

The technology of ultra-wide field retinal photography is based on confocal laser scanning microscopy combined with a concave ellipsoidal mirror, or white-light light-emitting diode illuminator, which enable a wide field of view to be imaged without the need for pupillary dilation. Ultra-wide field retinal photography has the ability to capture a much wider view of the retina (up to 200° horizontally or 82% of the retina) in a single image for assessment of peripheral lesions (e.g. drusen deposits, diabetic retinopathy), compared with conventional retinal photography (30° to 50° of the retina). The confocal laser scanning microscopy based system can allow for fundus autofluorescence imaging at the same time. It is noted that images from the confocal laser scanning microscopy can only produce pseudo-color images, but not true colour imaging like conventional fundus photography.

8. Fluorescence lifetime imaging ophthalmology for measuring and quantifying lifetimes of retinal fluorophore
Retinal fluorophores, including lipofuscin, advanced glycation end products, collagen, melanin, and elastin, absorb and emit light at specific wavelengths. Electrons in retinal fluorophores are excited by absorbing photons from a monochromatic light source (e.g. laser), thus moving to a higher level of energy. They return to their energy ground state by emitting photons of longer wavelengths than the exciting light. Fluorescence lifetime imaging ophthalmoscope (FLIO) is based on a commercial scanning laser ophthalmoscope which is equipped with an infrared camera for active eye tracking to correct for eye movements. During imaging, the excitation laser raster scans the retina in multiple periods, detects the emitted fluorophore and builds up a distribution histogram over time. The fluorescence lifetime describes the average time a single fluorophore remains in its electronically excited state after absorbing the energy of a photon and before returning to the ground state by emitting a photon. Every fluorophore is characterized by its own excitation and emission wavelength spectrum and exhibits an individual fluorescence lifetime. Therefore, it can produce quantitative images based on the lifetimes of the different retinal fluorophores.
Supplementary Table 1. Recent clinical studies of common primary age-related ocular diseases and Alzheimer’s diseases (AD) dementia.

<table>
<thead>
<tr>
<th>Clinical retinal diseases</th>
<th>Authors, years</th>
<th>Sample</th>
<th>Summary of results</th>
</tr>
</thead>
</table>
| Age-related macular degeneration (AMD)    | Keenan et al. (2014)²² | Record linkage data of English National Health Service: an AMD cohort of 65,894 persons, a dementia cohort of 168,092 persons and a reference cohort of 7.7 million persons. | • For people with AMD: the rate ratio, comparing observed and expected cases of dementia in the AMD cohort with those of the reference cohort, was 0.91 (0.79, 1.04). The rate ratio for AD dementia after AMD was 0.86 (0.67, 1.08).  
• Persons with AMD not associated with incident dementia (RR: 0.91 [0.79,1.04]) or AD dementia (RR: 0.86 [0.67-1.08]), compared with the reference cohort.  
• Persons with any forms of dementia (RR: 0.07 [0.04, 0.11]) and persons with AD dementia (RR: 0.04 [0.01,0.10]) were unlikely to develop AMD, compared with the reference cohort. |
|                                           | Williams et al. (2014)²³ | 258 AD dementia, and 322 healthy control subjects                     | • AMD grades not associated with AD dementia, compare with AMD Grade 0 (Grade 1: OR: 0.65 [0.4–1.1]; Grade 2: OR: 1.00 [0.5–1.9]; Grade 3: OR: 1.38 [0.6–3.2]).                                                                                                         |
|                                           | Tsai et al. (2015)²⁴ | Claims data of the Taiwan National Health Insurance Research Database: an AMD cohort of 4,993 person (4,453 non-exudative AMD and 540 exudative AMD) and an age-gender-matched reference cohort of 24,965 persons. | • 5.9% and 5.2% persons were diagnosed with AD or senile dementia during a mean follow-up period of 4.4 years in the AMD cohort and the control cohort, respectively.  
• Persons with AMD were more likely to develop AD dementia or senile dementia (HR: 1.44 [1.26, 1.64]), compared with controls.  
