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Optical coherence tomography angiography analysis methods: a systematic review and meta-analysis

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Optical coherence tomography angiography (OCTA) is widely used for non-invasive retinal vascular imaging, but the OCTA methods used to assess retinal perfusion vary. We evaluated the different methods used to assess retinal perfusion between OCTA studies. MEDLINE and Embase were searched from 2014 to August 2021. We included prospective studies including ≥ 50 participants using OCTA to assess retinal perfusion in either global retinal or systemic disorders. Risk of bias was assessed using the National Institute of Health quality assessment tool for observational cohort and cross-sectional studies. Heterogeneity of data was assessed by Q statistics, Chi-square test, and I^2 index. Of the 5974 studies identified, 191 studies were included in this evaluation. The selected studies employed seven OCTA devices, six macula volume dimensions, four macula subregions, nine perfusion analyses, and five vessel layer definitions, totalling 197 distinct methods of assessing macula perfusion and over 7000 possible combinations. Meta-analysis was performed on 88 studies reporting vessel density and foveal avascular zone area, showing lower retinal perfusion in patients with diabetes mellitus than in healthy controls, but with high heterogeneity. Heterogeneity was lowest and reported vascular effects strongest in superficial capillary plexus assessments. Systematic review of OCTA studies revealed massive heterogeneity in the methods employed to assess retinal perfusion, supporting calls for standardisation of methodology.

Abbreviations

| | |
|------|--|
| OCT | Optical coherence tomography |
| OCTA | Optical coherence tomography angiography |
| FFA | Fundus fluorescein angiography |
| PD | Perfusion density |
| VLD | Vessel length density |
| FD | Fractal dimension |
| FAZ | Foveal avascular zone |

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| | |
|------------|--|
| VD | Vessel density |
| MEDLINE | Medical Literature Analysis and Retrieval System Online |
| EMBASE | Excerpta Medica database |
| PRISMA | Preferred reporting items for systematic reviews and meta-analysis protocols |
| SVD | Skeletonised vessel density |
| SFD | Skeletonised fractal dimension |
| NIH | National Institutes of Health |
| VD% | Percentage vessel density |
| DCP | Deep capillary plexus |
| SCP | Superficial capillary plexus |
| RGC | Retinal ganglion cell |
| SVP | Superficial vascular plexus |
| DM | Diabetes mellitus |
| NDR | No diabetic retinopathy |
| Cross-sec | Cross-sectional |
| SRL | Superficial retinal layer |
| HD-OCT | High-definition optical coherence tomography |
| NPDR | Non-proliferative diabetic retinopathy |
| DRL | Deep retinal layer |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| PDR | Proliferative diabetic retinopathy |
| SRVP | Superficial retinal vascular plexus |
| DRVP | Deep retinal vascular plexus |
| DME | Diabetic macular oedema |
| GDM | Gestational diabetes mellitus |
| AD | Alzheimer's disease |
| MCI | Mild cognitive impairment |
| POAG | Primary open angle glaucoma |
| PD | Parkinson's disease |
| iRBD | Idiopathic rapid-eye-movement sleep behaviour disorder |
| NMOSD-ON | Neuromyelitis optica spectra disorder without optic neuritis |
| NMOSD + ON | Neuromyelitis optica spectra disorder with optic neuritis |
| MS-ON | Multiple sclerosis without optic neuritis |
| MS + ON | Multiple sclerosis with optic neuritis |
| aMCI | Amnesic mild cognitive impairment |
| CSVD | Cerebral small vessel disease |
| CKD | Chronic kidney disorder |
| VKHD + SGF | Vogt–Koyanagi–Harada disease with sunset glow fundus |
| VKHD-SGF | Vogt–Koyanagi–Harada disease without sunset glow fundus |
| VKHD | Vogt–Koyanagi–Harada disease |
| SD-OCT | Spectral-domain optical coherence tomography |
| SS-OCT | Swept-source optical coherence tomography |
| OMAG | Optical microangiography |
| SS-ADA | Split-spectrum amplitude decorrelation angiography |
| OCTARA | Optical coherence tomography angiography ratio analysis |
| CODAA | Complex optical coherence tomography signal difference analysis angiography |
| FSPA | Full spectrum probabilistic approach |
| NFL | Nerve fibre layer |
| GCL | Ganglion cell layer |
| IPL | Inner plexiform layer |
| INL | Inner nuclear layer |
| ONL | Outer nuclear layer |
| DVP | Deep vascular plexus |
| SCC | Superficial capillary complex |
| DCC | Deep capillary complex |

Optical coherence tomography (OCT) is a non-invasive, non-contact imaging modality which provides high resolution, cross-sectional images of the retina and is ubiquitous in ophthalmology practice to diagnose and monitor retinal disorders¹. OCT angiography (OCTA) uses moving red blood cells in the retinal vasculature as an intrinsic contrast agent to generate 3-dimensional images of retinal and choroidal blood flow^{2,3}. OCTA is widely used to evaluate retinal perfusion in retinal and systemic disorders⁴, and demonstrates microvascular impairment in disorders such as diabetes mellitus⁵, uveitis⁶, age-related macular degeneration⁷, atrial fibrillation⁸, haemorrhagic shock^{9,10}, and systemic hypertensive crisis¹¹. As OCTA is fast, cheap, and does not risk systemic reactions (as fundus fluorescein angiography (FFA) or indocyanine green angiography do), its use is fast becoming widespread in research and clinical practice. OCTA is now used alongside OCT and FFA in the diagnosis and management of retinal diseases¹².

Many OCTA platforms use proprietary algorithms to estimate and visualise retinal perfusion^{13,14}. However, as different OCTA devices use different algorithms, comparisons of results between studies are constrained¹³. Further, quantitative metrics derived from the OCTA signal and images lack consistent methodology¹⁵, also limiting comparison validity¹⁶. The raw signal may be used to derive limited scaled flow information¹⁵, and additional processing before image analysis includes thresholding to create binary images from grayscale¹⁷, and skeletonization to display vessels as one-pixel width tracings¹⁸. The most commonly calculated perfusion metrics from binarised and skeletonised images are^{17,19}:

1. Vessel density (VD)—the total area of perfused vasculature per unit area in a region of measurement (sometimes reported as “perfusion density”).
2. Vessel length density (VLD)—the total length of perfused vessels divided by the total number of pixels in the given area on the skeletonised image.
3. Fractal dimension (FD)—a mathematical parameter describing the complexity of a biological structure, usually applied to skeletonised images²⁰.
4. Foveal avascular zone (FAZ) measurements (Supplementary Fig. 1)—a change in FAZ measurements (e.g. area and perimeter) from baseline suggests altered blood flow²¹.

A scoping search on the National Library of Medicine PubMed (including Medical Literature Analysis and Retrieval System Online—MEDLINE) found no existing systematic reviews or meta-analyses comparing methods of quantitative OCTA analysis. We therefore conducted a systematic review and meta-analysis with the aim of assessing which OCTA perfusion analysis method most sensitively detects pathological change between patients with disorders affecting retinal perfusion and control patients with normal retinal perfusion. Our secondary aim was to look at the stability of OCTA imaging by identifying papers that studied the test–retest variability of OCTA.

Methods

This systematic review was performed following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA) statement²².

Inclusion criteria

Full inclusion and exclusion criteria are provided in Supplementary Table 1. We initially sought to investigate the sensitivity and stability of OCTA imaging, therefore we planned to include both studies comparing findings in normal patients with pathology and studies that included patients having repeated OCTA scans over time with or without a control group.

Prospective studies involving ≥ 50 participants were included where OCTA had been used to investigate changes to macula perfusion caused by either retinal or systemic disorders, using any one of the following analysis metrics (either on binarised or skeletonised images): VD, skeletonised VD (SVD), VLD, FD, skeletonised FD (SFD), capillary density index, FAZ measurements and; where agreement between repeated OCTA images was assessed by intra-class correlation coefficient. Included studies were limited to those with a sample size of at least 50 participants to minimise selection bias from the inclusion of small and selective case series. The year of publication was limited from 2014 to August 2021, as the clinical application of OCTA was first described in 2014²³. Only studies looking at foveal, parafoveal, and whole areas of the macula were included.

Papers published in medical journals and written in English were included—conference abstracts and papers written in languages other than English were excluded.

Exclusion criteria

We excluded studies investigating retinal disorders which cause focal anatomical change (e.g., age-related macular degeneration) or studies that only investigated perfusion in the choroid, choriocapillaris, or peripapillary region. Retrospective studies and studies that did not specify which region of the macula was analysed were excluded.

Search strategy

MEDLINE and Embase were searched using OVID. The applied search strategy is in Supplementary Fig. 2.

Risk of bias assessment

Two authors independently assessed the potential bias in the prospective studies using the National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies²⁴. A consensus was then reached between the two authors to create the risk of bias table (Supplementary Table 3).

Data extraction

Retinal perfusion was compared between healthy control patients and those with defined disease states. Two independent reviewers individually reviewed all titles and abstracts retrieved from the initial search. Duplicates were removed and each reviewer decided on the study's inclusion based on the title and abstract. Disagreements between reviewers on a paper's eligibility were resolved by discussion, involving the senior author (RJB) if a decision could not be reached. Reference management software was used to aid the screening process as per the PRISMA flow diagram (Fig. 1). Data were extracted by two reviewers working independently, with disagreements resolved by discussion. The following variables were recorded: study information (first author, year of publication, country location of study, study design), participant information (total number of eyes, total number of patients,

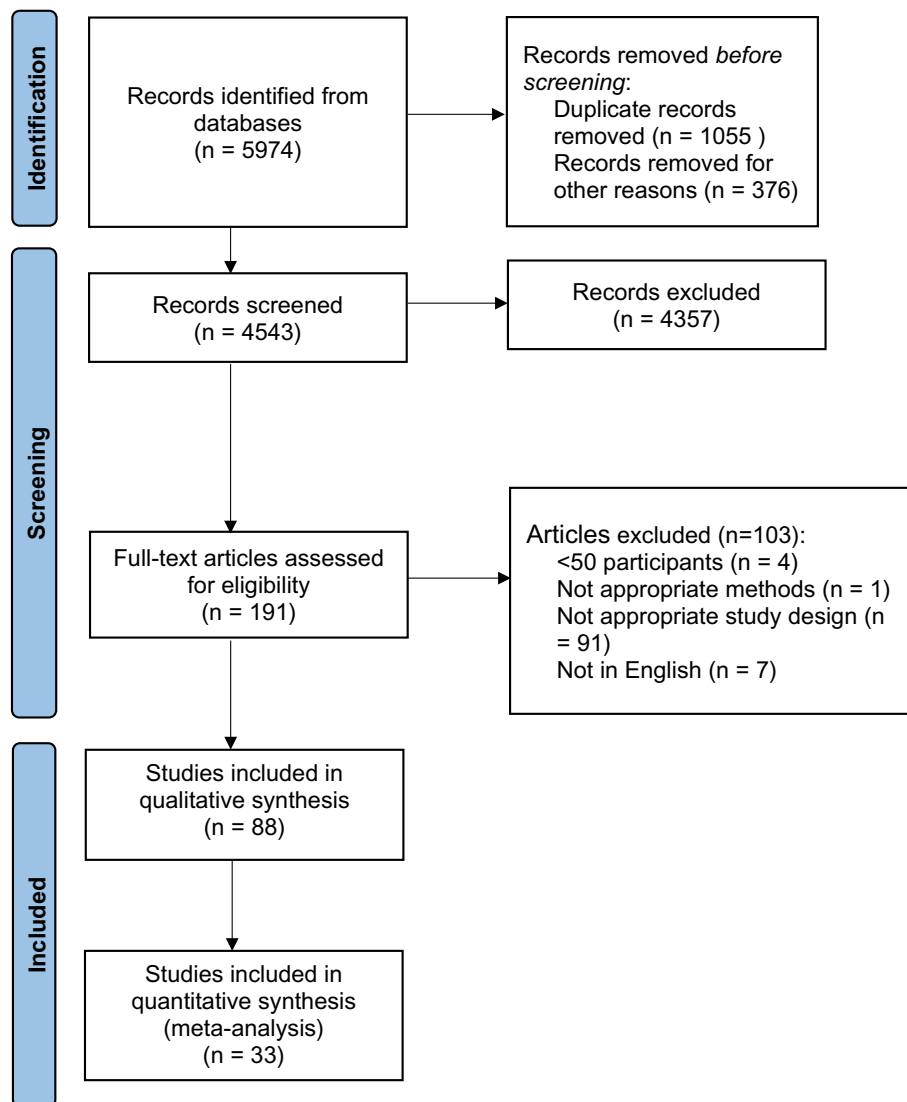


Figure 1. Systematic review and meta-analysis study flowchart.

sex, mean age), OCTA device and imaging information (instrument manufacturer, number of a-scans, scan size), and OCTA analysis information (vessel layer, macular region, analysis metric mean and standard deviation).

The outcome data (mean and standard deviation) collected included: percentage VD (VD%), SVD, VLD, FD, SFD, FAZ area, FAZ perimeter, FAZ acircularity ratio, and FAZ acircularity index. If unpublished information was required, the corresponding author of the study was contacted. If no response was received within one-month of contact, analysis proceeded based on published data. Only VD data given as a percentage and FAZ area presented as mm² were included in the study characteristics table.

Statistical methods for the effect of diabetic retinopathy on retinal perfusion

To combine measurements of the continuous variables VD and FAZ, and estimate a value for overall common and random effects, inverse variance weighting was used for pooling. When comparisons were made between pooled standardised mean differences for different sub-analyses, statistical differences were assessed using a Z test, with $p < 0.05$ considered statistically significant. An overall standardised mean difference was calculated using the random effects models. A funnel plot was used to detect publication and location bias in the selection of included trials according to the method of Egger et al.²⁵. The R statistical software (Version 4.1.1) (R Foundation for Statistical Computing, Vienna, Austria; see <http://www.r-project.org>) and its meta package (<http://cran.r-project.org/web/package/meta>) were used for these analyses.

Statistical methods for evaluating the effect of analysis methods on the assessment of retinal perfusion in diabetes without diabetic retinopathy or with mild non-proliferative retinopathy

Meta-analyses were performed on studies investigating diabetes mellitus with no diabetic retinopathy or with mild, non-proliferative diabetic retinopathy (the early stage of diabetic retinopathy in which symptoms are mild

or non-existent), using Review Manager 5 (RevMan Version 5.4. The Cochrane Collaboration, 2020). Statistical heterogeneity between studies was tested for using the Q-statistic (tests the null hypothesis that all studies share the same common effect) and heterogeneity was quantified using the I^2 measure of study heterogeneity (percentage of total variation across studies that is due to true heterogeneity rather than chance). A random effects model was used to address the issue of high levels of heterogeneity of results between studies.

Results

After removing duplicates, electronic searches retrieved 4543 records, of which 191 studies were included, and 88 eligible for qualitative analysis. A PRISMA flow diagram of search results is presented in Fig. 1. Excluded studies are presented in the Supplementary Table 2.

Characteristics of included studies

Study characteristics are presented in Tables 1 and 2. Of the 88 studies included, 78 were cross-sectional, six were longitudinal cohort studies, and four were case-control studies. Five papers met the original inclusion criteria but were not presented in the study characteristics table, as they did not include VD or FAZ data, instead using VLD or FD. Only summary data defined as VD or FAZ is presented as reporting of other analysis methods was too heterogeneous. Some studies did not specify which macula region was analysed for VD but did include FAZ data. In these instances, the paper was included but VD data were excluded. While the baseline data were presented from five longitudinal studies that included patients having repeated OCTA scans over time, no studies reported test-retest variability.

