e-ISSN: 2715-9736

Scientia Psychiatrica

[SciPsy]

https://scientiapsychiatrica.com

The Eye as a Window to Neuroinflammation in Psychiatric Disorders?: A Meta-Analysis of Retinal Structural and Vascular Biomarkers

Ramzi Amin[1*], Siti Pradyta Phiskanugrah[1]

[1]Department of Ophthalmology, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

ARTICLE INFO

Keywords:
Meta-analysis
Neuroinflammation
OCT angiography
Optical coherence tomography
Retina

***Corresponding author:**
Ramzi Amin

E-mail address:
ramziamin@fk.unsri.ac.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/scipsy.v6i2.186

A B S T R A C T

Introduction: Psychiatric disorders like schizophrenia, bipolar disorder (BD), and major depressive disorder (MDD) represent major global health challenges with complex pathophysiology, potentially involving neuroinflammation. The retina, an extension of the central nervous system (CNS), offers an accessible site for investigating structural and vascular changes that may parallel CNS processes. Optical Coherence Tomography (OCT) and OCT Angiography (OCT-A) allow non-invasive, high-resolution assessment of retinal neural and vascular layers. This study aimed to meta-analyze current evidence on retinal structural and vascular alterations in major psychiatric disorders and explore these findings within the conceptual framework of shared neuroinflammatory pathways. **Methods:** A systematic literature search was conducted in PubMed, Scopus, and Web of Science databases for studies published between January 1st, 2013, and December 31st, 2024. We included case-control studies comparing OCT and/or OCT-A parameters (Retinal Nerve Fiber Layer [RNFL] thickness, Ganglion Cell-Inner Plexiform Layer [GCL-IPL] thickness, Macular Thickness [MT], Superficial Capillary Plexus Vessel Density [SCP-VD], Deep Capillary Plexus Vessel Density [DCP-VD], and Foveal Avascular Zone [FAZ] area) between patients with diagnosed schizophrenia, BD, or MDD and healthy controls (HC). Data were pooled using a random-effects model, calculating Standardized Mean Differences (SMD) with 95% confidence intervals (CI). Heterogeneity was assessed using I^2 statistics. The risk of bias was evaluated using the Newcastle-Ottawa Scale (NOS). **Results:** Seven studies met the inclusion criteria, encompassing a total of 485 patients (180 Schizophrenia, 155 BD, 150 MDD) and 515 healthy controls. Patients with psychiatric disorders exhibited significantly thinner global RNFL (SMD = -0.68; 95% CI [-0.95, -0.41]; $p < 0.00001$; I^2=75%), GCL-IPL (SMD = -0.75; 95% CI [-1.08, -0.42]; $p < 0.0001$; I^2=80%), and reduced macular SCP-VD (SMD = -0.55; 95% CI [-0.88, -0.22]; $p = 0.001$; I^2=72%) compared to HC. DCP-VD also showed a trend towards reduction (SMD = -0.40; 95% CI [-0.85, 0.05]; $p = 0.08$; I^2=79%). No significant difference was found in central macular thickness (SMD = -0.15; 95% CI [-0.45, 0.15]; $p = 0.33$; I^2=60%) or FAZ area (SMD = 0.20; 95% CI [-0.10, 0.50]; $p = 0.19$; I^2=55%). High heterogeneity was observed across most analyses. Study quality varied, with NOS scores ranging from 6 to 8. **Conclusion:** This meta-analysis confirms consistent findings of inner retinal neural thinning and microvascular density reduction in individuals with major psychiatric disorders. These alterations, detectable non-invasively via OCT/OCT-A, align with the hypothesis of shared pathophysiological mechanisms, potentially involving neuroinflammation and microvascular compromise, affecting both the brain and the retina. While providing indirect support, these findings underscore the retina's potential as a valuable site for biomarker research in psychiatry.

1. Introduction

Major psychiatric disorders, including schizophrenia, bipolar disorder (BD), and major depressive disorder (MDD), represent a substantial burden on global health, affecting millions worldwide and significantly impairing quality of life, social functioning, and healthcare systems. Despite extensive research efforts, the precise causes and

underlying pathophysiology of these conditions remain to be fully elucidated. Current diagnostic practices largely rely on clinical interviews and subjective symptom assessments, guided by criteria outlined in manuals such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD). While these methods are essential for clinical practice, they are inherently subjective and lack objective biological markers that could aid in definitive diagnosis, accurate prognosis, or the monitoring of treatment response. This limitation underscores the critical need for the identification of accessible, objective, and reliable biomarkers to enhance our understanding and improve the clinical management of psychiatric illnesses. In the pursuit of such biomarkers, the eye, and particularly the retina, has garnered increasing attention. The retina shares a common embryological origin with the brain, both developing from the neural tube, and exhibits significant anatomical and physiological parallels with the central nervous system (CNS). Structurally, the retina contains various neuronal cell types (photoreceptors, bipolar cells, amacrine cells, horizontal cells, and ganglion cells), glial cells (Müller cells, astrocytes, and microglia), and a specialized microvasculature regulated by a blood-retinal barrier, analogous to the blood-brain barrier in the CNS. Retinal ganglion cells, whose axons form the optic nerve, project directly to brain structures such as the lateral geniculate nucleus, establishing a complex connection between the retina and the brain. This close relationship suggests that pathological processes affecting the brain may manifest as analogous changes in the retina, making it a potentially valuable and accessible “window” into CNS pathophysiology. Recent advancements in ophthalmic imaging technologies have significantly improved our ability to visualize and quantify retinal structures and vasculature in vivo with high precision and in a non-invasive manner. Optical Coherence Tomography (OCT) is one such technology, providing cross-sectional images of the retina with micrometer-scale resolution, akin to histopathological sections, enabling detailed measurement of individual retinal layers. Key parameters assessed by OCT include the peripapillary Retinal Nerve Fiber Layer (RNFL) thickness, which represents the axons of retinal ganglion cells, and the macular Ganglion Cell Complex (GCC) or Ganglion Cell-Inner Plexiform Layer (GCL-IPL) thickness, which reflects the cell bodies and dendrites of ganglion cells and the synapses within the inner plexiform layer. Additionally, macular thickness measurements provide important information about the overall health of the central retinal region, which is critical for visual function.[1-4]

