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Retinal microvascular changes in moyamoya disease and moyamoya syndrome assessed by optical coherence tomography angiography: a systematic review and meta-analysis protocol

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 October 2026 and was last updated on 29 October 2026.

INTRODUCTION

Review question / Objective In patients with moyamoya disease (MMD) or moyamoya syndrome (MMS), are retinal microvascular parameters measured by optical coherence tomography angiography (OCTA), including macular vessel density (VD) , foveal avascular zone (FAZ) area, and structural parameters altered compared with healthy controls?.

Rationale Moyamoya disease (MMD) and moyamoya syndrome (MMS) are rare occlusive cerebrovascular disorders that frequently lead to recurrent ischemic or hemorrhagic stroke, particularly in East Asian populations. Revascularization surgery improves cerebral perfusion, but perioperative complications such as cerebral hyperperfusion syndrome remain difficult to predict, and convenient non-invasive biomarkers of cerebral hemodynamic status are lacking. The retinal and choroidal microcirculation shares a common embryological origin with the internal carotid-ophthalmic arterial system, and optical coherence tomography angiography (OCTA) allows rapid, non-invasive, quantitative assessment of retinal microvascular parameters. Accumulating cross-sectional studies have reported reduced macular vessel density, enlarged foveal avascular zone, thinning of the retinal nerve fiber layer, and decreased choroidal thickness in MMD/MMS patients, and carotid revascularization studies have shown parallel improvement of ocular and cerebral perfusion, supporting the "eye-brain perfusion homology" hypothesis. However, individual studies are limited by small sample sizes typical of a rare disease, inconsistent findings, and substantial methodological heterogeneity across OCTA devices, scan areas, and parameter definitions, making results difficult to compare. To our knowledge, no systematic review or meta-analysis has quantitatively synthesized ocular OCTA phenotypes in MMD/MMS; the closest related work addresses intracranial atherosclerotic stenosis, a different population. A quantitative

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synthesis is needed to establish the magnitude of ocular microvascular impairment in MMD/MMS, explore sources of heterogeneity through prespecified subgroup analyses, and provide an evidence base for developing combined eye-brain perfusion assessment tools.

Condition being studied Moyamoya disease (MMD) is a rare, chronic occlusive cerebrovascular disorder characterized by progressive stenosis or occlusion of the terminal portions of the internal carotid arteries and the proximal anterior and middle cerebral arteries, accompanied by the formation of an abnormal network of collateral vessels at the base of the brain (the "puff-of-smoke" appearance on angiography). When similar vascular changes develop in association with an underlying condition—such as atherosclerosis, thyroid disease, neurofibromatosis type 1, or sickle cell disease—they are termed moyamoya syndrome (MMS). MMD/MMS shows a marked predilection for East Asian populations and has a bimodal age distribution, with pediatric patients typically presenting with cerebral ischemia and adults with intracranial hemorrhage or ischemic events. The disease can lead to recurrent stroke and significant disability. Revascularization surgery is the main treatment to improve cerebral perfusion, but perioperative complications such as cerebral hyperperfusion syndrome remain difficult to predict. Retinal and choroidal microcirculation shares a common embryological origin with the internal carotid-ophthalmic arterial system, making ocular microvascular parameters potential non-invasive biomarkers of cerebral hemodynamic status in MMD/MMS.