Heterogeneity of assessments

The included studies recruited patients with 64 different diagnoses, used seven different OCTA systems (Table 3), defined six different volume scan densities, with four different volume scan sizes, nine different perfusion analysis methods, five different vessel layer definitions for superficial and deep capillary plexi, and examined three different macula regions, giving a total of 197 distinct methods of assessing retinal perfusion, but a potential of more than 7000 different combinations (Table 4). Heterogeneity in OCTA analysis limited data synthesis, however the most studied condition was diabetes mellitus with or without diabetic retinopathy and the most reported analysis methods were VD and FAZ area. We therefore present detailed synthesis of VD and FAZ area in diabetes mellitus.

Risk of bias results

A risk of bias analysis using the NIH quality assessment tool for observational cohort and cross-sectional studies (14 questions) and the NIH tool of case-control studies (12 questions) graded 23 studies as good, 47 as fair, and 18 as poor quality (Supplementary Table 3). We retained studies rated as poor quality to illustrate heterogeneity.

Bias was identified predominantly in question 6 (“were the exposure(s) of interest measured prior to the outcome(s)?”), question 7 (“Was the timeframe sufficient so that one could reasonably expect to see an association?”) and question 10 (“Was the exposure(s) assessed more than once?”) of the NIH quality assessment tools because the included studies were mostly cross-sectional and not longitudinal by design. Sample size justification was rarely given (question 5) and study population was not always explicitly defined (question 2). Funnel plots (Fig. 2) showed no evidence of publication bias.

Effect of non-proliferative diabetic retinopathy on retinal perfusion

Twenty-six papers were included, as they had VD% results calculated from the same vessel layer, vascular region, and used the same scan size. In comparison to healthy controls, eyes with diabetic eye disease had, on average, a smaller VD% of -3.52% ($n=18$ studies, 95% CI $[-6.71; -0.32]$, $p=0.031$; Fig. 3b) and a larger FAZ area of 1.50 mm^2 ($n=26$ studies, 95% CI $[0.2999; 2.7007]$, $p=0.014$; Fig. 3a). In comparison to healthy controls, eyes of patients with diabetes had, on average, a smaller VD% of -1.7822% (95% CI $[-3.4935; -0.0708]$, $p=0.041$; Fig. 3d) and a larger FAZ area (0.7046 mm^2 (95% CI $[0.1826; 1.2266]$, $p=0.0082$; Fig. 3c). Study characteristics are summarised in Table 1.

Effect of analysis methods on the detection of diabetes without diabetic retinopathy

Nineteen papers were included. All included analysis methods across the different vascular plexi and retinal areas detected reduced perfusion in patients with diabetes without diabetic retinopathy compared to healthy controls (Fig. 4), although even within individual analysis methods, such as in the deep capillary plexus (DCP) with foveal perfusion assessed from a $6 \times 6\text{ mm}$ macular volume, heterogeneity was still high ($I^2=93\%$, $p<0.00001$). While all methods detected reduced retinal perfusion in diabetes without diabetic retinopathy (Fig. 4a–c), values for VD% in the superficial capillary plexus (SCP) and assessed in the parafoveal area tended to have the lowest heterogeneity and detected the greatest effect on perfusion (Fig. 4a). Study characteristics are summarised in Table 1.

Study characteristics of studies included looking at patients with diseases other than diabetes mellitus

Thirty-seven studies assessed VD and FAZ area in patients with diseases other than diabetes (summarised in Table 2), with a similar breadth of assessments as in the diabetes studies in terms of retinal area imaged, vascular layer segmented, and macular region assessed. Also similar to studies of diabetes, VD detected differences more frequently than FAZ area, parafoveal and whole macula VD more frequently than foveal VD and superficial VD more frequently than deep vessel VD.

Patients with Alzheimer’s disease (AD) and mild cognitive impairment (MCI) had reduced foveal, parafoveal, or whole macular perfusion, or increased FAZ area^{81,82,84–91,100}, except in one study⁸³. Similarly, patients with

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | | | | |
|--------------------------------|----------------------|--------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|----------|--------------|-------------|-------|------|--|--|--|--|
| Agra et al. ³⁸ | Optovue, Avanti | DM NDR | 60.00 | Cross-sec | 60 (60) | 19/41 | 6×6 | VD | SCP | Whole | 52.40 | 3.20 | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| | | DM NDR | 60.00 | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| Carnevali et al. ³⁹ | Zeiss, Cirrus HD-OCT | DM NDR | 22.0 | Cross-sec | 50 (50) | 30/20 | 3×3 | FAZ area | SCP | Fovea | 0.22 | 0.10 | | | | |
| | | Healthy controls | 23.0 | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| Choi et al. ⁴⁰ | Zeiss, Cirrus HD-OCT | DM NDR | 62.5 | Cross-sec | 103 (103) | 51/52 | 6×6 | FAZ area | SCP | Fovea | 0.37 | 0.13 | | | | |
| | | Healthy controls | 62.9 | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| Cinar et al. ⁴¹ | Optovue, Avanti | DM NDR | 49.5 | Cross-sec | 96 (96) | 48/48 | 6×6 | VD | SCP | Para-foveal | 55.11 | 1.11 | | | | |
| | | Healthy controls | 48.5 | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| Continued | | DM NDR | | | | | | FAZ area | DCP | Fovea | 0.75 | 0.20 | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |
| | | DM NDR | | | | | | | | | | | | | | |
| | | Healthy controls | | | | | | | | | | | | | | |

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | | |
|----------------------------------|----------------------|--------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|----------|--------------|-------------|-------------|----------|-------|------|
| De Carlo et al. ⁴² | Optovue, Avanti | DM NDR | 60.0 | Cross-sec | 89 (61) | 29/32 | 3×3 | FAZ area | Full | Fovea | 0.35 | 0.10 | | |
| | | Healthy controls | 54.0 | | | | | | | | | 0.29 | 0.14 | |
| Demir et al. ⁴³ | Optovue, Avanti | DM NDR | 12.30 | Cross-sec | 194 (97) | 44/53 | 3×3 | VD | SCP | Para-foveal | 50.10 | 3.20 | | |
| | | Healthy controls | 11.7 | | | | | | | | | 50.70 | 2.50 | |
| | | DM NDR | | | | | | | VD | DCP | Para-foveal | 54.60 | 3.50 | |
| | | Healthy controls | | | | | | | VD | SCP | Fovea | 55.10 | 3.50 | |
| | | DM NDR | | | | | | | VD | SCP | Fovea | 18.40 | 5.70 | |
| | | Healthy controls | | | | | | | VD | | | 18.50 | 5.80 | |
| | | DM NDR | | | | | | | VD | DCP | Fovea | 34.50 | 6.30 | |
| Durbin et al. ¹⁸ | Zeiss, Cirrus HD-OCT | Healthy controls | | | | | | | | | 34.50 | 7.20 | | |
| | | DM NDR/mild NPDR | 64.9 | Cross-sec | 100 (51) | 27/24 | 3×3 | FAZ area | SRL | Fovea | 0.26 | 0.10 | | |
| | | Healthy controls | 64.0 | | | | | | | | | 0.25 | 0.10 | |
| | | DM NDR | 58.3 | Cross-sec | 164 (82) | Unknown | 3×3 | VD | SCP | Un-known | Un-known | 14.22 | 1.40 | |
| Furino et al. ⁴⁴ | Topcon, Triton | Healthy controls | 56.4 | | | | | | | | 14.24 | 1.39 | | |
| | | DM NDR | | | | | | VD | DCP | Un-known | Un-known | 17.33 | 1.67 | |
| | | Healthy controls | | | | | | | | | | 17.95 | 1.58 | |
| | | DM NDR | | | | | | FAZ area | SCP | Fovea | Fovea | 2.98 | 1.26 | |
| | | Healthy controls | | | | | | | | | | 2.48 | 1.16 | |
| | | DM NDR | | | | | | FAZ area | DCP | Fovea | Fovea | 1.18 | 1.16 | |
| | | Healthy controls | | | | | | | | | | 1.01 | 0.97 | |
| | | DM NDR | | | | | | 4.5×4.5 | VD | SCP | Un-known | Un-known | 14.18 | 1.38 |
| | | Healthy controls | | | | | | | | | | 14.48 | 1.32 | |
| | | DM NDR | | | | | | | VD | DCP | Un-known | Un-known | 16.28 | 2.62 |
| Golebiewska et al. ⁴⁵ | Optovue, Avanti | Healthy controls | | | | | | | | | 17.00 | 1.89 | | |
| | | DM NDR | 15.3 | Cross-sec | 248 (130) | Unknown | 3×3 | VD | SCP | Whole | Whole | 51.98 | 2.43 | |
| | | Healthy controls | 13.6 | | | | | | | | | 52.45 | 2.74 | |
| | | DM NDR | | | | | | VD | DCP | Whole | Whole | 58.57 | 1.95 | |
| | | Healthy controls | | | | | | | | | | 58.57 | 5.03 | |
| | | DM NDR | | | | | | VD | SCP | Para-foveal | Para-foveal | 53.80 | 2.54 | |
| | | Healthy controls | | | | | | | | | | 54.41 | 2.62 | |
| Continued | | DM NDR | | | | | | VD | DCP | Para-foveal | 61.28 | 2.10 | | |
| | | Healthy controls | | | | | | | | | No Data | No Data | | |
| | | DM NDR | | | | | | VD | SCP | Fovea | Fovea | 32.51 | 5.26 | |

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD |
|------------|--------------|--------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|----------|--------------|-------------|-------|------|
| | | Healthy controls | | | | | | | | | 32.48 | 5.33 |
| | | DM NDR | | | | | | VD | DCP | Fovea | 32.37 | 6.17 |
| | | Healthy controls | | | | | | | | | 31.75 | 3.96 |
| | | DM NDR | | | | | | VD | SCP | Whole | 0.23 | 0.10 |
| | | Healthy controls | | | | | | | | | 0.24 | 0.08 |
| | | DM NDR | 13.8 | Cross-sec | 117 (117) | 47/70 | 6 × 6 | VD | SCP | Whole | 50.43 | 3.14 |
| | | Healthy controls | 14.1 | | | | | | | | 51.16 | 2.82 |
| | | DM NDR | | | | | | VD | DCP | Whole | 52.32 | 5.24 |
| | | Healthy controls | | | | | | | | | 53.36 | 4.66 |
| | | DM NDR | | | | | | VD | SCP | Para-foveal | 52.96 | 3.44 |
| | | Healthy controls | | | | | | | | | 54.18 | 2.78 |
| | | DM NDR | | | | | | VD | DCP | Para-foveal | 56.77 | 4.05 |
| | | Healthy controls | | | | | | | | | 57.64 | 3.50 |
| | | DM NDR | | | | | | VD | SCP | Fovea | 20.50 | 5.71 |
| | | Healthy controls | | | | | | | | | 20.72 | 6.14 |
| | | DM NDR | | | | | | VD | DCP | Fovea | 38.29 | 6.55 |
| | | Healthy controls | | | | | | | | | 39.24 | 6.66 |
| | | DM NDR | | | | | | FAZ area | Full | Fovea | 0.28 | 0.11 |
| | | Healthy controls | | | | | | | | | 0.27 | 0.13 |
| | | DM NDR | 13.8 | Cross-sec | 238 (119) | 46/73 | 6 × 6 | VD | SCP | Whole | 50.42 | 2.20 |
| | | Healthy controls | 13.4 | | | | | | | | 51.69 | 2.12 |
| | | DM NDR | | | | | | VD | DCP | Whole | 53.79 | 5.00 |
| | | Healthy controls | | | | | | | | | 56.11 | 4.76 |
| | | DM NDR | | | | | | VD | SCP | Para-foveal | 52.98 | 3.28 |
| | | Healthy controls | | | | | | | | | 53.94 | 3.01 |
| | | DM NDR | | | | | | VD | DCP | Para-foveal | 57.10 | 3.89 |
| | | Healthy controls | | | | | | | | | 58.85 | 3.78 |
| | | DM NDR | | | | | | VD | SCP | Fovea | 21.05 | 6.88 |
| | | Healthy controls | | | | | | | | | 23.13 | 6.90 |
| | | DM NDR | | | | | | VD | DCP | Fovea | 37.94 | 7.55 |
| | | Healthy controls | | | | | | | | | 40.17 | 7.59 |
| | | DM NDR | | | | | | FAZ area | Full | Fovea | 0.28 | 0.10 |
| | | Healthy controls | | | | | | | | | 0.27 | 0.11 |

Continued

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|--------------------------------|------------------------|--------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|----------|--------------|-------------|-------------|-------|-------|
| Meshi et al. ⁴⁸ | Optovue, Avanti | DM NDR | 58.5 | Case control | 105 (66) | 30/36 | 3×3 | VD | SCP | Un-known | 44.61 | 5.90 | |
| | | Healthy controls | 58.9 | | | | | | | | | 44.75 | 4.90 |
| | | DM NDR | | | | | | | VD | DCP | Un-known | 52.74 | 6.30 |
| | | Healthy controls | | | | | | | | | | 55.45 | 4.30 |
| | | DM NDR | | | | | | | FAZ area | SCP | Fovea | 0.251 | 0.09 |
| | | Healthy controls | | | | | | | | | | 0.261 | 0.11 |
| | | DM NDR | | | | | | | FAZ area | DCP | Fovea | 0.311 | 0.09 |
| | | Healthy controls | | | | | | | | | | 0.321 | 0.11 |
| | | DM NDR | 11.1 | Cross-sec | Unknown (91) | 39/52 | 6×6 | VD | SCP | Para-foveal | | 18.56 | 1.15 |
| | | Healthy controls | 10.2 | | | | | | | | | 19.18 | 0.46 |
| Li T et al. ⁴⁹ | Optovue, Avanti | DM NDR | | | | | | VD | SCP | Fovea | 11.24 | 3.30 | |
| | | Healthy controls | | | | | | | | | 11.80 | 2.54 | |
| Sacconi et al. ⁵⁰ | Zeiss, PLEX Elite 9000 | DM NDR | 21.0 | Cross-sec | 66 (66) | 34/32 | 3×3 | FAZ area | SCP | Fovea | 0.235 | 0.072 | |
| | | Healthy controls | 22.0 | | | | | | | | 0.199 | 0.100 | |
| | | DM NDR | | | | | | | FAZ area | DCP | Fovea | 0.670 | 0.178 |
| | | Healthy controls | | | | | | | | | 0.620 | 0.257 | |
| Vujosevic et al. ⁵¹ | Topcon, Triton | DM NDR | 57.4 | Cross-sec | 60 (60) | Unknown | 3×3 | FAZ area | SCP | Fovea | 0.359 | 0.120 | |
| | | Healthy controls | 44.4 | | 60 (60) | | | | | | 0.286 | 0.137 | |
| | | DM NDR | | | | | | | FAZ area | DCP | Fovea | 0.497 | 0.150 |
| | | Healthy controls | | | | | | | | | 0.364 | 0.142 | |
| | | DM NDR | 68.6 | Cross-sec | 372 (259) | 146/226 | 3×3 | VD | SRL | Whole | Whole | 42.40 | 5.09 |
| | | Healthy controls | 66.8 | | | | | | | | | 45.04 | 4.32 |
| | | DM NDR | | | | | | | VD | SRL | Para-foveal | 45.35 | 5.41 |
| | | Healthy controls | | | | | | | | | | 47.91 | 4.49 |
| | | DM NDR | | | | | | | VD | SRL | Fovea | 14.42 | 5.95 |
| | | Healthy controls | | | | | | | | | | 15.52 | 6.55 |
| Yang et al. ⁵² | Optovue, Avanti | DM NDR | | | | | | VD | DRL | Whole | 50.16 | 3.99 | |
| | | Healthy controls | | | | | | | | | 49.43 | 3.22 | |
| | | DM NDR | | | | | | | VD | DRL | Para-foveal | 52.75 | 4.05 |
| | | Healthy controls | | | | | | | | | 51.38 | 5.42 | |
| Continued | | DM NDR | | | | | 6×6 | VD | SRL | Whole | 45.93 | 4.61 | |
| | | Healthy controls | | | | | | | | | 48.46 | 4.03 | |
| Continued | | DM NDR | | | | | | VD | SRL | Para-foveal | 46.53 | 4.78 | |