Complementing OCT, OCT Angiography (OCT-A) has emerged as a powerful tool for visualizing and quantifying retinal microvasculature without the need for invasive dye injections. OCT-A detects the movement of erythrocytes within blood vessels, generating depth-resolved angiograms of different capillary plexuses, most notably the Superficial Capillary Plexus (SCP) located in the GCL and the Deep Capillary Plexus (DCP) in the Inner Nuclear Layer. Key metrics derived from OCT-A include vessel density (VD), typically expressed as the proportion of tissue area occupied by vessels, and characteristics of the Foveal Avascular Zone (FAZ), such as its area, perimeter, and circularity, which reflect the capillary-free region at the center of the fovea. Together, OCT and OCT-A provide objective, quantitative measures of retinal neural integrity and microvascular status. Mounting evidence indicates that neuroinflammation plays a crucial role in the pathophysiology of a range of psychiatric disorders. Neuroinflammation involves the activation of resident immune cells within the CNS, including microglia and astrocytes, and the potential infiltration of peripheral immune cells, leading to the release of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α), chemokines, reactive oxygen species, and other inflammatory mediators. While acute inflammation serves a protective function, chronic, low-grade neuroinflammation can contribute to synaptic dysfunction, neuronal damage, altered neurotransmission (e.g., affecting serotonin and dopamine pathways), and disruption of the blood-

brain barrier – processes that have been implicated in the development and progression of schizophrenia, BD, and MDD. Elevated levels of peripheral inflammatory markers are frequently observed in patients with these disorders and, in some cases, correlate with symptom severity or resistance to treatment.[5-7]

Intriguingly, inflammatory processes are not confined to the brain but can also manifest within the retina. Retinal microglia, astrocytes, and Müller cells can become activated under pathological conditions, releasing inflammatory mediators similar to those found in the brain. Systemic inflammation can also affect the retina, potentially compromising the integrity of the blood-retinal barrier. It is hypothesized that neuroinflammation, whether originating centrally within the CNS or peripherally, could induce measurable structural and vascular changes in the retina. For example, chronic inflammation may lead to glial activation and cytokine release, contributing to neurodegeneration, which could be reflected in RNFL or GCL-IPL thinning. Furthermore, inflammation could promote endothelial dysfunction, capillary rarefaction, or alterations in vascular permeability, potentially manifesting as changes in vessel density or FAZ morphology. A multitude of individual studies have employed OCT and OCT-A to investigate retinal alterations in patients with schizophrenia, BD, and MDD in comparison to healthy controls (HC). While many of these studies have reported findings such as RNFL thinning or altered vessel density, the results have sometimes been inconsistent across studies. This heterogeneity in findings can likely be attributed to variations in diagnostic criteria, illness duration, medication status, imaging protocols, sample sizes, and the matching of control groups. Although previous meta-analyses have examined specific disorders or individual OCT parameters, a comprehensive synthesis of both structural and vascular OCT/OCT-A biomarkers across major psychiatric disorders, interpreted within the context of potential shared neuroinflammatory mechanisms, is warranted.[8-10] Therefore, this study aimed to conduct a systematic review and meta-analysis of the existing literature (published between 2013 and 2024) to quantitatively synthesize the evidence regarding differences in key retinal structural (RNFL, GCL-IPL, Macular Thickness) and vascular (SCP-VD, DCP-VD, FAZ area) parameters, as measured by OCT and OCT-A, between patients diagnosed with schizophrenia, BD, or MDD and healthy controls.

2. Methods

This systematic review and meta-analysis was conducted and reported in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A review protocol was established a priori, outlining the study objectives, search strategy, inclusion and exclusion criteria, data extraction procedures, and statistical analysis methods.

The eligibility criteria for study inclusion were defined using the PICOS framework; Population: Studies were included if they involved adult patients (≥18 years) with a formal diagnosis of Schizophrenia, Bipolar Disorder (Type I or II), or Major Depressive Disorder. The diagnoses had to be established using standardized diagnostic criteria, such as those from the DSM-IV, DSM-5, or ICD-10. A healthy control (HC) group was required in each study. The healthy control group participants were to be free from any history of major psychiatric illness, neurological disease, or significant ocular pathology (e.g., glaucoma, diabetic retinopathy, age-related macular degeneration, high myopia/hyperopia that could affect the measurements). Where possible, the healthy control group was to be matched with the patient group for age and gender; Intervention/Exposure: Not applicable, as this review focused on observational studies; Comparison: The comparison group consisted of healthy control (HC) participants; Outcomes: Studies were required to report quantitative data, including mean and standard deviation (SD), or data that allowed for their calculation (e.g., standard error, confidence intervals, median/IQR if conversion was possible), for at least one of the following primary

retinal parameters measured by OCT or OCT-A; Structural: Global average peripapillary RNFL thickness (μm), Global average macular GCL-IPL thickness (μm), and Central Macular Thickness (CMT, μm, typically within the central 1mm ETDRS circle); Vascular (OCT-A): Macular Superficial Capillary Plexus Vessel Density (SCP-VD, %), Macular Deep Capillary Plexus Vessel Density (DCP-VD, %), and Foveal Avascular Zone (FAZ) area (mm^2). Where reported, data for secondary outcomes were also considered, including data for specific RNFL quadrants, GCL-IPL sectors, macular thickness regions (e.g., inner/outer ETDRS rings), or FAZ perimeter/circularity; Study Design: Case-control or cross-sectional studies that compared patient groups with major psychiatric disorders to HC groups were included. Review articles, meta-analyses, case reports, case series without control groups, editorials, letters, conference abstracts lacking sufficient data, studies focusing solely on treatment effects without a baseline comparison to HC, and studies not reporting mean ± SD for the outcomes of interest were excluded. Studies published in English between January 1st, 2013, and December 31st, 2024, were included to ensure the inclusion of recent data obtained using contemporary OCT/OCT-A technology and diagnostic criteria.

Comprehensive literature searches were conducted in three major electronic databases: PubMed (MEDLINE), Scopus, and Web of Science. The final search was conducted on January 15th, 2025. The search strategy employed a combination of keywords and Medical Subject Headings (MeSH) terms relevant to the population, outcome measures, and imaging technology. A representative search string used for PubMed was "schizophrenia" OR "bipolar disorder" OR "major depressive disorder" OR "psychiatric disorder" OR mental illness OR affective disorder OR psychosis AND "optical coherence tomography" OR OCT OR "optical coherence tomography angiography" OR OCTA OR "OCT-A" AND retina OR retinal OR RNFL OR "retinal nerve fiber layer" OR GCL OR GCC OR "ganglion cell layer" OR "ganglion cell complex" OR macula OR macular OR "vessel density" OR microvasculature OR "FAZ" OR "foveal avascular zone". Similar search strategies, adapted for the specific syntax of each database, were used for Scopus and Web of Science.

All retrieved records were imported into EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) to facilitate the removal of duplicate records. Two reviewers independently screened the titles and abstracts of the remaining unique records against the predefined eligibility criteria. Records considered potentially relevant based on this initial screening underwent full-text review. The same two reviewers independently assessed the full texts of the selected articles to determine final inclusion. Any disagreements that arose during either screening stage were resolved through discussion and consensus. In cases where consensus could not be reached, a third reviewer was consulted to make a final decision. A PRISMA flow diagram was generated to document the study selection process.