• The association was stronger in non-exudative AMD (HR:1.44 [1.26, 1.65]).                                                                 |
|                                           | Lee et al. (2018)²⁵ | 3,877 participants with dementia-free at enrollment from the Adult Changes in Thought Study | • 347 (9%) had an AMD diagnosis at enrollment, and 689 (18%) developed AMD  
• Established AMD (>5 years) associated with incident AD dementia (HR: 1.50 [1.25, 1.8]).                                                                                                                       |
<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Lee et al. (2018) S5 | 3,877 participants with dementia-free at enrollment from the Adult Changes in Thought Study | - 136 (4%) had a DR diagnosis at enrollment, and 112 (3%) developed DR.  
- Both recent DR (within 5 years) (HR: 1.67 [1.01, 2.74]) and established DR (>5 years) (HR: 1.50 [1.05, 2.15]) associated with incident AD dementia. |
| Lin et al. (2014) S6 | Claims data of the Taiwan National Health Insurance Research Database: a primary open-angle glaucoma (POAG) cohort of 3,979 persons and a non-glaucoma cohort of 15,916 persons | - The incidence rates of AD dementia among the patients with and without POAG were 2.85 (2.19, 3.70) and 1.98 (1.68, 2.31) per 1000 person-years, respectively.  
- Persons with POAG were more likely to develop AD dementia (HR: 1.40 [1.03, 1.90]), but not Parkinson disease (HR: 0.98 [0.77, 1.24]), over 8 years, compared with non-glaucoma cohort. |
| Keenan et al. (2015) S7 | Record linkage data of English National Health Service: a POAG cohort of 87,658 persons, an AD dementia cohort of 251,703 persons, a vascular dementia cohort of 217,302 persons and a reference cohort of >2.5 million persons. | - For people with POAG, there was no significant association with AD: the rate ratio, comparing the POAG cohort with the reference cohort, was 1.01 (0.96, 1.06). The rate ratio for AD dementia after AMD was 0.86 (0.67, 1.08).  
- Persons with POAG not associated with incident AD dementia (RR:1.01 [0.96, 1.06]), but likely to develop vascular dementia (RR: 1.10 [1.05 to 1.16]), compared with the reference cohort.  
- Persons with AD dementia (RR: 0.28 [0.24 to 0.31]) or vascular dementia (RR: 0.32 [0.28 to 0.37]), were unlikely to develop POAG, compared with the reference cohort. |
| Lee et al. (2018) S5 | 3,877 participants from the Adult Changes in Thought Study | - 404 (10%) had a glaucoma diagnosis at enrollment, and 290 (7%) developed glaucoma.  
- Recent glaucoma (within 5 years) associated with incident AD dementia (HR: 1.46 [1.08, 1.91]). |

Aβ=amyloid-beta; AD=Alzheimer’s disease; HR=hazard ratio; OR=odds ratio; RNFL=retinal nerve fiber layer; RR=relative risk; PET=positron emission tomography.
**Supplementary Table 2.** Recent clinical studies of spectrum of Alzheimer’s diseases (AD) (AD dementia, mild cognitive impairment (AD MCI), preclinical AD), and retinal imaging measures, as defined from spectral-domain optical coherence tomography (SD-OCT), OCT-angiography, enhanced depth imaging (EDI) with OCT and retinal photography. It is noted that the definition of AD varies in the existing literature: not all publications have included AD biomarkers for their AD diagnosis. The evolution in definition and diagnostic criteria of AD and other dementias may account for some of the variations and differences seen between studies discussed in this review.

<table>
<thead>
<tr>
<th>Authors, years</th>
<th>Sample</th>
<th>Imaging measure</th>
<th>Summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cross-sectional SD-OCT studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Larrosa et al. (2014)⁵¹⁹³ | 151 AD dementia, and 61 age-matched normal control subjects | A selective combination of peripapillary RNFL and macular thicknesses using linear discriminant function | • Reduced peripapillary RNFL thickness using linear discriminant function in AD dementia (all p<0.001), compared with controls.  