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|---------------------------------|-----------------|--------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|----------|--------------|-------------|-------------|-------|------|
| Zeng et al. ⁵³ | | Healthy controls | | | | | | | | | 49.06 | 4.36 | |
| | | DM NDR | | | | | | VD | SRL | Fovea | 16.58 | 7.48 | |
| | | Healthy controls | | | | | | | | | 17.58 | 7.25 | |
| | | DM NDR | | | | | | FAZ area | SRL | Fovea | 0.42 | 0.75 | |
| | | Healthy controls | | | | | | | | | 0.34 | 0.13 | |
| Zeng et al. ⁵³ | Optovue, Avanti | DM NDR | 58.8 | Cross-sec | 128 (128) | 69/59 | 6×6 | VD | SCP | Para-foveal | 49.97 | 4.45 | |
| | | Healthy controls | 55.2 | | | | | | | | 53.47 | 4.31 | |
| | | DM NDR | | | | | | | VD | DCP | Para-foveal | 52.70 | 4.51 |
| | | Healthy controls | | | | | | | | | 55.99 | 4.09 | |
| | | T1DM NDR | 34.5 | Cross-sec | 29 (17) | | 3×3 | FAZ area | SCP | Fovea | 0.283 | 0.08 | |
| Forte et al. ⁵⁴ | Topcon, Triton | T2DM NDR | 48.8 | | 32 (17) | | | | | | 0.296 | 0.12 | |
| | | Healthy controls | 41.8 | | 43 (23) | | | | | | 0.218 | 0.07 | |
| | | T1DM NDR | | | | | | | FAZ area | DCP | Fovea | 0.321 | 0.01 |
| | | T2DM NDR | | | | | | | | | 0.353 | 0.15 | |
| | | Healthy controls | | | | | | | | | 0.252 | 0.08 | |
| Bhanushali et al. ⁵⁵ | Optovue, Avanti | DM mild NPDR | 64.3 | Cross-sec | 269 (153) | 87/66 | 3×3 | VD | SRVP | Un-known | 39.20 | 1.21 | |
| | | DM moderate NPDR | 61.1 | | | | | | | | 40.10 | 0.58 | |
| | | DM severe NPDR | 59.6 | | | | | | | | 38.50 | 0.76 | |
| | | DM PDR | 59.1 | | | | | | | | 38.90 | 1.38 | |
| | | Healthy controls | Unknown | | | | | | | | 49.70 | 0.55 | |
| | | DM mild NPDR | | | | | | | VD | DRVP | Un-known | 39.70 | 1.57 |
| | | DM moderate NPDR | | | | | | | | | 40.20 | 0.53 | |
| | | DM severe NPDR | | | | | | | | | 39.40 | 0.68 | |
| | | DM PDR | | | | | | | | | 39.20 | 0.94 | |
| | | Healthy controls | | | | | | | | | 53.10 | 0.73 | |
| | | DM mild NPDR | | | | | | | FAZ area | SRVP | Fovea | 0.46 | 0.03 |
| | | DM moderate NPDR | | | | | | | | | 0.45 | 0.01 | |
| | | DM severe NPDR | | | | | | | | | 0.46 | 0.02 | |
| DM PDR | | | | | | | | | 0.47 | 0.02 | | | |
| Healthy controls | | | | | | | | | 0.30 | 0.01 | | | |

Continued

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|------------------------------|-----------------|--------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|----------|--------------|-------------|-------|-------|------|
| Bontzos et al. ⁵⁶ | Optovue, Avanti | DM NDR | 53.1 | Cross-sec | 162 (162) | 85/77 | 6 × 6 | VD | SCP | Fovea | 32.82 | 3.25 | |
| | | DM mild NPDR | 55.7 | | | | | | | | | 30.21 | 4.19 |
| | | Healthy controls | 48.2 | | | | | | | | | 33.60 | 3.52 |
| | | DM NDR | | | | | | VD | DCP | Fovea | | 48.67 | 4.41 |
| | | DM mild NPDR | | | | | | | | | | 41.55 | 4.37 |
| | | Healthy controls | | | | | | | | | | 50.22 | 3.48 |
| | | DM mild NPDR | 57.4 | Cross-sec | 138 (138) | 66/72 | 6 × 6 | VD | SCP | Whole | | 51.34 | 4.09 |
| | | Healthy controls | 53.7 | | | | | | | | | 55.72 | 2.43 |
| | | DM mild NPDR | | | | | | VD | DCP | Whole | | 57.66 | 5.73 |
| | | Healthy controls | | | | | | | | | | 62.10 | 2.11 |
| Cao et al. ⁵⁷ | Optovue, Avanti | DM mild NPDR | | | | | | FAZ area | SCP | Fovea | 0.32 | 0.18 | |
| | | Healthy controls | | | | | | | | | 0.35 | 0.09 | |
| | | DM mild NPDR | | | | | | VD | SCP | Para-foveal | | 53.99 | 4.72 |
| | | Healthy controls | | | | | | | | | 58.69 | 2.12 | |
| | | DM mild NPDR | | | | | | VD | DCP | Para-foveal | | 62.01 | 5.17 |
| | | Healthy controls | | | | | | | | | 65.25 | 2.01 | |
| | | DM mild NPDR | 56.6 | Cross-sec | 94 (94) | 50/44 | 3 × 3 | VD | SCP | Para-foveal | | 45.43 | 0.56 |
| | | Healthy controls | 54.1 | | | | | | | | | 52.17 | 0.58 |
| | | DM mild NPDR | | | | | | VD | DCP | Para-foveal | | 52.82 | 0.85 |
| | | Healthy controls | | | | | | | | | 60.68 | 0.90 | |
| Ciloglu et al. ⁵⁸ | Optovue, Avanti | DM mild NPDR | | | | | | VD | SCP | Fovea | 29.45 | 0.76 | |
| | | Healthy controls | | | | | | | | | 34.86 | 0.75 | |
| | | DM mild NPDR | | | | | | VD | DCP | Fovea | | 24.85 | 1.08 |
| | | Healthy controls | | | | | | | | | 33.47 | 0.56 | |
| | | DM mild NPDR | | | | | | FAZ area | SCP | Fovea | | 0.44 | 0.05 |
| | | Healthy controls | | | | | | | | | 0.25 | 0.02 | |
| | | DM mild NPDR | | | | | | FAZ area | DCP | Fovea | | 0.73 | 0.06 |
| | | Healthy controls | | | | | | | | | 0.34 | 0.02 | |

Continued

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|----------------------------|-----------------|--------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|----------|--------------|----------|-------------|-------|------|
| Czako et al. ⁵⁹ | Optovue, Avanti | DM mild NPDR | 58.5 | Cross-sec | 194 (97) | 58/39 | 3 × 3 | VD | SCP | Whole | 47.04 | 3.24 | |
| | | DM NDR | 58.5 | | | | | | | | | 48.94 | 3.33 |
| | | Healthy controls | 58.2 | | | | | | | | | 51.16 | 3.28 |
| | | DM mild NPDR | | | | | | | VD | SCP | Para-foveal | 48.47 | 3.93 |
| | | DM NDR | | | | | | | | | | 51.26 | 3.72 |
| | | Healthy controls | | | | | | | | | | 53.25 | 3.36 |
| | | DM mild NPDR | | | | | | | FAZ area | SCP | Fovea | 0.31 | 0.06 |
| | | DM NDR | | | | | | | | | | 0.29 | 0.07 |
| | | Healthy controls | | | | | | | | | | 0.28 | 0.06 |
| | | DM PDR | 65.9 | Cohort | 523 (Unknown) | 156/367 | 3 × 3 | VD | SCP | Un-known | | 34.77 | 0.70 |
| Kim et al. ⁶⁰ | Topcon, Triton | DM severe NPDR | 64.5 | | | | | | | | 35.27 | 0.84 | |
| | | DM moderate NPDR | 63.3 | | | | | | | | 35.14 | 0.79 | |
| | | DM mild NPDR | 67.1 | | | | | | | | 35.73 | 0.85 | |
| | | DM NDR | 65.7 | | | | | | | | 35.90 | 0.81 | |
| | | Healthy controls | 65.2 | | | | | | | | 35.95 | 0.59 | |
| | | DM PDR | | | | | | VD | DCP | Un-known | 23.05 | 3.07 | |
| | | DM severe NPDR | | | | | | | | | 24.18 | 3.76 | |
| | | DM moderate NPDR | | | | | | | | | 24.10 | 4.51 | |
| | | DM mild NPDR | | | | | | | | | 24.27 | 8.34 | |
| | | DM NDR | | | | | | | | | 24.20 | 4.38 | |
| | | Healthy controls | | | | | | | | | 24.87 | 4.35 | |
| | | DM PDR | | | | | | FAZ area | SCP | Fovea | 0.50 | 0.17 | |
| | | DM severe NPDR | | | | | | | | | 0.47 | 0.10 | |
| | | DM moderate NPDR | | | | | | | | | 0.42 | 0.11 | |
| | | DM mild NPDR | | | | | | | | | 0.41 | 0.10 | |
| DM NDR | | | | | | | | | 0.42 | 0.10 | | | |
| Healthy controls | | | | | | | | | 0.40 | 0.13 | | | |
| DM PDR | | | | | | FAZ area | DCP | Fovea | 0.64 | 0.19 | | | |
| DM severe NPDR | | | | | | | | | 0.60 | 0.15 | | | |
| DM moderate NPDR | | | | | | | | | 0.63 | 0.21 | | | |
| DM mild NPDR | | | | | | | | | 0.60 | 0.22 | | | |
| DM NDR | | | | | | | | | 0.55 | 0.18 | | | |
| Healthy controls | | | | | | | | | 0.52 | 0.14 | | | |

Continued

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|----------------------------|-----------------|--------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|--------|--------------|--------|-------------|-------|------|
| Koçer et al. ⁶¹ | Optovue, Avanti | DM PDR | 56.6 | Cross-sec | 128 (128) | 52/76 | 6 × 6 | VD | SCP | Whole | 45.30 | 3.70 | |
| | | DM severe NPDR | 56.8 | | | | | | | | | 46.90 | 2.60 |
| | | DM moderate NPDR | 53.9 | | | | | | | | | 47.00 | 2.90 |
| | | DM mild NPDR | 52.2 | | | | | | | | | 46.30 | 2.50 |
| | | DM NDR | 53.8 | | | | | | | | | 48.80 | 4.40 |
| | | Healthy controls | 53.9 | | | | | | | | | 49.90 | 3.20 |
| | | DM PDR | | | | | | | VD | SCP | Para-foveal | 45.10 | 4.60 |
| | | DM severe NPDR | | | | | | | | | | 47.40 | 2.80 |
| | | DM moderate NPDR | | | | | | | | | | 46.90 | 2.90 |
| | | DM mild NPDR | | | | | | | | | | 46.60 | 3.60 |
| | | DM NDR | | | | | | | | | | 49.90 | 5.20 |
| | | Healthy controls | | | | | | | | | | 52.00 | 4.20 |
| | | DM PDR | | | | | | | VD | SCP | Fovea | 14.70 | 6.30 |
| | | DM severe NPDR | | | | | | | | | | 16.40 | 5.30 |
| | | DM moderate NPDR | | | | | | | | | | 17.90 | 7.20 |
| | | DM mild NPDR | | | | | | | | | | 16.50 | 8.60 |
| | | DM NDR | | | | | | | | | | 17.70 | 7.10 |
| | | Healthy controls | | | | | | | | | | 21.20 | 6.00 |
| | | DM PDR | | | | | | | VD | DCP | Whole | 43.80 | 3.40 |
| | | DM severe NPDR | | | | | | | | | | 47.20 | 3.20 |
| | | DM moderate NPDR | | | | | | | | | | 45.90 | 4.40 |
| | | DM mild NPDR | | | | | | | | | | 46.70 | 5.20 |
| | | DM NDR | | | | | | | | | | 49.90 | 7.70 |
| | | Healthy controls | | | | | | | | | | 50.20 | 7.60 |
| | | DM PDR | | | | | | | VD | DCP | Para-foveal | 47.70 | 3.50 |
| | | DM severe NPDR | | | | | | | | | | 50.40 | 3.10 |
| | | DM moderate NPDR | | | | | | | | | | 49.90 | 3.30 |
| DM mild NPDR | | | | | | | | | | 51.00 | 3.50 | | |
| DM NDR | | | | | | | | | | 54.20 | 4.80 | | |
| Healthy controls | | | | | | | | | | 55.70 | 3.80 | | |
| DM PDR | | | | | | | VD | DCP | Fovea | 30.00 | 7.80 | | |
| DM severe NPDR | | | | | | | | | | 30.90 | 6.00 | | |
| DM moderate NPDR | | | | | | | | | | 30.80 | 5.90 | | |
| DM mild NPDR | | | | | | | | | | 29.40 | 10.40 | | |
| DM NDR | | | | | | | | | | 33.30 | 8.70 | | |
| Healthy controls | | | | | | | | | | 41.10 | 6.10 | | |
| DM PDR | | | | | | | FAZ area | SCP | Fovea | 0.34 | 0.13 | | |
| DM severe NPDR | | | | | | | | | | 0.33 | 0.09 | | |

Continued

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD |
|------------|-----------------|--------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|----------|--------------|-------------|-------|-------|
| | | DM moderate NPDR | | | | | | | | | 0.33 | 0.08 |
| | | DM mild NPDR | | | | | | | | | 0.36 | 0.15 |
| | | DM NDR | | | | | | | | | 0.30 | 0.11 |
| | | Healthy controls | | | | | | | | | 0.21 | 0.06 |
| | | DM mild NPDR | 57.0 | Cross-sec | 258 (132) | Unknown | 3×3 | VD | SCP | Whole | 40.40 | 5.20 |
| | | DM NDR | 53.0 | | | | | | | | 44.40 | 4.10 |
| | | Healthy controls | 53.0 | | | | | | | | 46.50 | 2.60 |
| | | DM mild NPDR | | | | | | VD | SCP | Para-foveal | 42.80 | 5.50 |
| | | DM NDR | | | | | | | | | 47.30 | 4.40 |
| | | Healthy controls | | | | | | | | | 49.40 | 3.10 |
| | Optovue, Avanti | DM mild NPDR | | | | | | VD | DCP | Whole | 45.30 | 4.50 |
| | | DM NDR | | | | | | | | | 49.10 | 3.70 |
| | | Healthy controls | | | | | | | | | 51.20 | 7.10 |
| | | DM mild NPDR | | | | | | VD | DCP | Para-foveal | 47.60 | 5.00 |
| | | DM NDR | | | | | | | | | 51.70 | 3.90 |
| | | Healthy controls | | | | | | | | | 53.80 | 7.40 |
| | | DM PDR | 57.4 | Cross-sec | 190 (190) | 103/87 | 3×3 | VD | SCP | Para-foveal | 39.88 | 4.82 |
| | | DM mild NPDR | 58.7 | | | | | | | | 43.97 | 4.18 |
| | | DM NDR | 60.7 | | | | | | | | 46.56 | 5.45 |
| | | Healthy controls | 57.8 | | | | | | | | 49.85 | 3.26 |
| | | DM PDR | | | | | | VD | DCP | Para-foveal | 44.40 | 4.31 |
| | | DM mild NPDR | | | | | | | | | 46.93 | 4.20 |
| | | DM NDR | | | | | | | | | 51.60 | 2.72 |
| | | Healthy controls | | | | | | | | | 43.97 | 4.18 |
| | Optovue, Avanti | DM PDR | | | | | | FAZ area | SCP | Fovea | 0.431 | 0.195 |
| | | DM mild NPDR | | | | | | | | | 0.386 | 0.109 |
| | | DM NDR | | | | | | | | | 0.307 | 0.101 |
| | | Healthy controls | | | | | | | | | 0.327 | 0.09 |
| | | DM PDR | | | | | | FAZ area | DCP | Fovea | 0.369 | 0.193 |
| | | DM mild NPDR | | | | | | | | | 0.293 | 0.083 |
| | | DM NDR | | | | | | | | | 0.253 | 0.054 |
| | | Healthy controls | | | | | | | | | 0.270 | 0.073 |