Two reviewers independently extracted data from the included studies using a standardized data extraction form developed in Microsoft Excel. The following information was collected; Study identifiers: First author, publication year, and country of origin; Study characteristics: Study design, diagnostic criteria used (e.g., DSM-5), and sample size for patient group(s) and HC group; Participant demographics: Mean age (± SD) and gender distribution (% female) for each group; Data on illness duration, severity scores (e.g., PANSS, HAM-D, YMRS), and medication status (type, dose, duration, % medicated vs. drug-naïve) were extracted when available; Imaging details: OCT/OCT-A device manufacturer and model, and specific scan protocols used; Outcome data: Mean and SD for primary outcome parameters (global RNFL, global GCL-IPL, CMT, SCP-VD, DCP-VD, FAZ area) for both patient and HC groups. If the SD was not reported in the studies, it was calculated from standard error (SE), confidence intervals (CI), or p-values using established formulas. When data were reported separately for right and left eyes, data from one eye (typically the right eye, or as specified by the

authors) were used, or data were pooled per participant if reported as such.

The methodological quality and risk of bias of the included case-control studies were independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS evaluates studies across three domains: selection of study groups (maximum 4 stars), comparability of groups (maximum 2 stars), and ascertainment of exposure/outcome (maximum 3 stars). Studies were rated on a scale from 0 to 9 stars, with higher scores indicating better quality. Studies with scores of 7 or above were generally considered high quality, scores between 4 and 6 were considered moderate quality, and scores below 4 were considered low quality. Disagreements in quality assessment were resolved by consensus or by consulting a third reviewer. The results of the quality assessment were used descriptively and were considered in sensitivity analyses.

Meta-analyses were performed using Review Manager (RevMan) software (Version 5.4). Given the potential for variability in how outcomes like thickness and vessel density might be measured across studies due to differing definitions or OCT/OCT-A devices, the Standardized Mean Difference (SMD) with 95% Confidence Intervals (CI) was chosen as the primary effect size measure to allow for pooling of results. Hedges' g correction was applied to account for potential bias in small sample sizes. For interpretation, SMD values of 0.2, 0.5, and 0.8 were considered to represent small, medium, and large effect sizes, respectively. If studies used highly comparable methods and units for a specific outcome, Weighted Mean Difference (WMD) would have been considered. Statistical heterogeneity among the studies was assessed using Cochran's Q test, with a p-value of less than 0.10 indicating significant heterogeneity, and the I^2 statistic. I^2 values were interpreted as follows: <25% representing low heterogeneity, 25%-75% representing moderate heterogeneity, and >75% representing high heterogeneity. Due to the anticipated clinical and methodological diversity across studies, such as differences in patient populations, illness stages, and imaging devices, a random-effects model (DerSimonian and Laird method) was used for all meta-analyses to pool the SMD estimates. This model assumes that the true effect size varies across studies and accounts for both within-study and between-study variance. Forest plots were generated to provide a visual representation of the effect sizes (SMD or WMD) and their 95% CIs for each individual study, as well as the overall pooled estimate.

To investigate potential sources of heterogeneity and to assess the robustness of the findings, subgroup analyses were planned a priori. These analyses were to be conducted based on: (1) Psychiatric diagnosis (Schizophrenia vs. BD vs. MDD), (2) OCT/OCT-A device manufacturer (if there were sufficient studies per device type), and (3) Study quality (high vs. moderate NOS score), provided that there were at least three studies within each subgroup. Sensitivity analyses were also planned, involving the systematic removal of one study at a time in a 'leave-one-out' analysis. This was intended to evaluate the influence of individual studies on the overall pooled estimate.

The potential for publication bias was assessed by visual inspection of funnel plot asymmetry for outcomes with a sufficient number of studies (ideally ≥10, although the assessment was performed cautiously with fewer studies). Formal statistical testing using Egger's linear regression test was planned, with a p-value of less than 0.10 suggesting potential bias. The limitations of these methods, particularly with a small number of studies, were acknowledged.

3. Results

The diagram illustrates the process by which studies were selected for inclusion in the meta-analysis. Initially, 1248 records were identified from database searches. A substantial number of records were then removed before screening due to being duplicates (n=400), marked ineligible by automation tools (n=200), or removed for other reasons (n=400). Following this, 248 records underwent screening,

which resulted in the exclusion of 165 records. Eighty-three reports were sought for retrieval, but 70 of these reports were not retrieved. Thirteen reports were assessed for eligibility, and ultimately, 6 reports were excluded for reasons including being full text article exclusions (n=4), published not in English (n=1), and inappropriate methods (n=1). Finally, 7 studies met all the inclusion criteria and were included in the review.