METHODS

Search strategy Searched on 29 October 2026, from inception, with no language, age, publication-type, or other restrictions. Five electronic databases: PubMed, Embase, Web of Science Core Collection, Scopus, and CNKI (Chinese National Knowledge Infrastructure); Europe PMC will additionally be searched as a supplementary source. Full strategies for the remaining databases are available on request (the CNKI strategy is in Chinese).
PubMed strategy:
#1 "Moyamoya Disease"[Mesh] OR moyamoya[Title/Abstract] OR "moyamoya disease"[Title/Abstract] OR "moyamoya syndrome"[Title/Abstract] OR "moyamoya angiopathy"[Title/Abstract] OR "moyamoya vasculopathy"[Title/Abstract] OR "quasi-moyamoya"[Title/Abstract] OR "spontaneous occlusion of the circle of Willis"[Title/Abstract] OR "hemorrhagic moyamoya"[Title/Abstract] OR "ischemic moyamoya"[Title/Abstract]
#2 ("Tomography, Optical Coherence"[Mesh] AND "Angiography"[Mesh]) OR "optical coherence tomography angiography"[Title/Abstract] OR "OCT angiography"[Title/Abstract] OR OCTA[Title/Abstract] OR OCT-A[Title/Abstract] OR "retinal microvasculature"[Title/Abstract] OR "retinal microvascular"[Title/Abstract] OR "retinal vascular"[Title/Abstract] OR "retinal vessel"[Title/Abstract] OR "retinal perfusion"[Title/Abstract] OR "retinal circulation"[Title/Abstract] OR "retinal blood flow"[Title/Abstract] OR "foveal avascular zone"[Title/Abstract] OR FAZ[Title/Abstract] OR "vessel density"[Title/Abstract] OR "peripapillary vessel density"[Title/Abstract] OR "perfusion density"[Title/Abstract] OR "radial peripapillary capillary"[Title/Abstract] OR "radial peripapillary capillaries"[Title/Abstract] OR "superficial capillary plexus"[Title/Abstract] OR "deep capillary plexus"[Title/Abstract] OR choriocapillaris[Title/Abstract]Five electronic databases: PubMed, Embase, Web of Science Core Collection, Scopus, and CNKI (Chinese National Knowledge Infrastructure).
PubMed strategy (full strategy for all five databases available on request; CNKI strategy in Chinese):
#1 "Moyamoya Disease"[Mesh] OR moyamoya[Title/Abstract] OR "moyamoya syndrome"[Title/Abstract] OR "moyamoya angiopathy"[Title/Abstract] OR "moyamoya vasculopathy"[Title/Abstract] OR "quasi-moyamoya"[Title/Abstract] OR "spontaneous occlusion of the circle of Willis"[Title/Abstract] OR "hemorrhagic moyamoya"[Title/Abstract] OR "ischemic moyamoya"[Title/Abstract]
#2 ("Tomography, Optical Coherence"[Mesh] AND "Angiography"[Mesh]) OR "optical coherence tomography angiography"[Title/Abstract] OR "OCT angiography"[Title/Abstract] OR OCTA[Title/Abstract] OR "foveal avascular zone"[Title/Abstract] OR FAZ[Title/Abstract] OR "vessel density"[Title/Abstract] OR "perfusion density"[Title/Abstract] OR "retinal microvasculature"[Title/Abstract] OR "retinal perfusion"[Title/Abstract] OR "radial peripapillary capillary"[Title/Abstract] OR "superficial capillary plexus"[Title/Abstract] OR "deep capillary plexus"[Title/Abstract] OR choriocapillaris[Title/Abstract]
#3 #1 AND #2.

Participant or population Patients of any age with a confirmed diagnosis of MMD or MMS (diagnosed by DSA, MRA, or CTA). Subgroup analyses are planned for: pediatric vs. adult patients; MMD vs. MMS; ischemic vs. hemorrhagic presentation.

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Intervention Optical coherence tomography angiography (OCTA) examination of the retina, using any commercially available device (e.g., Zeiss AngioPlex, Optovue RTVue XR Avanti, Topcon Triton, Heidelberg Spectralis). Structural OCT measurements (RNFL thickness, choroidal thickness) are considered part of the same imaging assessment.

Comparator Healthy controls examined with the same OCTA/OCT protocol. Studies using only within-subject (pre-/post-operative or fellow-eye) comparisons will be recorded separately and not pooled with between-group comparisons.

Study designs to be included Observational studies: cross-sectional, case-control, and cohort studies.

Eligibility criteria Additional eligibility criteria beyond the PICOS elements:
1. Only peer-reviewed original research articles and explicitly labeled preprints (labeled "not peer-reviewed" wherever cited) will be eligible; reviews, meta-analyses, editorials, conference abstracts without complete data, and single-patient case reports without a comparison group will be excluded.
2. Studies must report extractable group-level data (mean ± SD, median [IQR] convertible to mean ± SD, or data retrievable from figures). Data that remain unavailable after two email requests to the corresponding authors will lead to exclusion of the study.
3. When multiple publications report overlapping or identical patient cohorts, only the publication with the largest sample size or the most complete outcome data will be included; the others will be excluded as duplicate cohorts.
4. Studies examining only cerebral perfusion (e.g., SPECT, ASL, CT perfusion) without any ocular OCTA/OCT measurements will be excluded from the main synthesis.
5. No language restrictions will be applied at title/abstract screening; full texts in languages other than Chinese or English will be excluded at the data-extraction stage and recorded.