Continued

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|--|---------------------------|--------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|----------|--------------|-------------|-------------|-------|------|
| Shen et al. ⁶⁴ | Optovue, Avanti | DM mild NPDR | 56.4 | Cross-sec | 90 (90) | 49/41 | 3 × 3 | VD | SCP | Whole | 47.82 | 4.62 | |
| | | Healthy controls | 52.9 | | | | | | | | | 54.10 | 2.10 |
| | | DM mild NPDR | | | | | | | VD | SCP | Para-foveal | 49.30 | 5.12 |
| | | Healthy controls | | | | | | | VD | SCP | Fovea | 56.60 | 2.19 |
| | | DM mild NPDR | | | | | | | VD | SCP | Fovea | 28.38 | 5.57 |
| Simonett et al. ⁶⁵ | Optovue, Avanti | Healthy controls | | | | | | | | | 34.48 | 5.98 | |
| | | DM NDR/mild NPDR | 42.3 | Cross-sec | 51 (51) | 23/28 | 3 × 3 | VD | SCP | Para-foveal | 49.80 | 4.20 | |
| | | Healthy controls | 39.6 | | | | | | | | | 51.50 | 4.00 |
| | | DM NDR/mild NPDR | | | | | | VD | DCP | Para-foveal | Para-foveal | 57.00 | 3.10 |
| | | Healthy controls | | | | | | | FAZ area | SCP | Fovea | 60.70 | 2.40 |
| | | DM NDR/mild NPDR | | | | | | | FAZ area | DCP | Fovea | 0.26 | 0.12 |
| | | Healthy controls | | | | | | | | | | 0.26 | 0.11 |
| | | DM NDR/mild NPDR | | | | | | | | | | 0.40 | 0.15 |
| | | Healthy controls | | | | | | | | | | 0.38 | 0.15 |
| | | DM mild NPDR | 56.7 | Cross-sec | 77 (52) | 7/45 | 3 × 3 | VD | SCP | Whole | Whole | 18.45 | 1.73 |
| Somilleda-Ventura et al. ⁶⁶ | Zeiss, Cirrus HD-OCT 5000 | DM NDR | 55.7 | | | | | | | | 19.49 | 1.53 | |
| | | Healthy controls | 55.7 | | | | | | | | | 20.06 | 2.11 |
| | | DM mild NPDR | | | | | | VD | SCP | Para-foveal | Para-foveal | 19.90 | 1.80 |
| | | DM NDR | | | | | | | | | | 20.78 | 1.52 |
| | | Healthy controls | | | | | | | | | | 21.11 | 2.29 |
| | | DM mild NPDR | | | | | | VD | SCP | Fovea | Fovea | 7.00 | 2.07 |
| | | DM NDR | | | | | | | | | | 9.32 | 2.46 |
| | | Healthy controls | | | | | | | | | | 11.69 | 2.60 |
| | | DM mild NPDR | | | | | | FAZ area | SCP | Fovea | Fovea | 0.38 | 0.10 |
| | | DM NDR | | | | | | | | | | 0.28 | 0.09 |
| Healthy controls | | | | | | | | | | 0.22 | 0.10 | | |

Continued

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|--------------------------------|-----------------|--------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|--------|--------------|--------|-------------|-------|-------|
| Buyuktepe et al. ⁶⁷ | Optovue, Avanti | DM NPDR | 50.8 | Cross-sec | 52 (52) | | 6 × 6 | VD | SCP | Whole | 47.53 | 3.33 | |
| | | DM NDR | 55.5 | | 44 (44) | | | | | | | 45.36 | 13.28 |
| | | Healthy controls | 58.1 | | 20 (20) | | | | | | | 50.59 | 2.30 |
| | | DM NPDR | | | | | | | VD | SCP | Para-foveal | 55.02 | 5.67 |
| | | DM NDR | | | | | | | | | | 50.29 | 4.36 |
| | | Healthy controls | | | | | | | | | | 52.76 | 2.47 |
| | | DM NPDR | | | | | | | VD | SCP | Fovea | 19.13 | 6.19 |
| | | DM NDR | | | | | | | | | | 18.70 | 7.35 |
| | | Healthy controls | | | | | | | | | | 22.68 | 6.80 |
| | | DM NPDR | | | | | | | VD | DCP | Whole | 46.94 | 4.29 |
| | | DM NDR | | | | | | | | | | 50.46 | 5.99 |
| | | Healthy controls | | | | | | | | | | 49.25 | 3.56 |
| | | DM NPDR | | | | | | | VD | DCP | Para-foveal | 50.27 | 3.53 |
| | | DM NDR | | | | | | | | | | 54.76 | 4.43 |
| | | Healthy controls | | | | | | | | | | 53.56 | 2.73 |
| DM NPDR | | | | | | | VD | DCP | Fovea | 32.47 | 6.55 | | |
| DM NDR | | | | | | | | | | 37.10 | 3.72 | | |
| Healthy controls | | | | | | | | | | 41.57 | 4.32 | | |
| DM NPDR | | | | | | | FAZ area | SCP | Fovea | 0.327 | 0.107 | | |
| DM NDR | | | | | | | | | | 0.279 | 0.102 | | |
| Healthy controls | | | | | | | | | | 0.207 | 0.037 | | |

Continued

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|----------------------------|---------------------------|--------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|--------|--------------|-------------|-------------|-------|------|
| Veiby et al. ⁶⁸ | Nidek Co, RS-3000 AOCT | DM severe NPDR | 27.6 | Cross-sec | 483 (254) | 109/145 | 3 × 3 | VD | SCP | Fovea | 18.15 | 0.34 | |
| | | DM moderate NPDR | 27.1 | | | | | | | | | 16.94 | 2.22 |
| | | DM mild NPDR | 25.3 | | | | | | | | | 17.02 | 2.86 |
| | | DM NDR | 23.5 | | | | | | | | | 16.57 | 3.53 |
| | | Healthy controls | 23.9 | | | | | | | | | 17.98 | 3.52 |
| | | DM severe NPDR | | | | | | | VD | DCP | Fovea | 27.89 | 2.79 |
| | | DM moderate NPDR | | | | | | | | | | 33.23 | 2.91 |
| | | DM mild NPDR | | | | | | | | | | 35.53 | 1.92 |
| | | DM NDR | | | | | | | | | | 36.60 | 2.49 |
| | | Healthy controls | | | | | | | | | | 38.55 | 1.83 |
| | | DM severe NPDR | | | | | | | FAZ area | SCP | Fovea | 0.77 | 0.58 |
| | | DM moderate NPDR | | | | | | | | | | 0.29 | 0.15 |
| | | DM mild NPDR | | | | | | | | | | 0.28 | 0.12 |
| | | DM NDR | | | | | | | | | | 0.25 | 0.10 |
| Healthy controls | | | | | | | | | | 0.26 | 0.09 | | |
| Zeng et al. ⁶⁹ | Optovue, Avanti | DM severe NPDR | 56.5 | Cross-sec | 170 (170) | 89/81 | 6 × 6 | VD | SCP | Para-foveal | 44.57 | 4.88 | |
| | | DM moderate NPDR | 57.9 | | | | | | | | 48.42 | 4.58 | |
| | | DM mild NPDR | 56.9 | | | | | | | | 49.61 | 5.07 | |
| | | DM NDR | 59.6 | | | | | | | | 50.50 | 4.11 | |
| | | Healthy controls | 56.1 | | | | | | | | 52.79 | 3.29 | |
| | | DM severe NPDR | | | | | | | VD | DCP | Para-foveal | 48.15 | 4.42 |
| | | DM moderate NPDR | | | | | | | | | | 49.74 | 4.25 |
| | | DM mild NPDR | | | | | | | | | | 52.64 | 3.72 |
| | | DM NDR | | | | | | | | | | 52.72 | 4.62 |
| | | Healthy controls | | | | | | | | | | 55.62 | 4.60 |

Continued

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|--------------------------------------|-----------------|--------------------|------------------|--------------|-------------------------------------|-------------------------|----------------|----------|--------------|--------|-------------|-------|------|
| Li Rudvan et al. ⁷⁰ | Optovue, Avanti | Pre DM | Unknown | Cross-sec | 89 (89) | 45/54 | 3 × 3 | VD | SCP | Whole | 54.20 | 3.08 | |
| | | Healthy controls | | | | | | | | | | 54.29 | 2.89 |
| | | Pre DM | | | | | | | VD | SCP | Para-foveal | 56.48 | 3.53 |
| | | Healthy controls | | | | | | | | | | 56.68 | 3.18 |
| | | Pre DM | | | | | | | VD | SCP | Fovea | 28.71 | 6.08 |
| | | Healthy controls | | | | | | | | | | 29.78 | 5.17 |
| | | Pre DM | | | | | | | VD | DCP | Whole | 60.46 | 2.14 |
| | | Healthy controls | | | | | | | | | | 60.93 | 2.76 |
| | | Pre DM | | | | | | | VD | DCP | Para-foveal | 63.47 | 2.77 |
| | | Healthy controls | | | | | | | | | | 63.71 | 2.70 |
| Niestrata-Ortiz et al. ⁷¹ | Topcon, Triton | Pre DM | | | | | | VD | DCP | Fovea | 28.77 | 7.26 | |
| | | Healthy controls | | | | | | | | | 29.04 | 6.67 | |
| | | DM > 10 years | 16.0 | Cross-sec | 142 (142) | 81/61 | 3 × 3 | FAZ area | SCP | Fovea | 0.308 | 0.14 | |
| | | DM 5–10 years | 13.6 | | | | | | | | 0.293 | 0.12 | |
| | | DM < 5 years | 12.3 | | | | | | | | 0.315 | 0.116 | |
| | | Healthy controls | 11.8 | | | | | | | | 0.286 | 0.127 | |
| | | DM > 10 years | | | | | | | FAZ area | DCP | Fovea | 0.544 | 0.19 |
| | | DM 5–10 years | | | | | | | | | 0.524 | 0.16 | |
| | | DM < 5 years | | | | | | | | | 0.503 | 0.14 | |
| | | Healthy controls | | | | | | | | | 0.41 | 0.12 | |
| Oliverio et al. ⁷² | Topcon, Triton | T1DM NDR | 34.1 | Cross-sec | 300 (268) | 169/131 | 3 × 3 | VD | SCP | Fovea | 21.10 | 3.60 | |
| | | T2DM NDR | 61.5 | | | | | | | | 21.80 | 4.10 | |
| | | Healthy controls | 49.5 | | | | | | | | 22.60 | 5.10 | |
| | | T1DM NDR | | | | | | | VD | DCP | Fovea | 37.20 | 5.90 |
| | | T2DM NDR | | | | | | | | | 37.50 | 6.10 | |
| | | Healthy controls | | | | | | | | | 38.10 | 6.10 | |
| | | T1DM NDR | | | | | | | FAZ area | SCP | Fovea | 0.3 | 0.80 |
| | | T2DM NDR | | | | | | | | | 0.28 | 0.90 | |
| | | Healthy controls | | | | | | | | | 0.27 | 0.10 | |
| | | T1DM NDR | | | | | | | FAZ area | DCP | Fovea | 0.34 | 0.90 |
| T2DM NDR | | | | | | | | | 0.32 | 0.10 | | | |
| Healthy controls | | | | | | | | | 0.31 | 0.10 | | | |

Continued

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|--------------------------------------|-----------------|-------------------------|------------------|--------------|-------------------------------------|--------------------------|----------------|----------|--------------|-------------|-------------|-------|-------|
| Stulova et al. ⁷³ | Topcon, Triton | T1DM NDR | 26 | Case-control | 131(72) | 26/46 | 3×3 | VD | SVP | Para-foveal | 28.00 | 2.26 | |
| | | Healthy controls | 25 | | | | | | | | | 28.79 | 1.99 |
| | | T1DM NDR | | | | | | | VD | DCP | Para-foveal | 17.33 | 1.39 |
| | | Healthy controls | | | | | | | | | | 18.14 | 2.01 |
| | | T1DM NDR | | | | | | | FAZ area | SVP | Fovea | 0.272 | 0.095 |
| | | Healthy controls | | | | | | | | | | 0.254 | 0.076 |
| Niestrata-Ortiz et al. ⁷⁴ | Topcon, Triton | T1DM Male | 13.86 | Cross-sec | 142 (142) | 81/61 | 3×3 | FAZ area | SCP | Fovea | 0.266 | 0.180 | |
| | | T1DM Female | 13.68 | | | | | | | | | 0.342 | 0.118 |
| | | Healthy controls Male | 12.27 | | | | | | | | | 0.261 | 0.100 |
| | | Healthy controls Female | 10.53 | | | | | | | | | 0.348 | 0.261 |
| | | T1DM Male | | | | | | | FAZ area | SCP | Fovea | 0.474 | 0.138 |
| | | T1DM Female | | | | | | | | | | 0.572 | 0.167 |
| | | Healthy controls Male | | | | | | | | | | 0.281 | 0.111 |
| | | Healthy controls Female | | | | | | | | | | 0.572 | 0.167 |
| | | DME | 62.3 | Cross-sec | 50 (50) | 24/26 | | 3×3 | VD | SCP | Whole | 40.70 | 4.50 |
| | | Healthy controls | 61.8 | | | | | | | | | 50.20 | 3.60 |
| Toto et al. ⁷⁵ | Optovue, Avanti | DME | | | | | | | SCP | Para-foveal | 41.30 | 4.80 | |
| | | Healthy controls | | | | | | | | | | 51.70 | 4.30 |
| | | DME | | | | | | | | SCP | Fovea | 29.60 | 5.40 |
| | | Healthy controls | | | | | | | | | | 32.80 | 7.80 |
| | | DME | | | | | | | | DCP | Whole | 45.10 | 5.20 |
| | | Healthy controls | | | | | | | | | | 58.50 | 3.40 |
| | | DME | | | | | | | | DCP | Para-foveal | 47.90 | 5.10 |
| | | Healthy controls | | | | | | | | | | 61.10 | 4.30 |
| | | DME | | | | | | | | DCP | Fovea | 18.90 | 9.20 |
| | | Healthy controls | | | | | | | | | | 28.50 | 8.30 |