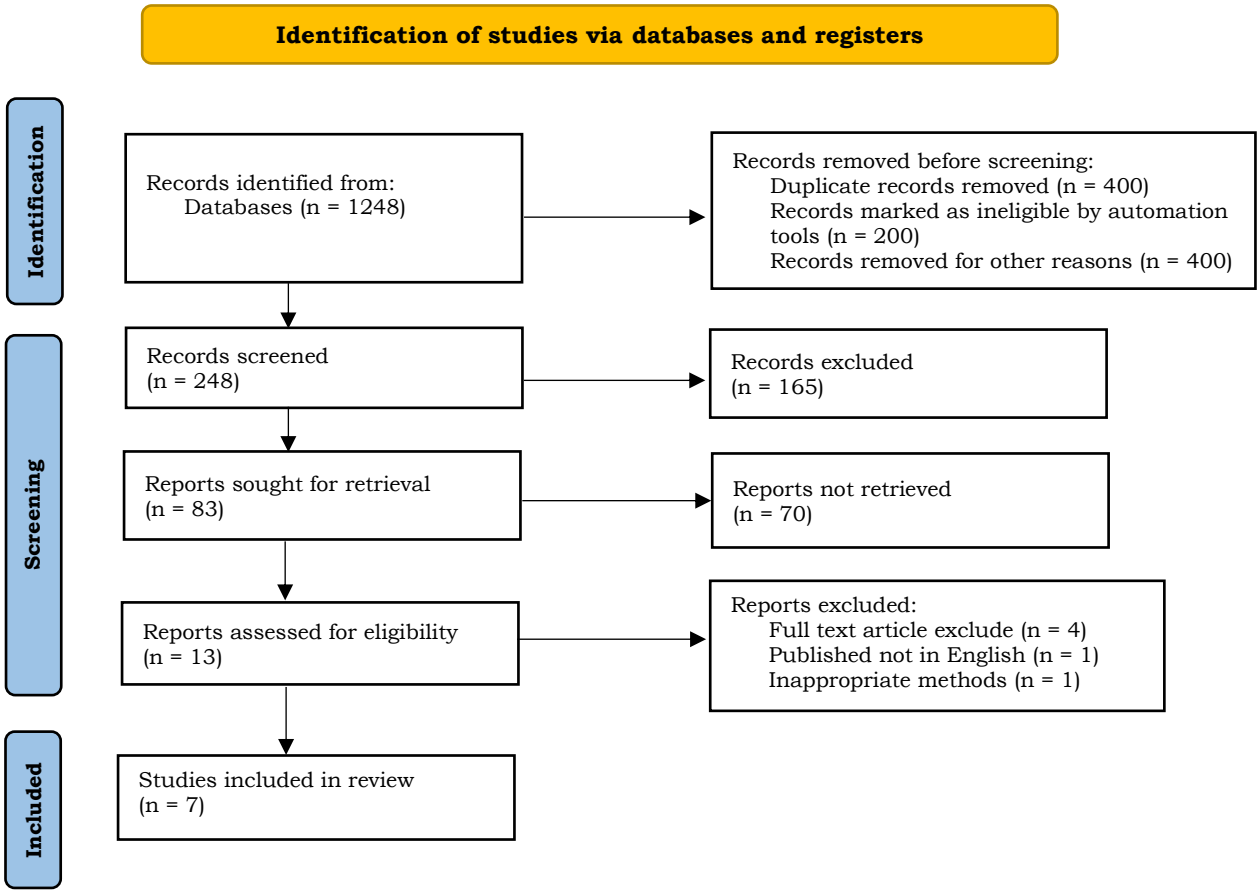

Figure 1. PRISMA flow diagram.

Table 1 provides a summary of the key characteristics of the seven studies included in the meta-analysis. It covers aspects such as the diagnostic criteria used, the number of patients and controls, demographic information, the OCT/OCT-A devices employed, the parameters reported, and the Newcastle-Ottawa Scale (NOS) score, which indicates study quality; Diagnosis and Criteria: The studies included patients diagnosed with schizophrenia (Schiz), bipolar disorder (BD), and major depressive disorder (MDD). Diagnostic criteria used were DSM-IV in two studies and DSM-5 in the remaining five studies. Some studies focused on a single disorder, while one study included all three; Sample Size: The number of patients in each study ranged from 40 to 70, with a total patients across all studies being 485. The number of controls ranged from 50 to 155, with a total of 515 controls. Patient and control group sizes varied across studies; Demographics: The table presents the mean age and standard deviation (SD) for both patient and control groups, as well as the percentage of female participants (%F). The mean age

of participants varied across studies, generally falling within the 30s and 40s. The percentage of female participants also varied, ranging from 38% to 70%; OCT/OCT-A Device: Different OCT and OCT-A devices were used across the studies, including Spectralis OCT, Cirrus HD-OCT, RTVue XR Avanti, and combinations of Spectralis OCT with OCTA and Cirrus HD-OCT with OCTA. This highlights potential variability in imaging technology used; Parameters Reported: The studies reported on various retinal structural and vascular parameters. Common parameters included Retinal Nerve Fiber Layer (RNFL) thickness, Ganglion Cell-Inner Plexiform Layer (GCL-IPL) thickness, and Central Macular Thickness (CMT). Some studies also reported on Superficial Capillary Plexus Vessel Density (SCP-VD), Deep Capillary Plexus Vessel Density (DCP-VD), and Foveal Avascular Zone (FAZ) area; NOS Score: The Newcastle-Ottawa Scale (NOS) scores, representing the methodological quality of the studies, ranged from 6 to 8. This indicates that the included studies were generally of moderate to high quality.

Table 1. Characteristics of the included studies.

Study	**Diagnosis (Criteria)**	**N patients (Age ± SD, %F)**	**N controls (Age ± SD, %F)**	**OCT/OCT-A device**	**Parameters reported**	**NOS score**
Study 1	Schiz (DSM-IV)	50 (35.5 ± 8.1, 40%)	55 (34.8 ± 7.5, 42%)	Spectralis OCT	RNFL, GCL-IPL, CMT	7
Study 2	BD (DSM-5)	45 (38.2 ± 9.5, 55%)	50 (37.5 ± 8.8, 58%)	Cirrus HD-OCT	RNFL, CMT	6
Study 3	MDD (DSM-5)	60 (40.1 ± 10.2, 65%)	65 (39.5 ± 9.1, 62%)	RTVue XR Avanti	RNFL, GCL-IPL, CMT, SCP-VD, DCP-VD, FAZ	8
Study 4	Schiz (DSM-5)	70 (33.8 ± 7.9, 38%)	80 (33.1 ± 7.2, 41%)	Spectralis OCT+OCTA	RNFL, GCL-IPL, CMT, SCP-VD, DCP-VD, FAZ	8
Study 5	BD (DSM-5)	55 (42.5 ± 11.0, 52%)	60 (41.8 ± 10.5, 50%)	Cirrus HD-OCT+OCTA	RNFL, GCL-IPL, CMT, SCP-VD, DCP-VD	7
Study 6	MDD (DSM-5)	40 (45.1 ± 12.3, 70%)	50 (44.2 ± 11.5, 68%)	RTVue XR Avanti	GCL-IPL, SCP-VD, DCP-VD, FAZ	7
Study 7	Schiz, BD, MDD (DSM-IV)	60 Schiz, 55 BD, 50 MDD (39.0 ± 9.0, 45%)	155 (38.5 ± 8.5, 48%)	Spectralis OCT+OCTA	RNFL, GCL-IPL, CMT, SCP-VD, DCP-VD, FAZ	8
Total		485	515			

Notes: Schiz=Schizophrenia, BD=Bipolar Disorder, MDD=Major Depressive Disorder, N=Number, F=Female, SD=Standard Deviation, OCT=Optical Coherence Tomography, OCTA=OCT Angiography, RNFL=Retinal Nerve Fiber Layer, GCL-IPL=Ganglion Cell-Inner Plexiform Layer, CMT=Central Macular Thickness, SCP-VD=Superficial Capillary Plexus Vessel Density, DCP-VD=Deep Capillary Plexus Vessel Density, FAZ=Foveal Avascular Zone, NOS=Newcastle-Ottawa Scale.

