INPLASY

# Structural Neurovascular Associations Between Retinal Thickness and Vascular Density in Diabetes and Diabetic Retinopathy: A Systematic Review and Meta-Analysis

INPLASY202660132
doi: 10.37766/inplasy2026.6.0132
Received: 28 June 2026
Published: 28 June 2026

Xia, YH; Dong, JL; Wang, MQ; Ye, HJ.

**Corresponding author:**
YIHAO XIA

surtr@stu.cdutcm.edu.cn

**Author Affiliation:**
Chengdu university of traditional chinese medicine.

**ADMINISTRATIVE INFORMATION**

**Support -** None.

**Review Stage at time of this submission -** The review has not yet started.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202660132

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 June 2026 and was last updated on 28 June 2026.

## INTRODUCTION

**Review question / Objective** Population
Patients with diabetes mellitus, including individuals without diabetic retinopathy and those with different stages of diabetic retinopathy.

Exposure
The presence of diabetes-related retinal changes, including no diabetic retinopathy, non-proliferative diabetic retinopathy, or proliferative diabetic retinopathy.

Comparator
Healthy controls and/or comparisons across different diabetic retinopathy severity groups, where available.

Outcome
The association between OCTA-derived retinal thickness measurements and vascular parameters, expressed as correlation coefficients or other convertible association measures.

Study design
Observational human studies, including cross-sectional studies, case-control studies, and cohort studies, will be included if they report extractable associations between retinal thickness measurements and retinal vascular parameters. Interventional studies may also be considered only when relevant pre-intervention baseline data can be clearly extracted.

Review question and objective
This systematic review and meta-analysis aims to evaluate the association between OCTA-derived retinal thickness and vascular metrics in individuals with diabetes mellitus, with or without diabetic retinopathy. Specifically, we will synthesize correlation-based evidence from OCTA studies, estimate pooled thickness–vascular metrics associations, and explore whether these associations differ from those observed in healthy controls or vary according to diabetic status, diabetic retinopathy severity, retinal region, and retinal layer.

**Rationale** Diabetic retinopathy has traditionally been regarded as a microvascular complication of diabetes mellitus; however, increasing evidence suggests that retinal neurodegeneration and microvascular impairment may occur concurrently and interact throughout the course of the disease. Optical coherence tomography and optical coherence tomography angiography provide non-invasive measurements of retinal structural and vascular changes, including retinal thickness and vascular density or related vascular metrics. The association between these structural and vascular parameters may provide indirect insight into diabetes-related alterations in retinal neurovascular integrity.

Although a number of studies have examined correlations between retinal thickness and vascular parameters in individuals with diabetes or diabetic retinopathy, the reported findings remain inconsistent. Existing studies differ in participant characteristics, diabetic retinopathy severity, retinal regions, retinal layers, imaging devices, and vascular metrics. In addition, some studies include healthy controls, whereas others report only diabetes-related groups, making it difficult to determine whether thickness–vascular associations are altered in diabetic eyes compared with non-diabetic eyes.

Therefore, a systematic review and meta-analysis is needed to summarize the available evidence and quantitatively synthesize the association between retinal thickness and vascular metrics in diabetes and diabetic retinopathy. By comparing these associations across diabetic status, diabetic retinopathy severity, retinal region, and retinal layer where data are available, this study may help clarify whether retinal structural and vascular measurements show altered interrelationships in diabetes-related retinal disease and provide a basis for future studies on retinal neurovascular changes.

**Condition being studied** Diabetes mellitus is a chronic metabolic disease characterized by persistent hyperglycaemia and is associated with multiple microvascular complications, including diabetic retinopathy. Diabetic retinopathy is one of the most common ocular complications of diabetes and is traditionally considered a retinal microvascular disease. It ranges from no clinically visible retinopathy to non-proliferative diabetic retinopathy and proliferative diabetic retinopathy, and may ultimately lead to diabetic macular oedema, retinal ischemia, neovascularization, and visual impairment.