Continued

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|----------------------------------|-----------------|--------------------|------------------|------------------------|-------------------------------------|--------------------------|----------------|----------|--------------|-------------|-------------|-------|------|
| Liu et al. ⁷⁶ | Optovue, Avanti | Pregnant + GDM | 30.6 | Cross-sec | 179 (99) | 0/99 | 3 × 3 | VD | SCP | Whole | 48.20 | 2.60 | |
| | | Pregnant-GDM | 30.7 | | | | | | | | | 48.50 | 2.40 |
| | | Healthy controls | 30.6 | | | | | | | | | 50.40 | 1.50 |
| | | Pregnant + GDM | | | | | | | VD | DCP | Whole | 53.30 | 3.10 |
| | | Pregnant-GDM | | | | | | | | | | 53.90 | 2.60 |
| | | Healthy controls | | | | | | | | | | 50.60 | 3.50 |
| | | Pregnant + GDM | | | | | | | VD | SCP | Para-foveal | 51.50 | 2.60 |
| | | Pregnant-GDM | | | | | | | | | | 51.80 | 2.80 |
| | | Healthy controls | | | | | | | | | | 53.20 | 1.60 |
| | | Pregnant + GDM | | | | | | | VD | DCP | Para-foveal | 56.20 | 2.70 |
| | | Pregnant-GDM | | | | | | | | | | 57.10 | 2.70 |
| | | Healthy controls | | | | | | | | | | 53.00 | 3.60 |
| | | Pregnant + GDM | | | | | | | VD | SCP | Fovea | 16.50 | 6.10 |
| | | Pregnant-GDM | | | | | | | | | | 14.50 | 4.30 |
| Healthy controls | | | | | | | | | | 24.00 | 6.30 | | |
| Pregnant + GDM | | | | | | | VD | DCP | Fovea | 30.30 | 7.50 | | |
| Pregnant-GDM | | | | | | | | | | 27.90 | 6.80 | | |
| Healthy controls | | | | | | | | | | 32.20 | 6.90 | | |
| Pregnant + GDM | | | | | | | FAZ area | SCP | Fovea | 0.35 | 0.12 | | |
| Pregnant-GDM | | | | | | | | | | 0.39 | 0.1 | | |
| Healthy controls | | | | | | | | | | 0.31 | 0.11 | | |
| Pregnant + GDM | | | 34.0 | Cross-sec | 51 (51) | 0/51 | 3 × 3 | FAZ area | SCP | Fovea | 0.41 | 0.16 | |
| DM NDR | | | 34.0 | | | | | | | | 0.43 | 0.1 | |
| Healthy controls | | | 29.6 | | | | | | | | 0.38 | 0.11 | |
| Pregnant + GDM | | | | | | | | FAZ area | DCP | Fovea | 0.69 | 0.16 | |
| DM NDR | | | | | | | | | | | 0.79 | 0.25 | |
| Healthy controls | | | | | | | | | | | 0.78 | 0.23 | |
| Non-diabetes phacoemulsification | | | 57.2 | Case-control | 60 (60) | 15/45 | 6 × 6 | VD | SCP | Fovea | 9.27 | 7.37 | |
| Diabetes phacoemulsification | | | 54.5 | | | | | | | | 13.37 | 6.45 | |
| Aschauer et al. ⁷⁹ | Optovue, Avanti | T2DM +/-DR | 57 | Cohort (baseline data) | 117 (59) | 38/21 | 6 × 6 | VD | SVC | Para-foveal | 51.00 | 5.77 | |
| | | | | | | | | VD | DVC | Para-foveal | 52.57 | 4.11 | |
| | | | | | | | | FAZ area | SVC | Fovea | 0.25 | 0.12 | |

Continued

| References | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/ females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | | |
|--------------------------|----------------|--------------------|------------------|------------------------|-------------------------------------|--------------------------|----------------|--------|--------------|-------------|-------------|-------|------|------|
| Sun et al. ⁸⁰ | Topcon, Triton | Diabetes NDR | 62.9 | Cohort (baseline data) | 205(129) | 61/68 | 3×3 | VD | SCP | Para-foveal | 76.29 | 7.00 | | |
| | | | | | | | | | VD | DCP | Para-foveal | 33.99 | 3.57 | |
| | | | | | | | | | | FAZ area | SCP | Fovea | 0.40 | 0.13 |
| | | | | | | | | | | FAZ area | DCP | Fovea | 1.09 | 0.43 |

Table 1. Study characteristics of studies included looking at patients with diabetes. VD data is given as percentage (%), FAZ data is given as mm². DM, diabetes mellitus; NDR, no diabetic retinopathy; VD, vessel density; FAZ, foveal avascular zone; cross-sec, cross-sectional; SRL, superficial retinal layer; HD-OCT, high-definition optical coherence tomography; NPDR, non-proliferative diabetic retinopathy; DRL, deep retinal layer; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; PDR, proliferative diabetic retinopathy; SRVP, superficial retinal vascular plexus; DRVP, deep retinal vascular plexus; DME, diabetic macular oedema; GDM, gestational diabetes mellitus.

| Author, ref | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD |
|----------------------------|---------------------------|--------------------|------------------|--------------|-------------------------------------|-------------------------|----------------|----------|--------------|-------------|-------|------|
| Bulut et al. ⁸¹ | Not specified | Late AD | 74.2 | Cross-sec | 52 (52) | 24/28 | 6×6 | VD | SVP | Whole | 45.50 | 3.85 |
| | | Healthy controls | 72.6 | | | | | | | | 48.67 | 3.29 |
| | | Late AD | | | | | | VD | SVP | Para-foveal | 47.96 | 4.86 |
| | | Healthy controls | | | | | | | | | 51.12 | 4.10 |
| | | Late AD | | | | | | VD | SVP | Fovea | 29.04 | 7.17 |
| | | Healthy controls | | | | | | | | | 34.80 | 6.76 |
| Chua et al. ⁸² | Cirrus HD-OCT 5000 | Late AD | 74.9 | Cross-sec | 90 (90) | 44/46 | 3×3 | VD | SCP | Para-foveal | 14.78 | 1.14 |
| | | MCI | 77.9 | | | | | | | | 14.94 | 1.02 |
| | | Healthy controls | 76.7 | | | | | | | | 15.66 | 0.96 |
| | | Late AD | | | | | | VD | DCP | Para-foveal | 20.42 | 1.60 |
| | | MCI | | | | | | | | | 20.81 | 1.65 |
| | | Healthy controls | | | | | | | | | 21.54 | 1.55 |
| | | Late AD | | | | | | FAZ area | SCP | Fovea | 0.34 | 0.14 |
| | | MCI | | | | | | | | | 0.35 | 0.12 |
| | | Healthy controls | | | | | | | | | 0.31 | 0.12 |
| | | Late AD | | | | | | FAZ area | DCP | Fovea | 1.13 | 0.43 |
| | | MCI | | | | | | | | | 1.24 | 0.39 |
| | | Healthy controls | | | | | | | | | 1.11 | 0.47 |
| Haan et al. ⁸³ | Zeiss, Cirrus HD-OCT 5000 | Late AD | 65.4 | Cross-sec | 86 (86) | 49/37 | 6×6 | VD | SCP | Para-foveal | 17.30 | 1.50 |
| | | Healthy controls | 60.6 | | | | | | | | 17.40 | 1.20 |
| | | Late AD | | | | | | FAZ area | SCP | Fovea | 0.24 | 0.06 |
| | | Healthy controls | | | | | | | | | 0.26 | 0.08 |
| Lahme et al. ⁸⁴ | Optovue, Avanti | Early AD | 70.0 | Cross-sec | 74 (74) | 29/44 | 3×3 | VD | SCP | Whole | 48.77 | 3.92 |
| | | Healthy Controls | 66.1 | | | | | | | | 51.64 | 3.28 |
| | | Early AD | | | | | | VD | SCP | Para-foveal | 50.93 | 4.05 |
| | | Healthy Controls | | | | | | | | | 53.55 | 3.31 |
| | | Early AD | | | | | | VD | SCP | Fovea | 29.40 | 5.72 |
| | | Healthy Controls | | | | | | | | | 31.06 | 5.35 |
| | | Early AD | | | | | | VD | DCP | Whole | 55.35 | 3.16 |
| | | Healthy Controls | | | | | | | | | 56.72 | 2.21 |
| | | Early AD | | | | | | VD | DCP | Para-foveal | 57.97 | 3.30 |
| | | Healthy Controls | | | | | | | | | 58.38 | 4.64 |
| | | Early AD | | | | | | VD | DCP | Fovea | 31.21 | 6.60 |
| | | Healthy Controls | | | | | | | | | 29.32 | 6.67 |
| | | Early AD | | | | | | FAZ area | SCP | Fovea | 0.28 | 0.08 |
| | | Healthy Controls | | | | | | | | | 0.28 | 0.09 |
| Early AD | | | | | | FAZ area | DCP | Fovea | 0.32 | 0.10 | | |
| Healthy Controls | | | | | | | | | 0.33 | 0.14 | | |

Continued

| Author, ref | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|------------------------------|---------------------------|--------------------|------------------|--------------|-------------------------------------|-------------------------|----------------|----------|--------------|-------------|-------------|-------|------|
| Robbins et al. ⁸⁵ | Zeiss, Cirrus HD-OCT 5000 | Early AD | 62.4 | Cross-sec | 224 (122) | 44/78 | 3 × 3 | VD | SCP | Whole | 20.15 | 1.97 | |
| | | Late AD | 76.9 | | | | | | | | 18.55 | 2.45 | |
| | | Healthy controls | 68.1 | | | | | | | | 20.36 | 1.50 | |
| | | Early AD | | | | | | VD | SCP | Para-foveal | 21.22 | 1.90 | |
| | | Late AD | | | | | | | | | 19.56 | 2.46 | |
| | | Healthy controls | | | | | | | | | 21.40 | 1.47 | |
| | | Early AD | | | | | | FAZ area | SCP | Fovea | 0.21 | 0.09 | |
| | | Late AD | | | | | | | | | 0.25 | 0.14 | |
| | | Healthy controls | | | | | | | | | 0.23 | 0.10 | |
| | | Early AD | | | | | | 6 × 6 | VD | SCP | Whole | 17.97 | 1.09 |
| | | Late AD | | | | | | | | | 16.96 | 2.06 | |
| | | Healthy controls | | | | | | | | | 17.71 | 1.13 | |
| | | Early AD | | | | | | | VD | SCP | Para-foveal | 18.10 | 1.36 |
| | | Late AD | | | | | | | | | 16.90 | 2.55 | |
| Healthy controls | | | | | | | | | 17.72 | 1.34 | | | |
| Wang X et al. ⁸⁶ | Optovue, Avanti | Late AD | 71.8 | Cross-sec | 158 (158) | 96/62 | 3 × 3 | VD | SCP | Whole | 44.66 | 3.36 | |
| | | MCI | 72.7 | | | | | | | | 44.00 | 3.07 | |
| | | Healthy controls | 69.5 | | | | | | | | 46.82 | 2.08 | |
| | | Late AD | | | | | | VD | DCP | Whole | 49.42 | 3.40 | |
| | | MCI | | | | | | | | | 49.57 | 2.89 | |
| | | Healthy controls | | | | | | | | | 50.89 | 2.86 | |
| | | Late AD | | | | | | VD | SCP | Para-foveal | 47.70 | 3.76 | |
| | | MCI | | | | | | | | | 47.12 | 3.35 | |
| | | Healthy controls | | | | | | | | | 49.86 | 2.26 | |
| | | Late AD | | | | | | VD | DCP | Para-foveal | 52.02 | 3.65 | |
| | | MCI | | | | | | | | | 52.36 | 2.96 | |
| | | Healthy controls | | | | | | | | | 53.40 | 2.77 | |
| | | Late AD | | | | | | | VD | SCP | Fovea | 15.89 | 5.34 |
| | | MCI | | | | | | | | | 14.09 | 5.21 | |
| | | Healthy controls | | | | | | | | | 16.18 | 5.27 | |
| | | Late AD | | | | | | | VD | DCP | Fovea | 28.53 | 6.80 |
| MCI | | | | | | | | | 26.83 | 7.11 | | | |
| Healthy controls | | | | | | | | | 28.94 | 6.70 | | | |
| Wu et al. ⁸⁷ | Optovue, Avanti | Late AD | 69.9 | Cross-sec | 88 (60) | 33/27 | 6 × 6 | VD | SCP | Para-foveal | 49.56 | 2.81 | |
| | | MCI | 67.8 | | | | | | | | 50.37 | 2.33 | |
| | | Healthy controls | 68.7 | | | | | | | | 50.47 | 2.73 | |
| | | Late AD | | | | | | VD | DCP | Para-foveal | 43.10 | 2.75 | |
| | | MCI | | | | | | | | | 48.09 | 3.88 | |
| | | Healthy controls | | | | | | | | | 52.28 | 2.89 | |
| | | Late AD | | | | | | FAZ area | Full | Fovea | 0.44 | 0.08 | |
| | | MCI | | | | | | | | | 0.37 | 0.06 | |
| Healthy controls | | | | | | | | | 0.26 | 0.07 | | | |

Continued

| Author, ref | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD |
|-------------------------------|---------------------------|--------------------|------------------|--------------|-------------------------------------|-------------------------|----------------|----------|--------------|-------------|-------|------|
| Zabel et al. ⁸⁸ | Optovue, Avanti | Late AD | 74.1 | Cross-sec | 81 (81) | 24/47 | 6×6 | VD | SVP | Whole | 47.92 | 3.04 |
| | | POAG | 71.9 | | | | | | | | 39.72 | 4.97 |
| | | Healthy controls | 74.3 | | | | | | | | 48.15 | 3.03 |
| | | Late AD | | | | | | VD | DVP | Whole | 43.95 | 5.15 |
| | | POAG | | | | | | | | | 47.44 | 6.07 |
| | | Healthy controls | | | | | | | | | 49.46 | 4.27 |
| Zabel et al. ⁸⁹ | Optovue, Avanti | Late AD | 74.4 | Cross-sec | 168 (108) | 41/68 | 6×6 | VD | SVP | Whole | 46.80 | 3.20 |
| | | POAG | 72.1 | | | | | | | | 42.40 | 5.40 |
| | | Healthy controls | 71.4 | | | | | | | | 48.50 | 3.40 |
| | | Late AD | | | | | | VD | DVP | Whole | 45.00 | 4.70 |
| | | POAG | | | | | | | | | 47.60 | 5.20 |
| | | Healthy controls | | | | | | | | | 48.50 | 5.10 |
| | | Late AD | | | | | | VD | SVP | Para-foveal | 49.40 | 4.00 |
| | | POAG | | | | | | | | | 46.70 | 5.50 |
| | | Healthy controls | | | | | | | | | 51.40 | 4.30 |
| | | Late AD | | | | | | VD | DVP | Para-foveal | 51.70 | 3.60 |
| | | POAG | | | | | | | | | 53.50 | 4.10 |
| | | Healthy controls | | | | | | | | | 53.20 | 3.40 |
| | | Late AD | | | | | | VD | SVP | Fovea | 19.70 | 6.20 |
| | | POAG | | | | | | | | | 18.40 | 5.70 |
| | | Healthy controls | | | | | | | | | 23.90 | 6.60 |
| | | Late AD | | | | | | VD | DVP | Fovea | 34.30 | 7.30 |
| POAG | | | | | | | | | 34.70 | 7.60 | | |
| Healthy controls | | | | | | | | | 39.60 | 5.60 | | |
| Yan et al. 2021 ⁹⁰ | Optovue, Avanti | Mild AD | Un-known | Cross-sec | 116(63) | Unknown | 3×3 | VD | SCP | Fovea | 15.80 | 6.92 |
| | | Healthy controls | | | | | | | | | 15.94 | 6.26 |
| | | Mild AD | | | | | | VD | DCP | Fovea | 28.80 | 8.15 |
| | | Healthy controls | | | | | | | | | 28.90 | 8.30 |
| | | Mild AD | | | | | | VD | SCP | Para-foveal | 46.62 | 5.14 |
| | | Healthy controls | | | | | | | | | 48.61 | 3.79 |
| | | Mild AD | | | | | | VD | DCP | Para-foveal | 51.57 | 3.68 |
| | | Healthy controls | | | | | | | | | 52.63 | 3.86 |
| Shin et al. ⁹¹ | Zeiss, Cirrus HD-OCT 5000 | MCI | 72.8 | Case control | 77 (55) | 42/13 | 6×6 | VD | SCP | Para-foveal | 14.00 | 3.90 |
| | | Healthy controls | 69.0 | | | | | | | | 25.50 | 1.90 |
| | | MCI | | | | | | VD | DCP | Para-foveal | 16.30 | 2.50 |
| | | Healthy controls | | | | | | | | | 25.60 | 1.80 |
| | | MCI | | | | | | FAZ area | SCP | Fovea | 0.31 | 0.11 |
| | | Healthy controls | | | | | | | | | 0.27 | 0.09 |
| | | MCI | | | | | | FAZ area | DCP | Fovea | 0.95 | 0.24 |
| | | Healthy controls | | | | | | | | | 0.80 | 0.20 |