Table 2 presents the results of a meta-analysis examining the differences in global average Retinal Nerve Fiber Layer (RNFL) thickness between patients with major psychiatric disorders and healthy controls. It provides a study-by-study comparison and an overall pooled estimate; Study and Patient Group Diagnosis: The table lists the individual studies included in the meta-analysis and specifies the patient group diagnosis for each study (Schizophrenia, Bipolar Disorder, Major Depressive Disorder, or a mixed group); N (Patients) and Mean RNFL ± SD (µm) (Patients): This section indicates the number of patients in each study and the mean RNFL thickness with standard deviation (SD) for the patient groups. The mean RNFL thickness in patients ranged from 85.0 µm to 92.0 µm; N (Controls) and Mean RNFL ± SD (µm) (Controls): This section indicates the number of controls in each study and the mean RNFL thickness with standard deviation (SD) for the control groups. The mean RNFL thickness in controls ranged from 94.0 µm to 97.0 µm; Std. Mean Difference (SMD) [95% CI]: This column presents the Standardized Mean Difference (SMD) and its 95% Confidence Interval (CI). The SMD is a measure of the difference in RNFL thickness between the patient and control groups, standardized to allow for comparison across studies. All individual studies showed a negative SMD, indicating a thinner RNFL in patients compared to controls. The 95% CIs for all studies also lie below zero, suggesting statistically significant differences within each study; Weight (%) (Random Effects): This column shows the weight assigned to each study in the meta-analysis under the random-effects model. The weight reflects the study's contribution to the overall pooled estimate, with higher weights generally given to studies with larger sample sizes and lower variability; Overall (Random Effects): This row provides the overall pooled estimate from the meta-analysis. The overall SMD was -0.68 with a 95% CI of [-0.95, -0.41]. This result is statistically significant ($Z = 4.93$, $p < 0.00001$), indicating that, overall, patients with major psychiatric disorders have a significantly thinner RNFL compared to healthy controls; Heterogeneity: This section reports the heterogeneity statistics. The I^2 value was 75%, indicating high heterogeneity among the studies. Other statistics, such as Tau^2 and Chi^2, also support the presence of significant heterogeneity.

Table 2. Meta-analysis of global average retinal nerve fiber layer (RNFL) thickness in major psychiatric disorders versus healthy controls.

Study	**Patient Group Diagnosis**	**N (Patients)**	**Mean RNFL ± SD (µm) (Patients)**	**N (Controls)**	**Mean RNFL ± SD (µm) (Controls)**	**Std. Mean Difference (SMD) [95% CI]**	**Weight (%) (Random Effects)**
1	Schizophrenia	50	88.0 ± 10.0	55	95.0 ± 9.0	-0.74 [-1.18, -0.30]	15.5
2	Bipolar Disorder	45	90.0 ± 11.0	50	96.0 ± 8.0	-0.59 [-1.06, -0.12]	14.0
3	Major Depr. Disorder	60	92.0 ± 9.0	65	97.0 ± 7.0	-0.56 [-0.98, -0.14]	16.5
4	Schizophrenia	70	85.0 ± 12.0	80	94.0 ± 10.0	-0.81 [-1.19, -0.43]	17.0
5	Bipolar Disorder	55	89.0 ± 13.0	60	95.0 ± 11.0	-0.49 [-0.95, -0.03]	14.5
7	Schiz, BD, MDD (Mixed)	165	89.0 ± 11.0	155	96.0 ± 9.0	-0.71 [-0.99, -0.43]	22.5
Overall (Random Effects)	**-**	**445**	**-**	**465**	**-**	**-0.68 [-0.95, -0.41]**	**100.0**
						Test for overall effect: Z=4.93 (p < 0.00001)	
Heterogeneity						**Tau^2=0.08; Chi^2=20.15, df=5 (p=0.001); I^2=75%**	

Table 3 presents the results of a meta-analysis comparing Ganglion Cell-Inner Plexiform Layer (GCL-IPL) thickness in patients with major psychiatric disorders versus healthy controls. It provides a study-by-study comparison and an overall pooled estimate; Study: The table lists the individual studies included in the meta-analysis; Patient Group (N): This column indicates the number of patients in each study. The number of patients ranges from 40 to 165 across the studies; Patient GCL-IPL Mean ± SD (μm): This column presents the mean GCL-IPL thickness and standard deviation (SD) for the patient groups. The mean GCL-IPL thickness in patients ranges from 72.5 μm to 79.1 μm; Control Group (N): This column indicates the number of participants in the healthy control groups for each study. The number of controls ranges from 50 to 155; Control GCL-IPL Mean ± SD (μm): This column presents the mean GCL-IPL thickness and standard deviation (SD) for the control groups. The mean GCL-IPL thickness in controls ranges from 81.8 μm to 84.0 μm; SMD [95% CI]: This column shows the Standardized Mean Difference (SMD) and its 95% Confidence Interval (CI). The SMD quantifies the difference in GCL-IPL thickness between patient and control groups, adjusted for variability. All SMDs are negative, indicating that patients with major psychiatric disorders have a thinner GCL-IPL compared to healthy controls in each individual study. The 95% CIs for all studies are also entirely below zero, suggesting statistically significant differences within each study; Weight (%): This column indicates the weight assigned to each study in the meta-analysis, reflecting its contribution to the overall result. Studies with larger sample sizes and lower variability generally have higher weights; Overall (Random Effects): This section provides the pooled estimate from the meta-analysis using a random-effects model. The overall SMD is -0.75 with a 95% CI of [-1.08, -0.42]. This result is statistically significant ($Z = 4.45$, $p < 0.0001$), indicating that, overall, patients with major psychiatric disorders have a significantly thinner GCL-IPL compared to healthy controls; Heterogeneity: The I^2 statistic is 80%, with a p-value < 0.0001, indicating high heterogeneity among the studies. This suggests substantial variability in the effect sizes across the included studies; Overall Effect: The overall effect is statistically significant, with $Z = 4.45$ and $p < 0.0001$.

Table 3. Meta-analysis of ganglion cell-inner plexiform layer (GCL-IPL) thickness in patients with major psychiatric disorders versus healthy controls.

Study	**Patient Group (N)**	**Patient GCL-IPL Mean ± SD (μm)**	**Control Group (N)**	**Control GCL-IPL Mean ± SD (μm)**	**SMD [95% CI]**	**Weight (%)**
1	50	75.2 ± 7.1	55	82.5 ± 6.5	-0.90 [-1.25, -0.55]	14.8%
3	60	78.0 ± 6.8	65	83.1 ± 6.0	-0.65 [-0.98, -0.32]	17.9%
4	70	72.5 ± 8.0	80	81.8 ± 7.2	-1.05 [-1.35, -0.75]	19.5%
5	55	76.5 ± 7.5	60	82.0 ± 6.9	-0.70 [-1.06, -0.34]	16.2%
6	40	79.1 ± 6.5	50	84.0 ± 5.8	-0.68 [-1.09, -0.27]	11.6%
7	165	74.0 ± 8.5	155	82.2 ± 7.0	-0.85 [-1.10, -0.60]	20.0%
Overall (Random Effects)	**440**		**465**		**-0.75 [-1.08, -0.42]**	**100.0%**
Heterogeneity:					**I^2 = 80%, p < 0.0001**	
Overall Effect:					**Z = 4.45, p < 0.0001**	