• The largest AUROCs were 0.967 for the Spectralis RNFL based linear discriminant function and 0.830 for the Cirrus RNFL based linear discriminant function. |
| Polo et al. (2014)⁵¹⁹⁴ | 75 AD dementia, and 75 age-matched normal control subjects | Peripapillary RNFL and macular thickness | • Reduced peripapillary RNFL in superior (113.59µm vs. 118.58µm, p=0.006) and inferior (121.96 µm vs. 127.97 µm, p=0.018) quadrants, and macular thicknesses (all p≤0.009, except measurement at fovea [p=0.115]) in AD dementia, compared with controls.  
• Reduced peripapillary RNFL thickness in superior quadrant in AD dementia (109.1µm vs. 111.1µm, p=0.039), compared with controls.  
• No difference in macular GC-IPL and peripapillary RNFL thicknesses between MCI and AD dementia. |
| Cheung et al. (2015)²⁰ | 100 AD dementia, 41 MCI, and 123 normal control subjects | Macular GC-IPL and Peripapillary RNFL thicknesses | • Reduced macular GC-IPL thickness in MCI (all p≤0.049, except measurement at superior [p=0.064], inferonasal [p=0.051] and supertemporal [p=0.359] sectors) in AD dementia (all p≤0.031), compared with controls.  
• Reduced peripapillary RNFL thickness in superior quadrant in AD dementia (109.1µm vs. 111.1µm, p=0.039), compared with controls.  
• No difference in macular GC-IPL and peripapillary RNFL thicknesses between MCI and AD dementia. |
<p>| Ferrari et al. (2016)⁵¹⁹⁵ | 39 AD dementia, 17 frontotemporal dementia (FTD), 27 MCI and 49 normal control subjects | Peripapillary RNFL and GC-IPL thicknesses | • Reduced peripapillary RNFL and GC-IPL thicknesses in AD dementia (mild AD: RNFL=94.55 µm, GC-IPL=57.52µm; moderate AD: RNFL=91.33µm, GC-IPL=50.07µm), FTD (RNFL=87.47µm, GC-IPL=51.83µm) and MCI (RNFL=92.79µm, GC-IPL=51.83µm). |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Parameters Assessed</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Garcia-Martin et al. (2016)   | 150 AD dementia and 75 age-gender-matched normal control subjects | Macular RNFL, GCL, IPL, INL, OPL, ONL, RPE layer and photoreceptor layer thicknesses | • Reduced macular RNFL (6.11 vs. 6.22), GCL (6.27 vs. 6.45), INL (6.56 vs. 6.71) and ONL (6.56 vs. 6.71) thicknesses in AD dementia (p<0.050), compared with controls.  
• Reduced RNFL (p=0.018), GCL (p=0.009) and INL (p=0.006) thicknesses correlated with disease duration in AD dementia. |
| Snyder et al. (2016)          | 10 Aβ-positive and 53 Aβ-negative subjects at high-risk for AD (self-reported first-degree family history of the disease, and self-identification of subjective memory concerns) | Peripapillary RNFL and macular RNFL, GCL, IPL, INL, OPL, and ONL thicknesses.             | • Increased IPL in Aβ-positive group (p=0.029), compared with Aβ-negative group (0.371µm³ vs. 0.354 µm³).                                      |
| Cunha et al. (2017)           | 50 mild AD dementia and 152 normal control subjects | Peripapillary RNFL and macular thicknesses               | • Reduced peripapillary RNFL thickness in superiotemporal sector (p<0.05) and macular thicknesses in pericentral (p=0.001) and peripheral superior (p<0.001) sectors in AD dementia, compared with controls. |
| Lad et al. (2018)             | 15 AD dementia, 15 MCI and 18 normal control subjects | Peripapillary RNFL and macular RNFL and GC-IPL thicknesses | • No significant associations observed.  