Continued

| Author, ref | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD |
|------------------------------|---------------------------|--------------------|------------------|--------------|-------------------------------------|-------------------------|----------------|----------|--------------|-------------|-------|------|
| Rascuna et al. ⁹² | Optovue, Avanti | PD | 61.5 | Cross-sec | 111 (57) | 32/25 | 3×3 | VD | SCP | Whole | 44.60 | 4.40 |
| | | iRBD | 58.8 | | | | | | | | 43.00 | 4.60 |
| | | Healthy controls | 65.1 | | | | | | | | 43.90 | 3.80 |
| | | PD | | | | | | VD | DCP | Whole | 47.80 | 4.30 |
| | | iRBD | | | | | | | | | 50.50 | 3.10 |
| | | Healthy controls | | | | | | | | | 46.10 | 4.30 |
| | | PD | | | | | | VD | SCP | Para-foveal | 46.90 | 4.50 |
| | | iRBD | | | | | | | | | 45.70 | 5.10 |
| | | Healthy controls | | | | | | | | | 46.10 | 4.30 |
| | | PD | | | | | | VD | DCP | Para-foveal | 49.80 | 4.50 |
| | | iRBD | | | | | | | | | 52.50 | 3.40 |
| | | Healthy controls | | | | | | | | | 49.90 | 3.60 |
| | | PD | | | | | | VD | SCP | Fovea | 19.30 | 5.70 |
| | | iRBD | | | | | | | | | 15.60 | 4.80 |
| | | Healthy controls | | | | | | | | | 18.40 | 5.90 |
| PD | | | | | | VD | DCP | Fovea | 33.80 | 6.60 | | |
| iRBD | | | | | | | | | 31.60 | 5.80 | | |
| Healthy controls | | | | | | | | | 32.90 | 7.90 | | |
| Robbins et al. ⁹³ | Zeiss, Cirrus HD-OCT 5000 | PD | 71.7 | Cross-sec | 372 (206) | 116/90 | 6×6 | VD | SCP | Whole | 17.34 | 1.38 |
| | | Healthy controls | 70.9 | | | | | | | | 17.69 | 1.46 |
| | | PD | | | | | | VD | SCP | Para-foveal | 17.17 | 1.74 |
| | | Healthy controls | | | | | | | | | 17.75 | 1.68 |
| | | PD | | | | | | FAZ area | SCP | Fovea | 0.22 | 0.10 |
| Healthy controls | | | | | | | | | 0.23 | 0.11 | | |
| Zou et al. ⁹⁴ | Zeiss, Angio-plex | PD | 61.9 | Cross-sec | 70 (70) | 36/34 | 6×6 | FAZ area | SCP | Fovea | 0.31 | 0.12 |
| | | Healthy controls | 60.2 | | | | | | | | 0.29 | 0.10 |
| Liu B et al. ⁹⁵ | Optovue, Avanti | Stroke | 62.0 | Cross-sec | 384 (384) | 210/174 | 6×6 | VD | SCP | Whole | 47.45 | 4.35 |
| | | Healthy controls | 61.7 | | | | | | | | 49.44 | 3.71 |
| | | Stroke | | | | | | VD | DCP | Whole | 47.64 | 6.07 |
| | | Healthy controls | | | | | | | | | 50.75 | 6.29 |
| | | Stroke | | | | | | VD | SCP | Para-foveal | 49.23 | 5.56 |
| | | Healthy controls | | | | | | | | | 51.78 | 4.67 |
| | | Stroke | | | | | | VD | DCP | Para-foveal | 52.26 | 5.10 |
| | | Healthy controls | | | | | | | | | 55.17 | 4.70 |
| | | Stroke | | | | | | VD | SCP | Fovea | 17.73 | 6.72 |
| | | Healthy controls | | | | | | | | | 18.55 | 7.26 |
| | | Stroke | | | | | | VD | DCP | Fovea | 32.72 | 7.36 |
| Healthy controls | | | | | | | | | 32.67 | 7.45 | | |

Continued

| Author, ref | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|--------------------------------|------------------------|------------------------------|------------------|--------------|-------------------------------------|-------------------------|----------------|----------|--------------|-------------|-------------|-------|------|
| Aly et al. ⁹⁶ | Optovue, Avanti | NMOSD-ON | 46.6 | Cross-sec | 114/58 | 13/45 | 6×6 | VD | SVC | Para-foveal | 51.00 | 3.80 | |
| | | NMOSD + ON | 46.6 | | | | | | | | 47.40 | 4.30 | |
| | | MS-ON | 38.0 | | | | | | | | 51.80 | 2.60 | |
| | | MS + ON | 38.0 | | | | | | | | 50.40 | 3.70 | |
| | | Healthy controls | 42.0 | | | | | | | | 53.30 | 2.50 | |
| | | NMOSD-ON | | | | | | | VD | DVC | Para-foveal | 56.90 | 5.10 |
| | | NMOSD + ON | | | | | | | | | 57.00 | 3.90 | |
| | | MS-ON | | | | | | | | | 57.20 | 5.70 | |
| | | MS + ON | | | | | | | | | 59.10 | 3.90 | |
| | | Healthy controls | | | | | | | | | 57.30 | 5.50 | |
| | | NMOSD-ON | | | | | | | FAZ area | SVC | Fovea | 0.29 | 0.09 |
| | | NMOSD + ON | | | | | | | | | 0.32 | 0.09 | |
| | | MS-ON | | | | | | | | | 0.22 | 0.10 | |
| | | MS + ON | | | | | | | | | 0.28 | 0.14 | |
| Healthy controls | | | | | | | | | 0.20 | 0.07 | | | |
| Cordon et al. ⁹⁷ | Topcon, Triton | MS-ON | 41.7 | Cross-sec | 241 (241) | 32/209 | 6×6 | VD | SVP | Para-foveal | 21.45 | 4.51 | |
| | | Healthy controls | 41.8 | | | | | | | | 21.89 | 4.80 | |
| Karaküçük et al. ⁹⁸ | Topcon, Triton | MS-ON | 36.5 | Cross-sec | 130 (130) | 91/39 | 6×6 | FAZ area | SCP | Fovea | 0.15 | 0.05 | |
| | | Healthy controls | 35.3 | | | | | | | | 0.16 | 0.07 | |
| | | MS-ON | | | | | | FAZ area | DCP | Fovea | 0.23 | 0.05 | |
| | | Healthy controls | | | | | | | | | 0.24 | 0.13 | |
| Yilmaz et al. ⁹⁹ | Nidek Co, RS-3000 AOCT | MS + ON | 39.3 | Cross-sec | 216 (108) | 20/88 | 4.5×4.5 | VD | SCP | Whole | 38.05 | 4.97 | |
| | | MS-ON | 39.3 | | | | | | | | 41.25 | 4.42 | |
| | | Healthy controls | 38.6 | | | | | | | | 42.35 | 2.68 | |
| | | MS + ON | | | | | | VD | DCP | Whole | 32.11 | 7.81 | |
| | | MS-ON | | | | | | | | | 34.69 | 5.96 | |
| | | Healthy controls | | | | | | | | | 38.21 | 4.53 | |
| | | MS + ON | | | | | | FAZ area | SCP | Fovea | 0.34 | 0.11 | |
| | | MS-ON | | | | | | | | | 0.33 | 0.13 | |
| Healthy controls | | | | | | | | | 0.30 | 0.09 | | | |
| Crisuolo et al. ¹⁰⁰ | Optovue, Avanti | aMCI | 73.0 | Cross-sec | 112 (56) | 26/30 | 6×6 | VD | SCP | Whole | 44.92 | 5.04 | |
| | | Healthy controls | 73.1 | | | | | | | | 48.12 | 4.53 | |
| | | aMCI | | | | | | | VD | DCP | Whole | 45.13 | 6.67 |
| | | Healthy controls | | | | | | | | | 50.58 | 4.69 | |
| | | aMCI | | | | | | | FAZ Area | Full | Fovea | 0.28 | 0.12 |
| | | Healthy controls | | | | | | | | | 0.19 | 0.06 | |
| Zhang Y et al. ¹⁰¹ | Optovue, Avanti | Large artery atherosclerosis | 60.1 | Cross-sec | 180 (180) | 134/46 | 6×6 | VD | SCP | Whole | 45.59 | 4.26 | |
| | | Small vessel occlusion | 58.8 | | | | | | | | 46.72 | 3.13 | |
| | | Healthy controls | 59.0 | | | | | | | | 45.65 | 2.82 | |
| | | Large artery atherosclerosis | | | | | | | VD | DCP | Whole | 47.49 | 3.12 |
| | | Small vessel occlusion | | | | | | | | | 48.11 | 3.70 | |
| | | Healthy controls | | | | | | | | | 49.46 | 3.14 | |

Continued

| Author, ref | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|-----------------------------------|---------------------------|----------------------------|------------------|--------------|-------------------------------------|-------------------------|----------------|--------|--------------|-------------|-------------|-------|------|
| Wang et al. ¹⁰² | Optovue, Avanti | CSVD | 63.9 | Cross-sec | 152 (77) | 41/36 | 3×3 | FAZ | DCP | Fovea | 0.33 | 0.13 | |
| | | Healthy controls | 61.3 | | | | | | | | 0.34 | 0.14 | |
| Zhang et al. ¹⁰³ | Zeiss, Cirrus HD-OCT 5000 | Cerebrovascular disease | 56.0 | Cross-sec | 295 (165) | 118/47 | 6×6 | VD | SCP | Para-foveal | 16.21 | 2.11 | |
| | | Healthy controls | 53.2 | | | | | | | | 18.19 | 1.07 | |
| | | Cerebrovascular disease | | | | | | | VD | SCP | Fovea | 6.93 | 2.96 |
| | | Healthy controls | | | | | | | | | | 8.81 | 2.84 |
| | | Cerebrovascular disease | | | | | | | FAZ area | SCP | Fovea | 0.306 | 0.12 |
| | | Healthy controls | | | | | | | | | | 0.306 | 0.11 |
| Kazanci et al. ¹⁰⁴ | Optovue, Avanti | β-thalassemia | 13.6 | Cross-sec | 62 (62) | 30/32 | 6×6 | VD | SCP | Whole | 51.58 | 2.01 | |
| | | Healthy controls | 12.6 | | | | | | | | 51.90 | 2.08 | |
| | | β-thalassemia | | | | | | | VD | DCP | Whole | 53.44 | 5.80 |
| | | Healthy controls | | | | | | | | | 55.54 | 5.58 | |
| | | β-thalassemia | | | | | | | VD | SCP | Fovea | 21.67 | 6.65 |
| | | Healthy controls | | | | | | | | | 22.90 | 6.11 | |
| | | β-thalassemia | | | | | | | VD | DCP | Fovea | 39.55 | 7.95 |
| | | Healthy controls | | | | | | | | | 38.98 | 8.54 | |
| | | β-thalassemia | | | | | | | VD | SCP | Para-foveal | 54.05 | 2.61 |
| | | Healthy controls | | | | | | | | | 54.40 | 3.76 | |
| | | β-thalassemia | | | | | | | VD | DCP | Para-foveal | 56.91 | 4.81 |
| | | Healthy controls | | | | | | | | | 58.62 | 4.56 | |
| | | β-thalassemia | | | | | | | FAZ area | SCP | Fovea | 0.265 | 0.11 |
| | | Healthy controls | | | | | | | | | 0.296 | 0.12 | |
| Peng et al. ¹⁰⁵ | Optovue, Avanti | CKD | 62.4 | Case control | 326 (326) | 184/142 | 3×3 | VD | SVP | Para-foveal | 46.90 | 4.50 | |
| | | Healthy controls | 63.0 | | | | | | | | 49.00 | 3.70 | |
| | | CKD | | | | | | | VD | DVP | Para-foveal | 50.90 | 3.90 |
| | | Healthy controls | | | | | | | | | 52.00 | 3.10 | |
| Wang et al. ¹⁰⁶ | Topcon, Triton | DM moderate-severe CKD | 72.6 | Cross-sec | 874 (874) | 353/521 | 3×3 | VD | SCP | Whole | 44.50 | 1.30 | |
| | | DM mild CKD | 65.0 | | | | | | | | 45.3 | 1.8 | |
| | | DM no CKD | 60.4 | | | | | | | | 45.7 | 1.5 | |
| | | DM moderate-severe CKD | | | | | | | VD | SCP | Para-foveal | 47.2 | 1.7 |
| | | DM mild CKD | | | | | | | | | 48.4 | 1.9 | |
| | | DM no CKD | | | | | | | | | 49.1 | 2.1 | |
| | | DM moderate-severe CKD | | | | | | | VD | SCP | Fovea | 20.4 | 5.3 |
| | | DM mild CKD | | | | | | | | | 19.3 | 5.2 | |
| DM no CKD | | | | | | | | | 20.1 | 5.0 | | | |
| Cankurtaran et al. ¹⁰⁷ | Optovue, Avanti | Diabetes normo-albuminuria | 55.7 | Cross-sec | 137 (137) | 69/68 | 6×6 | VD | SCP | Whole | 49.70 | 2.71 | |
| | | Diabetes micro-albuminuria | 56.7 | | | | | | | | 47.27 | 3.99 | |
| | | Healthy controls | 54.8 | | | | | | | | 50.43 | 2.61 | |