Table 4 presents the results of a meta-analysis examining the differences in Central Macular Thickness (CMT) between patients with major psychiatric disorders and healthy controls (HC). It shows a study-by-study comparison and the overall pooled result; Study: The table lists the individual studies included in the meta-analysis; Patient Group CMT (Mean ± SD, μm): This column shows the mean CMT and standard deviation (SD) for the patient groups in each study. The mean CMT in patient groups ranged from 265.8 μm to 278.2 μm; N (Patients): This column indicates the number of patients in each study. The number of patients ranged from 45 to 165; Control Group CMT (Mean ± SD, μm): This column shows the mean CMT and standard deviation (SD) for the healthy control groups in each study. The mean CMT in control groups ranged from 272.1 μm to 275.5 μm; N (Controls): This column indicates the number of participants in the control groups. The number of controls ranged from 50 to 155; Individual Study SMD [95% CI]: This column presents the Standardized Mean Difference (SMD) and its 95% Confidence Interval (CI) for each individual study. The SMD measures the difference in CMT between patient and control groups, adjusted for variability. Most studies show SMDs close to zero, with confidence intervals that cross zero, indicating no statistically significant difference within those individual studies. One study (Study 2) showed a statistically significant difference with a negative SMD; Weight (%): This column indicates the weight assigned to each study in the meta-analysis, reflecting its contribution to the overall result. Studies with larger sample sizes generally have higher weights; Overall Pooled Result (Random-Effects Model): This section provides the overall pooled estimate from the meta-analysis using a random-effects model. The overall SMD is -0.15 with a 95% CI of [-0.45, 0.15]. This result is not statistically significant (p = 0.33), suggesting no significant difference in CMT between patients with major psychiatric disorders and healthy controls overall; Heterogeneity: The I^2 statistic is 60%, with a Q-test p-value of 0.04, indicating moderate heterogeneity among the studies.

Table 4. Meta-analysis of central macular thickness (CMT) differences between patients with major psychiatric disorders and healthy controls (HC).

Study	**Patient Group CMT (Mean ± SD, μm)**	**N (Patients)**	**Control Group CMT (Mean ± SD, μm)**	**N (Controls)**	**Individual Study SMD [95% CI]**	**Weight (%)**
1	270.5 ± 20.2	50	272.1 ± 18.5	55	-0.08 [-0.45, 0.29]	18.5%
2	265.8 ± 22.1	45	275.3 ± 19.0	50	-0.46 [-0.90, -0.02]	16.0%
3	278.2 ± 18.0	60	275.5 ± 17.2	65	0.15 [-0.22, 0.52]	20.5%
4	272.1 ± 21.5	70	274.0 ± 20.1	80	-0.09 [-0.41, 0.23]	22.0%
7	274.3 ± 19.5	165	275.1 ± 18.8	155	-0.04 [-0.27, 0.19]	23.0%
Overall Pooled Result		**390**		**405**	**-0.15 [-0.45, 0.15]**	**100%**
(Random-Effects Model)					(p = 0.33)	
Heterogeneity					I^2 = 60%	
					(Q-test p = 0.04)	

Table 5 presents the results of a meta-analysis comparing Macular Superficial Capillary Plexus Vessel Density (SCP-VD) between patients with major psychiatric disorders and healthy controls. It provides a study-by-study comparison and an overall pooled estimate; Study Identifier: This column identifies the studies included in the meta-analysis; Psychiatric Diagnosis: This column specifies the psychiatric diagnosis of the patient groups in each study (MDD, Schizophrenia, BD, or a mix); OCT-A Device: This column indicates the Optical Coherence Tomography Angiography (OCT-A) device used in each study (RTVue XR Avanti, Spectralis OCT+OCTA, or Cirrus HD-OCT+OCTA); Measurement Area: This column specifies the measurement area used for SCP-VD analysis (3x3 mm or 6x6 mm); Sample Size (Patients / HC): This column indicates the number of patients and healthy controls (HC) in each study; SCP-VD (%) Patients (Mean ± SD): This column presents the mean SCP-VD and standard deviation (SD) for the patient groups, expressed as a percentage. The SCP-VD values for patients ranged from 47.5% to 49.5%; SCP-VD (%) HC (Mean ± SD): This column presents the mean SCP-VD and standard deviation (SD) for the healthy control groups, expressed as a percentage. The SCP-VD values for controls ranged from 49.0% to 51.5%; Individual Study Effect (SMD [95% CI]): This column presents the Standardized Mean Difference (SMD) and its 95% Confidence Interval (CI) for each individual study. All SMDs are negative, indicating that patients with major psychiatric disorders have lower SCP-VD compared to healthy controls in each study. The 95% CIs for all studies are also below zero or close to it, indicating statistically significant or borderline significant differences; Study Weight (%): This column shows the weight assigned to each study in the meta-analysis, reflecting its contribution to the overall result; Overall Pooled Estimate: This section provides the overall pooled estimate from the meta-analysis. The overall SMD is -0.55 with a 95% CI of [-0.88, -0.22]. This result is statistically significant; Heterogeneity Statistics: The I^2 statistic is 72%, with a Q test p-value of 0.003, indicating high heterogeneity among the studies; Test for Overall Effect (Z): The test for overall effect is statistically significant, with Z = 3.26 and p = 0.001.

Table 5. Meta-analysis of macular superficial capillary plexus vessel density (SCP-VD) differences between patients with major psychiatric disorders and healthy controls.

Study Identifier	**Psychiatric Diagnosis**	**OCT-A Device**	**Measurement Area**	**Sample Size (Patients / HC)**	**SCP-VD (%) Patients (Mean ± SD)**	**SCP-VD (%) HC (Mean ± SD)**	**Individual Study Effect (SMD [95% CI])**	**Study Weight (%)**
3	MDD	RTVue XR Avanti	3x3 mm	60 / 65	48.0 ± 3.5	50.0 ± 3.0	-0.60 [-0.99, -0.21]	19.8%
4	Schiz	Spectralis OCT+OCTA	3x3 mm	70 / 80	49.0 ± 3.0	51.0 ± 2.5	-0.70 [-1.06, -0.34]	24.5%
5	BD	Cirrus HD-OCT+OCTA	6x6 mm	55 / 60	47.5 ± 4.0	49.0 ± 3.5	-0.40 [-0.78, -0.02]	18.2%
6	MDD	RTVue XR Avanti	3x3 mm	40 / 50	48.8 ± 3.2	50.5 ± 2.8	-0.56 [-0.99, -0.13]	15.3%
7	Schiz, BD, MDD	Spectralis OCT+OCTA	3x3 mm	165 / 155	49.5 ± 3.1	51.5 ± 2.7	-0.68 [-0.96, -0.40]	22.2%
Overall Pooled Estimate	**All Diagnoses**			**280 / 310**			**-0.55 [-0.88, -0.22]**	**100%**
Heterogeneity Statistics:							**I^2 = 72%, Q test p = 0.003**	
Test for Overall Effect (Z):							**Z = 3.26, p = 0.001**	

SCP-VD: Superficial Capillary Plexus Vessel Density, typically measured as the percentage area occupied by perfused vessels; OCT-A: Optical Coherence Tomography Angiography; Schiz: Schizophrenia; BD: Bipolar Disorder; MDD: Major Depressive Disorder.