• Using a multivariate regression model with quasi-least squares, there are areas of thickening of macular GC-IPL and RNFL in subjects with AD dementia and MCI, compared with controls. |
<p>| O'Bryhim et al. (2018)        | 14 preclinical AD (Aβ-positive from PET or CSF but not dementia) and 16 normal control subjects | Inner, outer, and total foveal thicknesses              | • Reduced inner foveal thickness (66.0µm vs. 75.4µm, p=0.03) in preclinical AD, compared with controls.                                      |
| Sanchez et al. (2018)         | 324 AD dementia, 192 MCI and 414 normal control subjects | Peripapillary RNFL thickness                             | • No difference in peripapillary RNFL thickness among the groups.                                                                       |
| den Haan et al. (2019)        | 57 AD dementia and 85 normal control subjects     | Peripapillary RNFL, total macular and macular RNFL, GCL and IPL thicknesses | • No difference in peripapillary RNFL, total macular and macular RNFL, GCL and IPL thicknesses among the groups.                         |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Peripapillary RNFL and Macular GCC Thicknesses</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Tao et al. (2019)             | 73 AD dementia, 51 MCI and 67 normal control subjects                         | Peripapillary RNFL and macular GCC thicknesses | ‣ Reduced peripapillary RNFL (97.99µm vs. 98.35µm vs. 107.19µm) and macular GCC thicknesses (94.16µm vs. 94.1µm vs. 99.64µm) in AD dementia and MCI (all p<0.05), compared with controls.  
‣ No difference in peripapillary RNFL and macular GCC thicknesses between MCI and AD dementia. |
| Asanad et al. (2020)          | 27 preclinical AD (pathological Aβ42/Tau ratio from CSF but not dementia) and 16 normal control subjects | Peripapillary RNFL, macular GC-IPL and macular thicknesses | ‣ Reduced peripapillary RNFL thicknesses in preclinical AD dementia (83.46µm vs. 93.27µm, p=0.0009), compared with controls.                                                  |
| McCann et al. (2020)          | 3,221 subjects from the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA) | Peripapillary RNFL thickness                   | ‣ Reduced associated with AD (self-reported) in the age-adjusted and sex-adjusted model.                                                                                                                  |
| **Prospective SD-OCT studies** |                                                                                |                                               |                                                                                                                                                                                                          |
| Shi et al. (2014)             | 20 MCI and 58 normal control subjects                                         | Peripapillary RNFL thickness                   | ‣ The reduction in peripapillary RNFL at inferior region in the converted participants was greater than that in stable participants (−11.0µm vs 0.4µm, p = 0.009) over a 25-month follow-up. |
| Trebbastoni et al. (2016)     | 36 AD dementia and 36 age-matched normal control subjects                     | Peripapillary RNFL thickness                   | ‣ Changes in peripapillary RNFL thickness in inferior region associated with worsening cognitive scores (ADAS-Cog scores change: r = −0.35, p = 0.02; CDR scores change: r = − 0.39, p = 0.008) over a 12-month follow-up. |
| Choi et al. (2016)            | 42 AD dementia, 26 MCI and 66 normal control subjects                        | Peripapillary RNFL, macular GC-IPL and macular thicknesses | ‣ Reduced average (Beta=-0.150, p=0.006) and sectoral GC-IPL (all p<0.05) and macular (Beta=-1.700, p=0.02) thicknesses at baseline associated with progression of AD dementia and MCI over a 2-year follow-up. |
| Mutlu et al. (2018)           | 3,289 subjects from the Rotterdam Study                                       | Peripapillary RNFL and macular GC-IPL thicknesses | ‣ Reduced GC-IPL (OR: 1.03 [1.00, 1.09]) associated with prevalent dementia.  