In addition to vascular abnormalities, increasing evidence suggests that diabetes-related retinal changes may also involve neurodegenerative alterations, including thinning or dysfunction of inner retinal layers. Retinal neural tissue and microvasculature are closely related anatomically and functionally, and disruption of this relationship may contribute to the development and progression of diabetic retinal disease. Optical coherence tomography and optical coherence tomography angiography allow non-invasive assessment of retinal structural and vascular features, such as retinal thickness and vascular density or related vascular metrics. Therefore, evaluating the association between retinal thickness and vascular parameters may help characterize diabetes-related retinal neurovascular changes and provide further insight into the structural and microvascular alterations associated with diabetes and diabetic retinopathy.

## METHODS

**Search strategy** A systematic literature search will be conducted in PubMed, Embase, and Web of Science. The search strategy will combine terms related to diabetes and diabetic retinopathy, OCT angiography, retinal thickness, and retinal vascular parameters. The diabetes-related terms will include "diabetes mellitus," "diabetic retinopathy," "diabetic," "diabetes," "NPDR," "PDR," "T1DM," and "T2DM." The imaging-related terms will include "optical coherence tomography angiography," "OCT angiography," and "OCTA." Retinal structural terms will include "retinal thickness," "macular thickness," "retinal layer," "retinal layer thickness," "inner retinal thickness," "outer retinal thickness," "GCL," "IPL," "GCIPL," "GCL-IPL," "GCC," "RNFL," "pRNFL," "INL," "OPL," and "ONL." Retinal vascular terms will include "vessel density," "vascular density," "capillary density," "perfusion density," "flow density," "fractal dimension," "branch node density," "vessel length density," "vascular length density," and "lacunarity." Medical Subject Headings, Emtree terms, and free-text terms will be used where appropriate according to the requirements of each database. The reference lists of included studies and relevant reviews will also be screened manually to identify additional eligible studies.

**Participant or population** This review will include human participants with diabetes mellitus, including individuals without clinically diagnosed diabetic retinopathy and patients with diabetic retinopathy at different stages, such as non-proliferative diabetic retinopathy and proliferative

diabetic retinopathy. Studies involving type 1 or type 2 diabetes mellitus will be considered eligible if they report retinal thickness measurements and retinal vascular parameters obtained using OCT and/or OCTA, and provide correlation coefficients or other convertible measures of association between these parameters. Healthy non-diabetic participants will also be considered when included as control groups in eligible studies. Studies based exclusively on animal models, in vitro experiments, or participants with ocular diseases unrelated to diabetes that may substantially affect retinal thickness or vascular measurements will be excluded.

**Intervention** No therapeutic or preventive intervention will be evaluated in this review. This systematic review and meta-analysis will include observational studies that assess the association between retinal thickness and retinal vascular parameters measured by OCT and/or OCTA in individuals with diabetes mellitus or diabetic retinopathy. The exposure of interest is the presence of diabetes mellitus and diabetes-related retinal changes, including no diabetic retinopathy, non-proliferative diabetic retinopathy, and proliferative diabetic retinopathy.

**Comparator** No comparative intervention will be applied, as this review does not evaluate therapeutic or preventive interventions. Where available, the primary comparator will be healthy non-diabetic control participants. Additional comparisons may include different diabetes-related groups, such as individuals with diabetes but no diabetic retinopathy, patients with non-proliferative diabetic retinopathy, and patients with proliferative diabetic retinopathy. These comparisons will be used to explore whether the association between retinal thickness and retinal vascular parameters differs according to diabetic status or diabetic retinopathy severity.

**Study designs to be included** This review will include observational human studies that report the association between retinal thickness measurements and retinal vascular parameters in individuals with diabetes mellitus or diabetic retinopathy. Eligible study designs will include cross-sectional studies, case-control studies, and cohort studies if relevant baseline or observational correlation data are available. Interventional studies may also be considered only when pre-intervention baseline data can be clearly extracted and are relevant to the review question. Reviews, editorials, letters without original data, case rep.

**Eligibility criteria** Studies will be eligible if they provide original human data on the association between retinal thickness measurements and retinal vascular parameters in participants with diabetes mellitus, diabetic retinopathy, or healthy control participants. Eligible studies must use OCT and/or OCTA to obtain retinal structural and vascular measurements, and must report correlation coefficients or other association measures that can be extracted or converted for quantitative synthesis. Studies reporting data from different retinal regions, retinal layers, diabetic status groups, or diabetic retinopathy severity groups will be included when relevant data are available.