Continued

| Author, ref | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD |
|----------------------------------|------------------------|-------------------------------|------------------|--------------|-------------------------------------|-------------------------|----------------|----------|--------------|-------------|-------|-------|
| | | Diabetes normo-albuminuria | | | | | | VD | DCP | Whole | 50.43 | 5.76 |
| | | Diabetes micro-albuminuria | | | | | | | | | 49.08 | 7.06 |
| | | Healthy controls | | | | | | | | | 53.59 | 6.04 |
| | | Diabetes normo-albuminuria | | | | | | VD | SCP | Para-foveal | 52.25 | 3.64 |
| | | Diabetes micro-albuminuria | | | | | | | | | 49.88 | 4.87 |
| | | Healthy controls | | | | | | | | | 53.44 | 3.57 |
| | | Diabetes normo-albuminuria | | | | | | VD | DCP | Para-foveal | 55.30 | 4.19 |
| | | Diabetes micro-albuminuria | | | | | | | | | 53.61 | 5.04 |
| | | Healthy controls | | | | | | | | | 55.97 | 4.61 |
| | | Diabetes normo-albuminuria | | | | | | VD | SCP | Fovea | 18.52 | 5.08 |
| | | Diabetes micro-albuminuria | | | | | | | | | 17.94 | 6.04 |
| | | Healthy controls | | | | | | | | | 2.13 | 5.81 |
| | | Diabetes normo-albuminuria | | | | | | VD | DCP | Fovea | 34.29 | 5.89 |
| | | Diabetes micro-albuminuria | | | | | | | | | 33.94 | 8.61 |
| Healthy controls | | | | | | | | | 37.52 | 6.85 | | |
| Değirmenci et al. ¹⁰⁸ | Optovue, Avanti | Behcet's-ocular involvement | 45.7 | Cross-sec | 23 (12) | 27/15 | 6×6 | FAZ area | SCP | Fovea | 0.331 | 0.121 |
| | | Healthy controls | 51.4 | | 49 (29) | | | | | | 0.240 | 0.072 |
| | | Behcet's-ocular involvement | | | | | | FAZ area | DCP | Fovea | 0.352 | 0.126 |
| | | Healthy controls | | | | | | | | | 0.257 | 0.070 |
| Smid et al. ¹⁰⁹ | Heidelberg, Spectralis | Behcet's + ocular involvement | 51.0 | Cross-sec | 68 (68) | 38/20 | 3×3 | VD | SCP | Para-foveal | 30.0 | 9.00 |
| | | Behcet's-ocular involvement | 48.0 | | | | | | | | 36.00 | 4.00 |
| | | Healthy controls | 44.0 | | | | | | | | 38.90 | 1.60 |
| | | Behcet's + ocular involvement | | | | | | VD | DCP | Para-foveal | 25.00 | 7.00 |
| | | Behcet's-ocular involvement | | | | | | | | | 30.00 | 4.00 |
| | | Healthy controls | | | | | | | | | 33.50 | 1.90 |
| Yilmaz et al. ¹¹⁰ | Optovue, Avanti | Behcet's + ocular involvement | 36.0 | Cross-sec | 70 (70) | 26/44 | 6×6 | VD | SCP | Para-foveal | 41.70 | 6.90 |
| | | Behcet's-ocular involvement | 40.1 | | | | | | | | 47.30 | 4.40 |
| | | Healthy controls | 39.6 | | | | | | | | 47.90 | 7.20 |
| | | Behcet's + ocular involvement | | | | | | VD | SCP | Fovea | 20.10 | 7.30 |

Continued

| Author, ref | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD |
|-------------------------------|------------------------|-------------------------------|------------------|--------------|-------------------------------------|-------------------------|----------------|----------|--------------|-------------|-------|-------|
| | | Behcet's-ocular involvement | | | | | | | | | 18.90 | 9.90 |
| | | Healthy controls | | | | | | | | | 19.50 | 9.40 |
| | | Behcet's + ocular involvement | | | | | | VD | DCP | Para-foveal | 47.20 | 6.30 |
| | | Behcet's-ocular involvement | | | | | | | | | 52.70 | 3.70 |
| | | Healthy controls | | | | | | | | | 52.90 | 4.20 |
| | | Behcet's + ocular involvement | | | | | | VD | DCP | Fovea | 32.80 | 8.90 |
| | | Behcet's-ocular involvement | | | | | | | | | 34.50 | 10.00 |
| | | Healthy controls | | | | | | | | | 32.11 | 7.81 |
| Aksoy et al. ¹¹¹ | Optovue, Avanti | Uveitis | 38.0 | Cross-sec | 65 (65) | 33/32 | 6×6 | VD | SCP | Para-foveal | 49.06 | 5.56 |
| | | Healthy controls | 37.0 | | | | | | | | 55.85 | 2.93 |
| | | Uveitis | | | | | | VD | SCP | Fovea | 32.57 | 5.43 |
| | | Healthy controls | | | | | | | | | 32.59 | 4.07 |
| | | Uveitis | | | | | | VD | DCP | Para-foveal | 55.60 | 7.22 |
| | | Healthy controls | | | | | | | | | 66.02 | 1.79 |
| | | Uveitis | | | | | | VD | DCP | Fovea | 34.06 | 4.49 |
| | | Healthy controls | | | | | | | | | 34.91 | 7.81 |
| Agarwal et al. ¹¹² | Topcon, Triton | Uveitis | 34.7 | Cross-sec | 68 (50) | 29/21 | 3×3 | FAZ area | SCP | Fovea | 0.34 | 0.08 |
| | | Healthy controls | 33.6 | | | | | | | | 0.26 | 0.08 |
| Kim et al. ⁶ | Zeiss, Prototype | Uveitis | Unknown | Cross-sec | 155 (92) | 37/55 | 3×3 | VD | SRL | Para-foveal | 37.80 | 4.10 |
| | | Healthy controls | Unknown | | | | | | | | 42.60 | 1.90 |
| | | Uveitis | | | | | | VD | DRL | Para-foveal | 41.20 | 2.90 |
| | | Healthy controls | | | | | | | | | 42.50 | 1.70 |
| Tian et al. ¹¹³ | Zeiss, PLEX Elite 9000 | Uveitis + vasculitis | 45.9 | Cross-sec | 92 (58) | 26/32 | 3×3 | FAZ area | SCP | Fovea | 0.20 | 0.10 |
| | | Uveitis-vasculitis | 45.9 | | | | | | | | 0.10 | 0.11 |
| | | Healthy controls | 42.0 | | | | | | | | 0.30 | 0.50 |
| Fan et al. ¹¹⁴ | Optovue, Avanti | VKHD + SGF | 40.6 | Cross-sec | 106 (53) | 23/30 | 3×3 | VD | SCP | Whole | 44.8 | 2.40 |
| | | VKHD-SGF | 38.0 | | | | | | | | 47.00 | 2.30 |
| | | Healthy controls | 39.6 | | | | | | | | 47.70 | 1.90 |
| | | VKHD + SGF | | | | | | VD | SCP | Para-foveal | 47.70 | 2.70 |
| | | VKHD-SGF | | | | | | | | | 50.20 | 2.20 |
| | | Healthy controls | | | | | | | | | 50.70 | 2.00 |
| | | VKHD + SGF | | | | | | VD | SCP | Fovea | 14.50 | 8.80 |
| | | VKHD-SGF | | | | | | | | | 16.50 | 6.70 |
| | | Healthy controls | | | | | | | | | 18.80 | 4.20 |
| | | VKHD + SGF | | | | | | VD | DCP | Whole | 47.70 | 2.50 |
| | | VKHD-SGF | | | | | | | | | 51.40 | 2.60 |
| | | Healthy controls | | | | | | | | | 51.60 | 2.80 |
| | | VKHD + SGF | | | | | | VD | DCP | Para-foveal | 50.50 | 2.70 |
| VKHD-SGF | | | | | | | | | 53.90 | 2.70 | | |

Continued

| Author, ref | Manufacturer | Diagnosis included | Mean age (years) | Study Design | Number of eyes (number of patients) | Number of males/females | Scan size (mm) | Metric | Vessel layer | Region | Mean | SD | |
|------------------------------|-----------------|------------------------|------------------|--------------|-------------------------------------|-------------------------|----------------|--------|--------------|-------------|-------|-------|------|
| | | Healthy controls | | | | | | | | | 53.80 | 3.20 | |
| | | VKHD + SGF | | | | | | VD | DCP | Fovea | 26.70 | 11.40 | |
| | | VKHD-SGF | | | | | | | | | 30.60 | 7.60 | |
| | | Healthy controls | | | | | | | | | 33.50 | 4.60 | |
| Karaca et al. ¹¹⁵ | Optovue, Avanti | Inactive VKHD | 39.9 | Cross-sec | 51 (51) | 23/28 | 6 × 6 | VD | SCP | Whole | 50.60 | 4.70 | |
| | | Healthy controls | 38.9 | | | | | | | | 54.30 | 2.60 | |
| | | Inactive VKHD | | | | | | VD | SCP | Para-foveal | 53.50 | 4.80 | |
| | | Healthy controls | | | | | | | | | 56.70 | 2.80 | |
| | | Inactive VKHD | | | | | | VD | SCP | Fovea | 18.20 | 6.90 | |
| | | Healthy controls | | | | | | | | | 24.60 | 3.40 | |
| | | Inactive VKHD | | | | | | VD | DCP | Whole | 53.10 | 4.60 | |
| | | Healthy controls | | | | | | | | | 61.10 | 2.80 | |
| | | Inactive VKHD | | | | | | VD | DCP | Para-foveal | 55.90 | 3.40 | |
| | | Healthy controls | | | | | | | | | 61.90 | 3.10 | |
| | | Inactive VKHD | | | | | | VD | DCP | Fovea | 33.60 | 6.90 | |
| | | Healthy controls | | | | | | | | | 41.90 | 3.80 | |
| Aksoy et al. ¹¹⁶ | Optovue, Avanti | Fuch's eye | 34.3 | Cross-sec | 30 (30) | 14/16 | 6 × 6 | VD | SCP | Fovea | 18.69 | 6.91 | |
| | | Fellow eye (no Fuch's) | 34.3 | | 30 (30) | 14/16 | | | | | 30.23 | 6.90 | |
| | | Healthy control | 35.5 | | 30 (30) | 14/16 | | | | | 31.58 | 4.07 | |
| | | Fuch's eye | | | | | | VD | DCP | Fovea | 33.83 | 6.18 | |
| | | Fellow eye (no Fuch's) | | | | | | | | | 39.63 | 6.01 | |
| | | Healthy control | | | | | | | | | 34.06 | 4.49 | |
| | | Fuch's eye | | | | | | VD | SCP | Para-foveal | 45.56 | 6.56 | |
| | | Fellow eye (no Fuch's) | | | | | | | | | 52.28 | 6.26 | |
| | | Healthy control | | | | | | | | | 55.85 | 2.93 | |
| | | Fuch's eye | | | | | | VD | DCP | Para-foveal | 54.01 | 5.15 | |
| | | Fellow eye (no Fuch's) | | | | | | | | | 64.11 | 4.83 | |
| | | Healthy control | | | | | | | | | 65.02 | 4.75 | |
| | | Fuch's eye | | | | | | | FAZ area | SCP | Fovea | 0.39 | 0.25 |
| | | Fellow eye (no Fuch's) | | | | | | | | | 0.36 | 0.25 | |
| Healthy control | | | | | | | | | 0.30 | 0.25 | | | |

Table 2. Study Characteristics of studies included looking at patients with diseases other than diabetes. VD data is given as percentage (%), FAZ data is given as mm². AD, Alzheimer's disease; cross-sec, cross-sectional; VD, vessel density; MCI, mild cognitive impairment; FAZ, foveal avascular zone; POAG, primary open angle glaucoma; PD, Parkinson's disease; iRBD, idiopathic rapid-eye-movement sleep behaviour disorder; NMOSD-ON, neuromyelitis optica spectra disorder without optic neuritis; NMOSD + ON, neuromyelitis optica spectra disorder with optic neuritis; MS-ON, multiple sclerosis without optic neuritis; MS + ON, multiple sclerosis with optic neuritis; aMCI, amnestic mild cognitive impairment; CSVD, cerebral small vessel disease; CKD, chronic kidney disorder; Behcet's-ocular involvement, Behcet's without ocular involvement; Behcet's + ocular involvement, Behcet's with ocular involvement; VKHD + SGF, Vogt-Koyanagi-Harada disease with sunset glow fundus; VKHD-SGF, Vogt-Koyanagi-Harada disease without sunset glow fundus; VKHD, Vogt-Koyanagi-Harada disease. Papers from Hirano¹¹⁷, Karst¹¹⁸, Marques¹¹⁹, Vujosevic¹²⁰ and Yoon¹²¹ were not presented as they did not include VD or FAZ data.

| Company | Instrument | Source | Software | µm between B-scan |
|------------|--------------------|--------|----------|-------------------|
| Zeiss | Cirrus HD-OCT 5000 | SD-OCT | OMAG | 12.2 |
| Zeiss | PLEX Elite 9000 | SS-OCT | OMAG | 30 |
| Zeiss | AngioPlex | SD-OCT | OMAG | Unknown |
| Optovue | Avanti | SD-OCT | SS-ADA | 9.9 |
| Topcon | Triton | SS-OCT | OCTARA | 9.4 |
| Nidek Co | RS-3000 AOCT | SD-OCT | CODAA | 11.7 |
| Heidelberg | OCT2 | SD-OCT | FSPA | 5.7 |

Table 3. OCTA equipment and software in included studies. Kim et al.[6] used a Zeiss prototype instrument that is not included in this table. OCTA, optical coherence tomography angiography; SD-OCT, Spectral-domain optical coherence tomography; SS-OCT, swept-source optical coherence tomography; OMAG, optical microangiography; SS-ADA, split-spectrum amplitude decorrelation angiography; OCTARA, optical coherence tomography angiography ratio analysis; CODAA, complex optical coherence tomography signal difference analysis angiography; FSPA, full spectrum probabilistic approach.

| Macula volume dimension | A-scans in volume | Macula region of interest | Perfusion metric | Retinal layer | Retinal layer definition |
|-------------------------|-------------------|---|------------------------|---------------|---|
| 3 × 3 mm | 245 × 245 | Foveal | VD | SCP | NFL + GCL + IPL ¹²² |
| 6 × 6 mm | 256 × 256 | Parafoveal | SVD | DCP | INL + OPL ¹²² |
| 12 × 12 mm | 304 × 304 | Whole macula (9 or 36 mm ²) | VLD | SVP | GCL + IPL ¹²² |
| 4.5 × 4.5 mm | 320 × 320 | | FD | DVP | IPL + INL + OPL ¹⁰⁵ |
| | 400 × 400 | | SFD | SVC | NFL + GCL + IPL ¹²² |
| | 512 × 512 | | PD | DVC | IPL + INL + OPL ¹²² |
| | | | FAZ area | SRL | Inner 60–70% of the whole retina (ILM-RPE) ^{6,18} or NFL + GCL + IPL ⁵² |
| | | | FAZ perimeter | DRL | Outer 30–40% of the inner retina (ILM-RPE) ^{6,18} or IPL + INL + OPL ^{52,117} |
| | | | FAZ acircularity ratio | SCC | NFL + GCL + IPL ¹¹⁸ |
| | | | FAZ acircularity index | DCC | IPL + INL + OPL ¹¹⁸ |

Table 4. Different parameters available for assessing retinal perfusion in included studies. VD, vessel density; SVD, skeletonised vessel density; VLD, vessel length density; FD, fractal dimension; SFD, skeletonised fractal dimension; PD, perfusion density; FAZ, foveal avascular zone; NFL, nerve fibre layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; SCP, superficial capillary plexus; DCP, deep capillary plexus; SVP, superficial vascular plexus; DVP, deep vascular plexus; SVC, superficial vascular plexus; DVC, deep vascular plexus; SRL, superficial retinal layer; DRL, deep retinal layer; SCC, superficial capillary complex; DCC, deep capillary complex. Retinal layer illustrations are in Supplementary Fig. 1.

Parkinson's disease (PD) had reduced retinal VD and larger FAZ area in two studies^{93,94}, and not in one⁹², as did patients with atherosclerosis, stroke and cerebrovascular disease^{95,101–103}, and patients with beta thalassaemia¹⁰⁴, and diabetic patients with CKD^{105,106}, and microalbuminuria¹⁰⁷.