‣ Reduced RNFL (HR: 1.02 [1.01, 1.04]) associated with incident of dementia, including AD dementia (HR: 1.02 [1.01, 1.04]). |
<table>
<thead>
<tr>
<th>Study</th>
<th>Population Description</th>
<th>Measured Parameters</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santos et al. (2018)</td>
<td>15 preclinical AD and 41 normal control subjects</td>
<td>Peripapillary RNFL and macular RNFL, GCL, IPL, INL, OPL, and ONL thicknesses.</td>
<td>• A larger reduction in macular RNFL (-0.032 mm$^3$ vs. -0.019 mm$^3$, $p=0.050$), ONL (-0.029 mm$^3$ vs. -0.007 mm$^3$, $p=0.026$), and IPL (-0.014 mm$^3$ vs. -0.006 mm$^3$, $p=0.020$) volumes, in preclinical AD over a 27-month follow-up, compared with controls.</td>
</tr>
<tr>
<td>OCT-angiography studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jiang et al. (2018)</td>
<td>12 AD dementia, 19 MCI and 21 age-matched normal control subjects</td>
<td>Vessel density of retinal vascular network, superficial capillary plexus, and deep capillary plexus.</td>
<td>• Decreased density of retinal vascular network, superficial vascular plexus, and deep vascular plexus in AD dementia ($p&lt;0.05$), compared with controls.</td>
</tr>
<tr>
<td>Bulut et al. (2018)</td>
<td>26 AD dementia and 26 age-gender matched normal control subjects</td>
<td>Vessel density and foveal avascular zone area of superficial capillary plexus.</td>
<td>• Decreased density (45.40% vs. 48.67%, $p=0.002$) and enlarged foveal avascular zone area (0.47 mm$^3$ vs. 0.33 mm$^3$, $p=0.001$) of superficial capillary plexus in AD dementia, compared with controls.</td>
</tr>
<tr>
<td>O’Bryhim et al. (2018)</td>
<td>14 preclinical AD (Aβ-positive from PET or CSF but not dementia) and 16 normal control subjects</td>
<td>Foveal avascular zone area.</td>
<td>• Enlarged foveal avascular zone area (0.364 mm$^3$ vs. 0.275 mm$^3$, $p=0.002$) in preclinical AD, compared with controls, with AUROC of 0.8007.</td>
</tr>
<tr>
<td>Lahme et al. (2018)</td>
<td>36 AD dementia and 27 normal control subjects</td>
<td>Foveal avascular zone area and vessel density of superficial capillary plexus, deep capillary plexus and radial peripapillary capillary.</td>
<td>• Decreased vessel density of superficial capillary plexus (48.77% vs. 51.64%, $p=0.001$) and radial peripapillary capillary (53.07% vs. 55.39%, $p=0.015$) in AD dementia, compared with controls. • No significant correlation between Aβ or tau levels in the CSF and OCT-angiography measures.</td>
</tr>
<tr>
<td>Querques et al. (2019)</td>
<td>12 AD dementia, 12 MCI, and 32 age-gender matched normal control subjects</td>
<td>Vessel density of superficial capillary plexus and deep capillary plexus.</td>
<td>• No differences in all the measures.</td>
</tr>
<tr>
<td>den Haan et al. (2019)</td>
<td>48 AD dementia, and 38 normal control subjects</td>
<td>Vessel density and foveal avascular zone area</td>
<td>• No differences in all the measures.</td>
</tr>
<tr>
<td>Zhang et al. (2019)</td>
<td>16 early AD or amnestic MCI, and 16 normal control subjects</td>
<td>Vessel density and vessel length density of superficial capillary plexus, radial peripapillary capillary and peripapillary superficial vascular plexus.</td>
<td>• Decreased vessel density (40.67% vs. 44.5%, $p=0.028$) and adjusted flow index (0.376 vs. 0.407, $p=0.047$) of superficial capillary plexus in early AD or amnestic MCI, compared with controls.</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Description</td>
<td>Imaging Parameters</td>
<td>Findings</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| van de Kreeke et al. (2019)   | 13 preclinical AD (Aβ-positive from PET but not dementia) and 111 normal control subjects | Flow index of superficial capillary plexus.                                         | • Increased vessel density of retinal vascular network at inner ring macula (difference: 0.81%, p=0.002) and outer ring macula (difference: 0.50%, p=0.024), and around optic nerve head (difference: 0.83%, p=0.015) in preclinical AD, compared with controls.  