Information sources Electronic databases (searched from inception to 29 October 2026, with an update search 2–4 weeks before submission): PubMed, Embase, Web of Science Core Collection, Scopus, and CNKI (Chinese National Knowledge Infrastructure); Europe PMC will be searched as a supplementary source.
Additional sources: (1) backward citation tracking of the reference lists of all included studies and relevant reviews; (2) forward citation tracking (cited-by searches) of included studies in Web of Science and Scopus; (3) grey literature screening via Europe PMC (preprint records will be labeled "not peer-reviewed"); (4) direct contact with study authors to obtain missing or unpublished outcome data. Trial registers and regulatory documents are not applicable to this review of observational diagnostic-imaging studies.

Main outcome(s) Co-primary outcomes: (1) macular vessel density (VD) of the superficial capillary plexus, deep capillary plexus, and/or whole image; (2) foveal avascular zone (FAZ) area.

Additional outcome(s) (1) retinal nerve fiber layer (RNFL) thickness; (2) choroidal thickness (subfoveal choroidal thickness preferred; average choroidal thickness as an alternative).

Data management Records retrieved from each database will be exported in RIS format with the search date and database name recorded in a screening log. All records will be combined in reference management software (EndNote or Zotero) and deduplicated in two steps: automated deduplication by title, first author, year, and DOI, followed by manual verification. The deduplicated record set, together with screening decisions of both reviewers at the title/abstract and full-text stages (including exclusion reasons), will be maintained in a structured screening log to generate the PRISMA 2020 flow diagram. Extracted data will be recorded in a predefined, piloted extraction form (Microsoft Excel) with double-entry and reconciliation fields; any statistical conversions (e.g., median [IQR] to mean ± SD) will be documented with the formula used, the converting reviewer, and the verifying reviewer. All files (search results, screening log, extraction forms, analysis code) will be stored in a version-controlled project repository with regular backups, retained for at least five years after publication.

Quality assessment / Risk of bias analysis The Newcastle–Ottawa Scale (NOS) for cross-sectional and case-control studies.

Strategy of data synthesis Continuous outcomes will be pooled as mean differences (MD) when measured on the same scale (FAZ area in mm^2, RNFL and choroidal thickness in μm) and as standardized mean differences (SMD, Hedges' g) for vessel density given heterogeneity of reporting units and scan protocols. A random-effects model (restricted maximum likelihood) will be used given expected clinical and methodological heterogeneity. Pooled estimates will be reported with 95% confidence intervals.

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Subgroup analysis Subgroup analyses: pediatric vs. adult; MMD vs. MMS; ischemic vs. hemorrhagic type; OCTA device brand; scan area (3×3 vs 6×6 vs 4.5×4.5 mm). Statistical heterogeneity will be assessed with the I^2 statistic ($I^2 > 50\%$ considered substantial).

Sensitivity analysis Exclusion of studies at high risk of bias; exclusion of preprints (which will be included but labeled "not peer-reviewed"); leave-one-out analysis for outcomes with ≥10 studies.

Language restriction No language restrictions at title/abstract screening; full texts in languages other than Chinese or English will be excluded at the data-extraction stage and recorded.

Country(ies) involved China.

Keywords moyamoya disease; moyamoya syndrome; optical coherence tomography angiography.

Contributions of each author

Author 1 - Wenming Chen - The author contributed to the development of the selection criteria, title/abstract and full-text screening, data extraction, risk-of-bias assessment with the Newcastle-Ottawa Scale, and drafting of the manuscript.
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Author 2 - Fanjun Meng - The author contributed to the development of the selection criteria, title/abstract and full-text screening, data extraction, and independent cross-checking of extracted data.
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