Patients with MS and NMO/MSD also had lower VD (in the superficial more than the deep retinal circulation) and larger FAZ area^{96,97,99}, with patients with a history of optic neuritis having lower retinal perfusion than patients with MS or NMO/MSD without prior optic neuritis.

Posterior uveitis, including Behcet's, Vogt-Koyanagi-Harada disease, and Fuch's heterochromic cyclitis had lower retinal VD and higher FAZ area compared to patients or eyes without uveitis^{6,108–116}.

Discussion

To our knowledge, we present here the first systematic review and meta-analysis of OCTA analysis methods, demonstrating very high heterogeneity of both OCTA analysis methodology employed and reported OCTA data for individual methods. Heterogeneity in analysis methods is demonstrated by the fact that there were more methods of analysing retinal perfusion (197 in this review) than included studies. The included studies varied in perfusion metric used, macula area analysed, equipment manufacturer, and retinal layer segmentation studied, although VD and FAZ area were commonly reported. Although studies investigating the effect of diabetes mellitus on retinal perfusion reporting similar perfusion metrics offered variable and heterogeneous results, the OCTA data consistently demonstrated reduced retinal perfusion in patients with diabetes who had, or did not have, diabetic retinopathy when compared to healthy controls.

Reduced retinal perfusion in diabetes and diabetic retinopathy matches the known pathophysiology of the condition²⁶, reinforcing the clinical validity of retinal perfusion measurement assessment by OCTA in these patients. However, given that early diabetic retinopathy is associated with retinal ganglion cell (RGC) loss²⁷, and

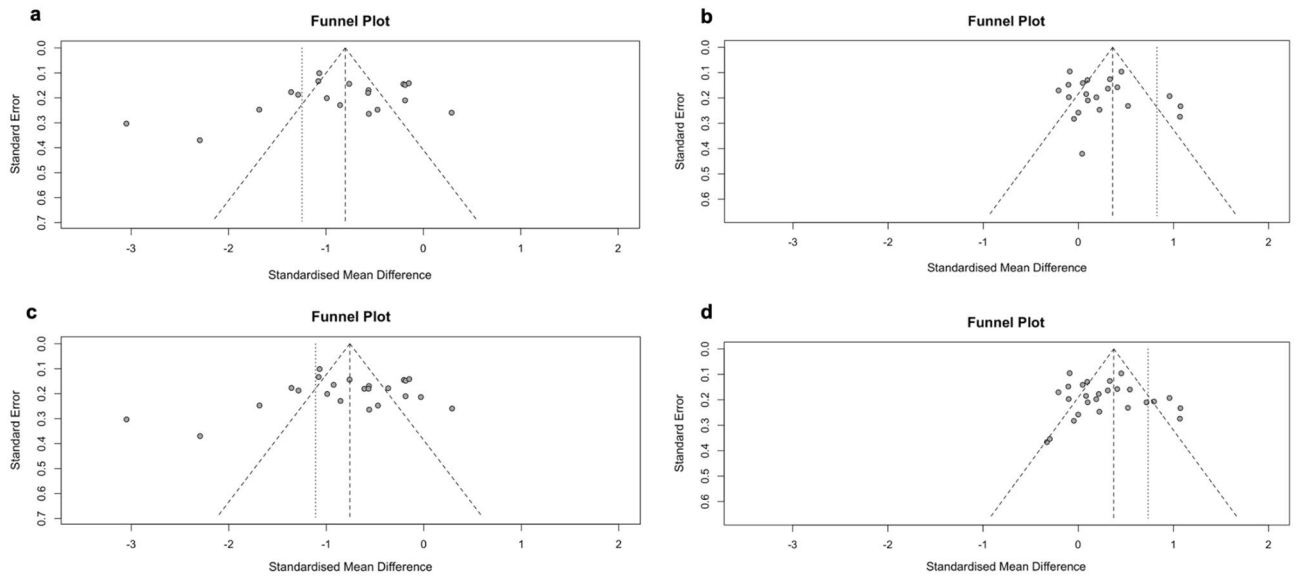


Figure 2. Funnel plots of the effect of diabetic retinopathy on retinal perfusion. (a) VD in patients with diabetic eye disease. (b) FAZ in patients with diabetic eye disease. (c) VD in all patients with diabetes mellitus. (d) FAZ in all patients with diabetes mellitus. VD, vessel density; FAZ, foveal avascular zone.

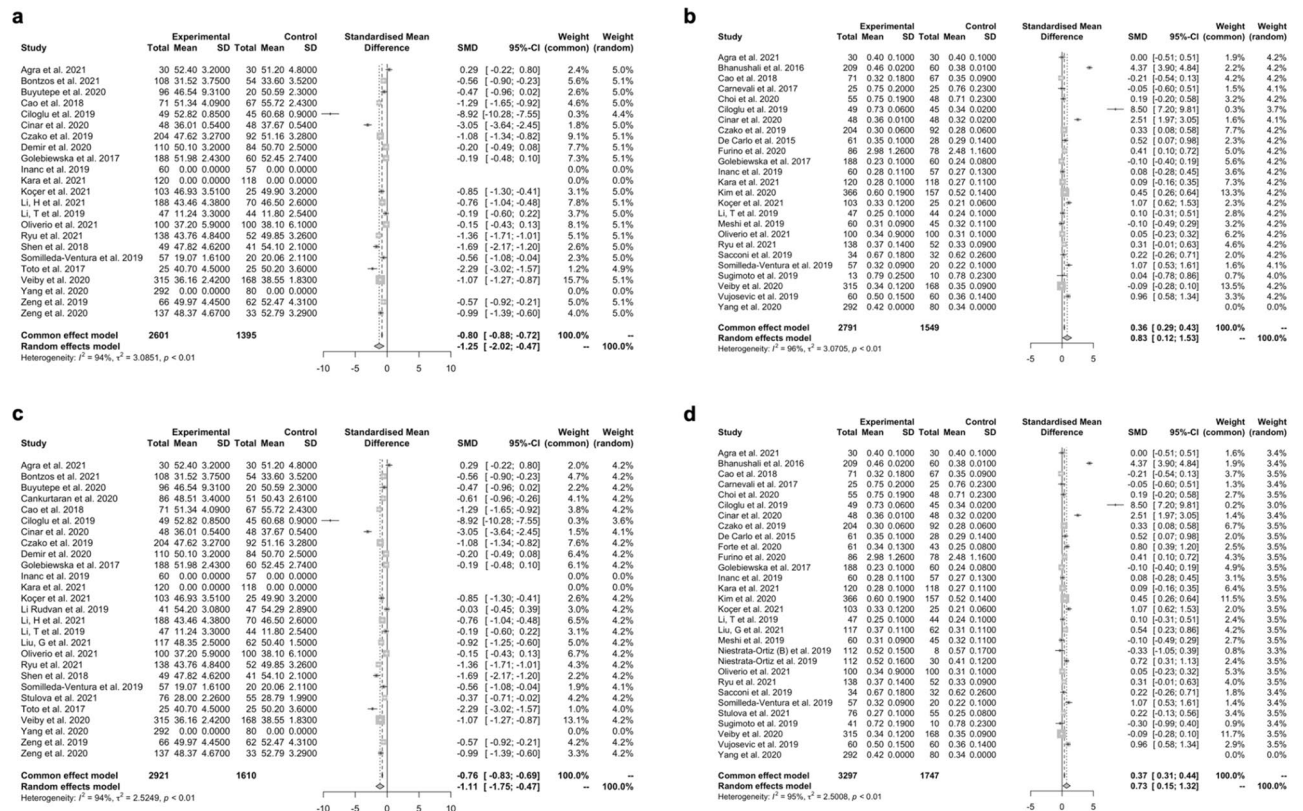
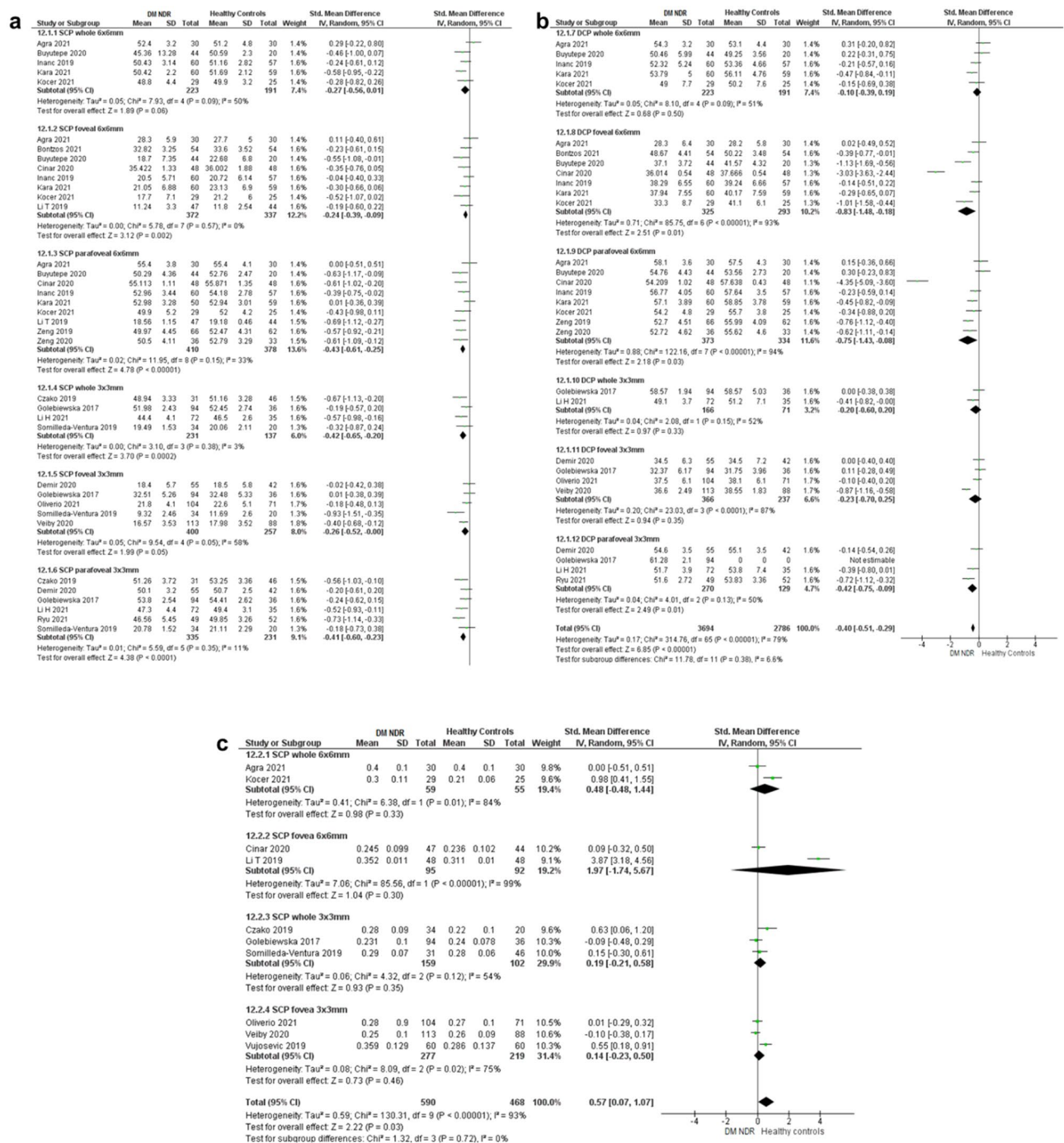


Figure 3. Meta-analysis forest plots for diabetic retinopathy. Forest plots analysing the effect of diabetic retinopathy on retinal perfusion by comparing healthy controls with diabetic retinopathy patients for (a) VD%, and (b) FAZ and; comparing healthy controls with all diabetic patients for (c) VD% and (d) FAZ comparing healthy controls with all diabetic patients with diabetic retinopathy and without diabetic retinopathy. VD%, percentage vessel density; FAZ, foveal avascular zone; SD, standard deviation.



with correspondingly higher perfusion³⁰ and greater potential for regulation of changes in perfusion³⁰. Similarly, retinal perfusion is highest in the parafoveal area, consistent with perfusion assessment in this region detecting the greatest changes.

There are growing calls to standardise OCTA methodology^{16,31,32}. We previously compared different OCTA analysis methods, and they concluded that the high variability between metrics and software meant that the different approaches were often not analogous¹⁵, but that VD data was the most reproducible across platforms and should be reported in OCTA studies, potentially being preferred to skeletonized metrics in the absence of software standardization. It is therefore encouraging that VD was most frequently reported in this study, although heterogeneity was still high. A different study by Rabiolo et al.³³ compared different OCTA algorithms and found that, while the different algorithms all identified important differences between healthy and affected eyes, absolute values were not comparable. This lack of between-platform comparability limits the wider potential of population-level OCTA data. One meta-analysis of fractal dimension perfusion metrics³⁴ found that heterogeneity due to different analysis methods limited comparisons, similar to our findings, and again supports calls for standardisation in OCTA protocols. In our meta-analyses we saw high levels of heterogeneity at both the macroscopic level and when analysing different individual analysis methods. One explanation for high individual analysis heterogeneity is the variety of OCTA devices used from different manufacturers that implement different algorithms to determine blood flow or segment vascular layers. A standardised method of quantifying Heidelberg OCTA of the macula and peripapillary vessels has been proposed³⁵, although uptake may be limited when manufacturers' own proprietary algorithms are available¹⁵.

Limitations of this study include the heterogeneity in reported OCTA methods, which limited synthesis and comparison of analysis methods and findings across different disease states, but highlights the need for standardisation. VD and PD were often used interchangeably and occasionally not defined. The definitions we include in the introduction were the most common definitions in our included studies. Due to high levels of heterogeneity, it was not possible to reliably meet the initial study aims of determining the most sensitive method of OCTA analysis. There were also no papers that studied the test–retest variability of OCTA. Papers did not routinely report reliability, stability, sensitivity, or specificity data for OCTA analyses, which are crucial for test evaluation approaches to the clinical application of OCTA. Finally, while we report increased FAZ area and decreased VD percentages in both patients with diabetes and with diabetic eye disease compared to healthy controls, we recognise that the breadth of the confidence intervals suggest uncertainty about the exact magnitude of this difference.

Currently, there are no standardised reporting guidelines for studies using OCTA—in contrast to the APOSTEL guidelines for OCT studies³⁶—and the many thousands of possible OCTA analysis methods available limit reliable comparison of data. To ensure valid comparison of OCTA study results and robust definition of disease characteristics in which retinal perfusion is impaired, we support the suggestion that reporting guidelines and standardisation are urgently required. This would allow consistent reporting to support development of OCTA to its full potential as a ubiquitous clinical imaging modality, similar to OCT, rather than the research tool that it often remains at present³⁷. As an initial step, we suggest reporting VD in the parafoveal area and FAZ area as a minimum dataset.

Conclusion

Analysis and reporting of retinal perfusion using OCTA is highly heterogenous, meaning that despite the myriad of published papers assessing retinal perfusion across different diseases, few direct comparisons can be made. In addition, the stability and reliability of OCTA analyses has been under-studied. We strongly support the need for standardisation of methodology along with OCTA reporting guidelines, and suggest that a minimum dataset for OCTA reporting should include parafoveal VD and FAZ area.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions

E.C. and J.R.M.K. were major contributors in writing the manuscript. E.C. conducted the search, and E.C. and M.T. conducted the initial screening of titles and abstracts. E.C. and J.R.M.K. extracted data. L.F. and E.C. conducted analysis. All authors read, edited, and approved the final manuscript.

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