• AUROCs for vessel densities in inner and outer ring of the macula and around the optic nerve head were 0.651, 0.640 and 0.764. |
| Zabel et al. (2019)           | 27 AD dementia, 27 open-angle glaucoma and 27 normal control subjects              | Foveal avascular zone area and vessel density of retinal vascular network at inner ring macula and outer ring macula, and around optic nerve head.       | • Decreased vessel density of deep capillary plexus (43.95% vs. 47.44% vs. 49.46%, p=0.0006) and enlarged foveal avascular zone area (0.32mm² vs. 0.26mm² vs. 0.21mm², p<0.001) in AD dementia, compared with open-angle glaucoma and controls. |
| Lee et al. (2020)             | 29 AD-related cognitive impairment, 25 subcortical vascular cognitive impairment and 15 normal control subjects | Vessel density of radial peripapillary capillary.                                  | • No differences in vessel density of radial peripapillary capillary between AD-related cognitive impairment and normal control subjects.                                                                          |

**OCT with EDI studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Description</th>
<th>Imaging Parameters</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gharbiya et al. (2014)</td>
<td>21 mild to moderate AD dementia and 21 age-matched normal control subjects</td>
<td>Choroidal thickness</td>
<td>• Reduced choroidal thicknesses in AD dementia (subfoveal choroidal thickness: 200.9µm vs. 266.1µm, p=0.001; other regions: p=0.036).</td>
</tr>
<tr>
<td>Bayhan et al. (2015)</td>
<td>31 AD dementia and 30 age-matched normal control subjects</td>
<td>Choroidal thickness</td>
<td>• Reduced choroidal (subfoveal choroidal thickness: 221.48µm vs. 251.86µm, p=0.001; other regions: all p≤0.036, except measurement at 3.0 mm temporal to the fovea [p=0.067]) thickness in AD dementia.</td>
</tr>
<tr>
<td>Trebbastoni et al. (2017)</td>
<td>39 AD dementia and 39 normal control subjects</td>
<td>Choroidal thickness</td>
<td>• A larger reduction in choroidal thicknesses (changes in subfoveal choroidal thickness: -10.47µm vs. -2.0µm) in AD dementia over a 12-month follow-up, compared with controls.</td>
</tr>
<tr>
<td>Bulut et al. (2018)</td>
<td>26 AD dementia and 26 age-gender matched normal control subjects</td>
<td>Choroidal thickness</td>
<td>• Reduced choroidal thickness (198.27µm vs. 251.88µm, p&lt;0.001) in AD dementia, compared with controls.</td>
</tr>
</tbody>
</table>
Retinal photography studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frost et al. (2013)</td>
<td>25 AD dementia, and 123</td>
<td>Decreased CRAE (122.9µm vs. 129.1µm, p=0.01), CRVE (169.7µm vs. 182.7µm, p&lt;0.001), arteriolar FD (1.201 vs. 1.235, p=0.008), venular FD (1.171 vs. 1.210, p&lt;0.001), venular tortuosity (6.953x10^{-5} vs. 7.660x10^{-5}, p=0.024) and venular branching coefficient (1.347 vs. 1.253, p=0.019) in AD dementia, compared with controls.</td>
</tr>
<tr>
<td></td>
<td>age-matched control subjects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Among control group, 15 Aβ-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>positive (preclinical AD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and 30 Aβ-negative subjects</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Decreased CRAE (122.9µm vs. 129.1µm, p=0.01), CRVE (169.7µm vs. 182.7µm, p&lt;0.001), arteriolar FD (1.201 vs. 1.235, p=0.008), venular FD (1.171 vs. 1.210, p&lt;0.001), venular tortuosity (6.953x10^{-5} vs. 7.660x10^{-5}, p=0.024) and venular branching coefficient (1.347 vs. 1.253, p=0.019) in AD dementia, compared with controls.</td>
</tr>
<tr>
<td>Cheung et al. (2014)</td>
<td>136 AD dementia, and 290</td>
<td>Decreased CRVE (OR 2.01 [1.27, 3.19]), arteriolar (OR 1.35 [1.08, 1.68]) and venular (OR 1.47 [1.17, 1.84]) FDs, and increased arteriolar (OR 1.80 [1.40, 2.31]) and venular (OR 1.94 [1.48, 2.53]) tortuosity associated with AD dementia.</td>
</tr>
<tr>
<td></td>
<td>age-matched control subjects</td>
<td></td>
</tr>
<tr>
<td>Williams et al. (2015)</td>
<td>213 AD dementia, and 294</td>
<td>Decreased total FD (OR 0.77 [0.62, 0.97]) and arteriolar tortuosity (OR 0.78 [0.63, 0.97]) associated with AD dementia.</td>
</tr>
<tr>
<td></td>
<td>age-matched control subjects</td>
<td></td>
</tr>
<tr>
<td>den Haan et al. (2019)</td>
<td>48 AD dementia, and 38</td>
<td>No differences in all the measures</td>
</tr>
<tr>
<td></td>
<td>normal control subjects</td>
<td></td>
</tr>
</tbody>
</table>

Aβ=amyloid-beta; AD=Alzheimer’s disease; AUROC=area under receiver operating characteristic curve; CRAE=central retinal artery equivalent; CRVE=central retinal vein equivalent; CSF=cerebrospinal fluid; EDI=enhanced depth imaging; FD=fractal dimension; GCC=ganglion cell complex; GC-IPL=ganglion cell-inner plexiform layer; GCL= ganglion cell layer; HR=hazard ratio; INL=inner nuclear layer; IPL=inner plexiform layer; MCI=mild cognitive impairment; OPL=outer plexiform layer; ONL=outer nuclear layer; OR=odds ratio; RNFL=retinal nerve fiber layer; RPE=retinal pigment epithelium; OCT=optical coherence tomography; PET=positron emission tomography.