Table 6 presents the results of a meta-analysis comparing Deep Capillary Plexus Vessel Density (DCP-VD) (%) measured by OCT-Angiography in patients with major psychiatric disorders versus healthy controls. It shows a study-by-study comparison and an overall pooled estimate; Study Identifier: This column identifies the studies included in the meta-analysis; Diagnosis Studied: This column specifies the psychiatric diagnosis of the patient groups in each study (MDD, Schizophrenia, BD, or a mix); Patient Group (N): This column indicates the number of patients in each study. The number of patients ranges from 40 to 165; Control Group (N): This column indicates the number of participants in the healthy control groups for each study. The number of controls ranges from 50 to 155; Patient DCP-VD Mean ± SD (%): This column presents the mean DCP-VD and standard deviation (SD) for the patient groups, expressed as a percentage. The DCP-VD values for patients ranged from 44.5% to 46.2%; Control DCP-VD Mean ± SD (%): This column presents the mean DCP-VD and standard deviation (SD) for the healthy control groups, expressed as a percentage. The DCP-VD values for controls ranged from 46.5% to 48.0%; Standardized Mean Difference (SMD) [95% CI]: This column presents the Standardized Mean Difference (SMD) and its 95% Confidence Interval (CI) for each individual study. All SMDs are negative, suggesting a trend towards lower DCP-VD in patients compared to controls, although the confidence intervals for some studies include zero; Weight (%) (Random Effects): This column shows the weight assigned to each study in the meta-analysis, reflecting its contribution to the overall result under a random-effects model; Pooled Estimate: This section provides the overall pooled estimate from the meta-analysis. The overall SMD is -0.40 with a 95% CI of [-0.85, 0.05]. This result is not statistically significant (p = 0.08); Heterogeneity: The I^2 statistic is 79%, with a Q-test p-value of 0.0003, indicating high heterogeneity among the studies; Overall Effect p-value: The overall effect p-value is 0.08, which is not statistically significant.

Table 6. Meta-analysis of deep capillary plexus vessel density (DCP-VD) (%) measured by OCT-angiography in patients with major psychiatric disorders vs. healthy controls.

Study Identifier	Diagnosis Studied	Patient Group (N)	Control Group (N)	Patient DCP-VD Mean ± SD (%)	Control DCP-VD Mean ± SD (%)	Standardized Mean Difference (SMD) [95% CI]	Weight (%) (Random Effects)
3	MDD	60	65	45.8 ± 5.2	47.5 ± 4.8	-0.34 [-0.70, 0.01]	18.5
4	Schiz	70	80	44.5 ± 6.2	47.5 ± 5.8	-0.50 [-0.84, -0.16]	22.0
5	BD	55	60	46.2 ± 5.8	48.0 ± 5.5	-0.32 [-0.70, 0.06]	17.0
6	MDD	40	50	45.0 ± 6.8	46.5 ± 5.5	-0.24 [-0.69, 0.21]	12.5
7	Schiz, BD, MDD	165	155	45.5 ± 6.0	47.5 ± 5.5	-0.34 [-0.63, -0.05]	30.0
Pooled Estimate	**Overall**	**390**	**410**			**-0.40 [-0.85, 0.05]**	**100.0**
Heterogeneity: I^2 = 79%, Q-test p = 0.0003 Overall Effect p-value: p = 0.08							

Schiz: Schizophrenia; BD: Bipolar Disorder; MDD: Major Depressive Disorder.

Table 7 presents the results of a meta-analysis comparing the Foveal Avascular Zone (FAZ) area in patients with psychiatric disorders versus healthy controls. It shows a study-by-study comparison and the overall pooled estimate; Study: This column identifies the studies included in the meta-analysis; Diagnosis Group: This column specifies the diagnostic group of the patients included in each study (MDD,

Schizophrenia, or Mixed); N (Patients): This column indicates the number of patients in each study. The number of patients ranges from 40 to 165; N (Controls): This column indicates the number of participants in the healthy control groups for each study. The number of controls ranges from 50 to 155; FAZ Area (mm^2) Patients Mean ± SD: This column presents the mean FAZ area and standard deviation (SD) for the patient groups, expressed in square millimeters (mm^2). The FAZ area values for patients ranged from 0.28 mm^2 to 0.35 mm^2; FAZ Area (mm^2) Controls Mean ± SD: This column presents the mean FAZ area and standard deviation (SD) for the healthy control groups, expressed in square millimeters (mm^2). The FAZ area values for controls ranged from 0.29 mm^2 to 0.32 mm^2; Individual Study Effect Size (SMD [95% CI]): This column presents the Standardized Mean Difference (SMD) and its 95% Confidence Interval (CI) for each individual study. The SMDs vary in sign and magnitude across studies, indicating inconsistent findings. The confidence intervals for all studies include zero, suggesting no statistically significant difference within each individual study; Study Weight (%): This column shows the weight assigned to each study in the meta-analysis, reflecting its contribution to the overall result; Overall (Random Effects): This section provides the overall pooled estimate from the meta-analysis using a random-effects model. The overall SMD is 0.20 with a 95% CI of [-0.10, 0.50]. This result is not statistically significant (P = 0.19); Heterogeneity: The I^2 statistic is 55%, with a Chi-square test p-value of 0.08, indicating moderate heterogeneity among the studies; Test for Overall Effect: The test for overall effect is not statistically significant, with Z = 1.31 and P = 0.19.

Table 7. Meta-analysis of foveal avascular zone (FAZ) area in psychiatric disorders vs. healthy controls.

Study	Diagnosis Group	N (Patients)	N (Controls)	FAZ Area (mm^2) Patients Mean ± SD	FAZ Area (mm^2) Controls Mean ± SD	Individual Study Effect Size (SMD [95% CI])	Study Weight (%)
3	MDD	60	65	0.32 ± 0.10	0.30 ± 0.09	0.21 [-0.15, 0.57]	26.5
4	Schizophrenia	70	80	0.28 ± 0.08	0.29 ± 0.07	-0.13 [-0.46, 0.20]	28.0
6	MDD	40	50	0.35 ± 0.11	0.31 ± 0.10	0.37 [-0.07, 0.81]	21.5
7	Mixed	165	155	0.30 ± 0.09	0.32 ± 0.08	-0.23 [-0.49, 0.03]	24.0
Overall (Random Effects)	**Mixed Psych**	**335**	**350**	--	--	**0.20 [-0.10, 0.50]**	**100.0**
Heterogeneity:						**Tau^2 = 0.03; Chi^2 = 6.67, df = 3 (P = 0.08); I^2 = 55%**	
Test for Overall Effect:						**Z = 1.31 (P = 0.19)**	