Studies will be excluded if they do not report extractable associations between retinal thickness and retinal vascular parameters; if the vascular outcomes are not derived from OCTA; if the study population is not related to diabetes or diabetic retinopathy; or if the results are based exclusively on animal experiments, in vitro studies, case reports, reviews, editorials, conference abstracts without sufficient data, or letters without original data. Studies involving participants with major coexisting ocular diseases or ocular interventions that may substantially affect retinal thickness or vascular measurements, such as glaucoma, retinal vein occlusion, age-related macular degeneration, high myopia, previous vitrectomy, or recent intraocular surgery, will be excluded unless diabetes-related data can be separately extracted. When multiple publications report overlapping populations, the most complete or most relevant dataset will be used.

**Information sources** A systematic literature search will be conducted in PubMed, Embase, and Web of Science from database inception to the date of the final search. The reference lists of included studies and relevant review articles will also be manually screened to identify additional eligible studies. Data will be extracted from published full texts, tables, figures, and supplementary materials.

**Main outcome(s)** The main outcome of this review will be the association between retinal thickness measurements and retinal vascular parameters in individuals with diabetes mellitus or diabetic retinopathy. Retinal thickness measurements may include total retinal thickness, macular thickness, retinal layer thickness, or specific layer-based measurements such as RNFL, GCL, IPL, GCIPL, GCC, INL, OPL, and ONL thickness. Retinal vascular parameters may include vessel density, vascular density, capillary density, perfusion density, flow density, fractal dimension, branch

node density, vessel length density, vascular length density, or lacunarity, as reported in the included studies.

The primary effect measure will be the correlation coefficient between retinal thickness and retinal vascular parameters. Pearson's or Spearman's correlation coefficients will be extracted where available. Other reported association measures will be included if they can be converted into correlation coefficients or otherwise synthesized appropriately. For meta-analysis, correlation coefficients will be transformed using Fisher's z transformation and then back-transformed to pooled correlation coefficients with 95% confidence intervals for interpretation.

As most eligible studies are expected to be observational imaging studies, the outcomes will generally be based on measurements obtained at a single cross-sectional time point. For cohort or interventional studies, only relevant baseline or pre-intervention observational data will be used when available.

**Additional outcome(s)** Additional outcomes will include exploratory subgroup analyses of thickness–vascular parameter associations according to diabetic status, diabetic retinopathy severity, retinal region, and retinal layer, where sufficient data are available. Comparisons may be made between healthy controls and diabetes-related groups, or across different stages of diabetic retinopathy.

Study heterogeneity will be assessed, and sensitivity analyses may be performed to evaluate the robustness of the pooled estimates. Findings that cannot be quantitatively synthesized because of insufficient data or inconsistent reporting will be summarized narratively.

**Data management** All records retrieved from electronic database searches will be exported to a reference management software for initial organization and duplicate removal. After deduplication, titles and abstracts will be screened according to the predefined eligibility criteria, followed by full-text assessment of potentially eligible studies. The study selection process will be documented and reported using a PRISMA flow diagram.

Data from eligible studies will be extracted into a standardized data extraction spreadsheet. Extracted information will include study characteristics, participant characteristics, diabetes and diabetic retinopathy status, imaging device, retinal region, retinal layer or thickness parameter, vascular parameter, statistical method, effect measure, sample size, and other relevant details. Correlation coefficients or other convertible association measures will be recorded for quantitative synthesis. Any data transformations, including conversion to Fisher's z values and back-transformation to pooled correlation coefficients, will be documented to ensure transparency and reproducibility.

**Quality assessment / Risk of bias analysis** The methodological quality and risk of bias of included studies will be assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies for most eligible observational imaging studies. If case-control or cohort studies are included, the corresponding JBI checklist will be used according to study design.

**Strategy of data synthesis** Extracted association measures between retinal thickness and retinal vascular parameters will be synthesized where sufficient and clinically comparable data are available. Correlation coefficients will be used as the primary effect measure. Pearson's and Spearman's correlation coefficients will be extracted directly when reported. Other association measures will be considered for quantitative synthesis only if they can be appropriately converted to correlation coefficients or comparable effect measures.