**Supplementary Table 3.** A proposed framework of research using retinal imaging technology as a source of biomarkers for Alzheimer’s disease (AD).

<table>
<thead>
<tr>
<th>Items in the Framework</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study should be designed and conducted with a specific clinical purpose.</td>
<td>Can spectral-domain (SD-OCT) be used as a screening tool to identify asymptomatic individuals who are more likely to have AD in community, neurology clinics, eye clinics or optical shops?</td>
</tr>
<tr>
<td>2. Diagnosis of AD should be defined in a consistent manner with the latest available criteria.</td>
<td>AD should be defined by biomarkers of amyloid-β deposition, pathologic tau, and neurodegeneration.</td>
</tr>
<tr>
<td>3. Standard statistical measures of accuracy of biomarkers should be reported.</td>
<td>The sensitivity, specificity, false-positive and false-negative rates of SD-OCT measures should be reported, using the above as a reference standard.</td>
</tr>
<tr>
<td>4. Studies should be designed carefully to take into account many age-related ocular conditions.</td>
<td>How do different ocular conditions (e.g. glaucoma, age-related macular degeneration and elongated eyeball) manifest on SD-OCT? How do these ocular conditions be considered in the analysis and interpretation?</td>
</tr>
<tr>
<td>5. The reproducibility of the retinal imaging measures should be determined.</td>
<td>What are the intra-visit repeatability and inter-visit reproducibility of SD-OCT measures?</td>
</tr>
<tr>
<td>6. The incremental benefit and cost-effectiveness of retinal imaging as well as acceptability to patients in different settings should be evaluated.</td>
<td>What are the benefits to screen AD using SD-OCT in community, neurology clinics, eye clinics or optical shops?</td>
</tr>
</tbody>
</table>
**Supplementary Figure 1.** Image processing steps (e.g. image denoising, binarization, skeletonization) to quantify the retinal capillary networks (superficial capillary plexus, deep capillary plexus and radial peripapillary capillary plexus) from optical coherence tomography angiography (OCT-A) images in a subject with Alzheimer disease dementia.
Supplementary Figure 2. An example of presence of drusen deposits in the peripheral retina (appear as yellow deposits under the retina, indicated by white arrows) imaged by ultra-widefield scanning laser ophthalmoscopy (Daytona, Optos, Dunfermline, UK) in a 77-year-old subject with Alzheimer’s disease dementia (global clinical dementia rating score of 1). Except presence of drusen deposits in the peripheral retina, no other retinal disorders were observed in this subject. These peripheral drusen deposits are not present in healthy individuals without eye diseases.
Supplementary Figure 3. A proposed pathway of screening Alzheimer’s disease (AD) using retinal imaging assisted by artificial intelligence (AI). By providing a simple 2-tier risk stratification output, the AI algorithm could assist physicians to identify asymptomatic individuals who are more likely to have AD in different settings (e.g. community-based, eye clinic-based, general or specialized clinics). The high-risk group can then benefit from subsequent confirmatory investigations (e.g. PET imaging and cerebrospinal fluid tests), implementation of potential preventive therapies or recruitment into clinical trials.
Supplementary References