For meta-analysis, correlation coefficients will be transformed using Fisher's z transformation to stabilize variance. The transformed values will be pooled using a random-effects model, considering the expected heterogeneity across study populations, diabetic retinopathy severity, retinal regions, retinal layers, imaging devices, and vascular parameters. Pooled Fisher's z estimates will then be back-transformed to correlation coefficients with 95% confidence intervals for interpretation.

When multiple eligible correlation coefficients are reported within the same study, such as results from different retinal regions, layers, or vascular parameters, they will be handled according to the purpose of each analysis. Where appropriate, separate analyses will be conducted by retinal region, retinal layer, or diabetic status. If multiple estimates from the same study contribute to the same analysis, within-study estimates may be combined before pooling to reduce unit-of-analysis problems.

Statistical heterogeneity will be assessed using Cochran's Q test, $I^2$ statistics, and between-study variance where applicable. Subgroup analyses may be performed according to diabetic status, diabetic retinopathy severity, retinal region, and retinal layer when sufficient data are available. Sensitivity analyses may be conducted to evaluate the robustness of the pooled results, such as excluding studies with high risk of bias or studies contributing influential effect estimates.

If quantitative synthesis is not appropriate because of insufficient data, substantial methodological heterogeneity, inconsistent reporting, or non-convertible effect measures, the findings will be summarized narratively. The synthesis will distinguish between evidence suitable for meta-analysis and evidence included only in the qualitative review.

**Subgroup analysis** Subgroup analyses will be performed where sufficient data are available to explore potential sources of heterogeneity in thickness–vascular parameter associations. Planned subgroup analyses may include comparisons according to diabetic status, diabetic retinopathy severity, retinal region, and retinal layer or structural parameter. Specifically, associations may be examined separately in healthy controls, individuals with diabetes but no diabetic retinopathy, patients with non-proliferative diabetic retinopathy, and patients with proliferative diabetic retinopathy when data permit.

Additional subgroup analyses may be conducted according to scan region, such as macular, parafoveal, perifoveal, or peripapillary regions, and according to retinal structural parameters, such as total retinal thickness, RNFL, GCIPL, GCC, or other layer-specific thickness measurements. If the number of studies is insufficient for formal subgroup meta-analysis, subgroup findings will be summarized narratively.

**Sensitivity analysis** Sensitivity analyses will be performed, where sufficient studies are available, to assess the robustness of the pooled estimates. Leave-one-study-out analyses may be conducted by sequentially excluding one study at a time to evaluate the influence of individual studies on the overall results. Additional sensitivity analyses may include excluding studies judged to have a high risk of bias, studies with non-standard or converted association measures, or studies with methodological characteristics that may substantially influence the pooled estimates.

The results of sensitivity analyses will be compared with the primary analysis to determine whether the direction, magnitude, or statistical significance of the pooled thickness–vascular parameter associations remains stable. If the number of included studies is too small for formal sensitivity analysis, the potential influence of individual studies and methodological differences will be discussed narratively.

**Language restriction** Only studies published in English will be included.

**Country(ies) involved** China.

**Keywords** Diabetic retinopathy; optical coherence tomography angiography; retinal thickness; vessel metrics; meta-analysis.

**Dissemination plans** The findings of this systematic review and meta-analysis will be submitted for publication in a peer-reviewed academic journal. The results may also be presented at relevant ophthalmology, diabetes, or medical imaging conferences. Any important findings may be further disseminated through academic presentations or institutional research activities to inform clinicians and researchers interested in diabetic retinopathy, OCT/OCTA imaging, and retinal neurovascular changes.

**Contributions of each author**

Author 1 - Yihao Xia - Conceptualization, methodology, literature search, data extraction, formal analysis, visualization, and writing – original draft.
Email: surtr@stu.cdutcm.edu.cn
Author 2 - Jialing Dong - Literature screening, data extraction, quality assessment, validation, and writing – review and editing.
Author 3 - Mengqi Wang - Methodology, statistical analysis supervision, interpretation of results, and writing – review and editing.
Author 4 - Hejiang Ye - Conceptualization, supervision, project administration, critical revision of the manuscript, and final approval of the submitted version.
Email: yehejiang@cdutcm.edu.cn