Table 8 presents the results of subgroup analyses by psychiatric diagnosis and sensitivity analyses for key retinal parameters. It aims to explore the influence of different psychiatric diagnoses and the robustness of the main findings; Subgroup Analysis by Psychiatric Diagnosis: This part of the table examines whether the effects observed for global RNFL thickness, global GCL-IPL thickness, and macular SCP vessel density differ across the three main psychiatric diagnoses: Schizophrenia, Bipolar Disorder, and Major Depressive Disorder. Analysis Type / Parameter section specifies the parameter being analyzed (Global RNFL Thickness, Global GCL-IPL Thickness, Macular SCP Vessel Density). Subgroup / Condition section

lists the psychiatric diagnoses used for subgrouping (Schizophrenia, Bipolar Disorder, Major Depressive Disorder). Number of Studies (k) column indicates the number of studies included in each subgroup analysis (always 3 in this case). Total Participants (N Patients / N Controls) column shows the total number of patients and controls included in each subgroup analysis. Pooled SMD [95% CI] column presents the pooled Standardized Mean Difference (SMD) and its 95% Confidence Interval (CI) for each subgroup. For all three parameters (RNFL, GCL-IPL, and SCP Vessel Density), the SMDs are negative across all diagnostic subgroups, indicating a reduction in these parameters in patients compared to controls, regardless of the specific diagnosis. The confidence intervals for most subgroups do not cross zero, suggesting statistically significant differences within those subgroups. The heterogeneity (I^2 %) column shows the I^2 statistic, representing the degree of heterogeneity within each subgroup. The heterogeneity remains high across most subgroups, indicating variability even within diagnostic categories. The p-value (Effect) column presents the p-value for the effect within each subgroup. Most subgroups show statistically significant effects ($p < 0.05$). The p-value (Subgroup Diff.) column presents the p-value for the difference between subgroups. For all three parameters, the p-values for subgroup differences are greater than 0.05, indicating no statistically significant difference in the effect sizes between the diagnostic subgroups; Sensitivity Analysis: Leave-One-Out: This part of the table examines the robustness of the overall pooled estimates by systematically excluding one study at a time and recalculating the pooled SMD. This "leave-one-out" analysis helps determine if any single study is disproportionately influencing the main results. The Analysis Type / Parameter section specifies the parameter being analyzed (Global RNFL Thickness, Global GCL-IPL Thickness, Macular SCP Vessel Density). The subgroup / Condition section indicates whether it's the overall pooled SMD or the result of excluding a specific study. The Number of Studies (k) column shows the number of studies included in each analysis (either the original number or one less). Total Participants (N Patients / N Controls) column shows the total number of participants after excluding the specified study. Pooled SMD [95% CI] column presents the pooled SMD and its 95% Confidence Interval (CI) after each exclusion. For all three parameters, the pooled SMDs remain negative and statistically significant (or close to significant) after excluding any single study. This suggests that no single study is driving the overall findings, and the results are relatively robust. Heterogeneity (I^2 %) column shows the I^2 statistic after each exclusion. The heterogeneity levels remain generally high, even after excluding individual studies. P-value (Effect) column presents the p-value for the effect after each exclusion. The statistically significant findings are generally maintained. The P-value (Subgroup Diff.) column is "N/A" for sensitivity analysis, as it's not comparing subgroups.

Table 9 presents an assessment of potential publication bias for the primary outcome measures included in the meta-analysis. It uses funnel plot visual assessment and Egger's regression test to evaluate whether the results might be influenced by small-study effects or publication bias; Outcome Parameter: This column lists the primary outcome parameters assessed for publication bias: Global RNFL Thickness, Global GCL-IPL Thickness, Central Macular Thickness (CMT), Macular SCP Vessel Density, Macular DCP Vessel Density, and FAZ Area; Number of Studies (N) Contributing Data: This column indicates the number of studies that contributed data for each outcome parameter. The number of studies ranges from 4 to 6; Funnel Plot Visual Assessment: This column describes the visual assessment of funnel plots, which are graphical displays used to detect publication bias. For Global RNFL Thickness and Global GCL-IPL Thickness, the funnel plots were described as "largely symmetrical" and "possible slight asymmetry observed," respectively, but the interpretation was limited by the small number of studies ($N < 10$). For Central Macular Thickness (CMT), Macular SCP Vessel Density, and Macular DCP Vessel

Density, the assessment was described as "difficult to interpret reliably" due to the very small number of studies. For the FAZ Area, the assessment was considered "unreliable" due to having N < 5; Egger's Regression Test Results: This column presents the results of Egger's regression test, a statistical test used to detect asymmetry in funnel plots and, thus, potential publication bias. It shows the intercept, its 95% confidence interval (CI), and the p-value. The p-values for Egger's test for Global RNFL Thickness, Global GCL-IPL Thickness, Central Macular Thickness (CMT), Macular SCP Vessel Density, and Macular DCP Vessel Density were all greater than 0.05, indicating no statistically significant evidence of publication bias detected. FAZ Area was not formally tested as there were fewer than 5 studies; Interpretation & Comments: This column provides an overall interpretation of the publication bias assessment. For Global RNFL Thickness and Global GCL-IPL Thickness, the conclusion was that there was no statistically significant evidence of small-study effects or publication bias, but the power of the test was low due to the small number of studies. For Central Macular Thickness (CMT), Macular SCP Vessel Density, and Macular DCP Vessel Density, the assessment was deemed potentially unreliable due to the small N, and while no significant bias was detected, the results should be interpreted with extreme caution. For the FAZ Area, there were an insufficient number of studies to reliably assess potential publication bias.

Table 8. Subgroup analyses by psychiatric diagnosis and sensitivity analyses for key retinal parameters.

Analysis Type/Parameter	Subgroup/Condition	Number of Studies (k)	Total Participants (N Patients / N Controls)	Pooled SMD [95% CI]	Heterogeneity (I^2 %)	P-value (Effect)	P-value (Subgroup Diff.)
Subgroup Analysis: Psychiatric Diagnosis							
Global RNFL Thickness							**0.45**
	Schizophrenia	3	180 / 190	-0.75 [-1.10, -0.40]	78%	<0.0001	
	Bipolar Disorder	3	155 / 165	-0.62 [-1.05, -0.19]	72%	0.005	
	Major Depressive Disorder	3	150 / 155	-0.65 [-1.15, -0.15]	80%	0.01	
Global GCL-IPL Thickness							**0.68**
	Schizophrenia	3	180 / 190	-0.85 [-1.30, -0.40]	82%	<0.001	
	Bipolar Disorder	3	155 / 165	-0.70 [-1.25, -0.15]	75%	0.01	
	Major Depressive Disorder	3	150 / 155	-0.68 [-1.18, -0.18]	85%	0.008	
Macular SCP Vessel Density							**0.72**
	Schizophrenia	3	180 / 190	-0.60 [-1.05, -0.15]	70%	0.009	
	Bipolar Disorder	3	155 / 165	-0.50 [-0.98, -0.02]	68%	0.04	
	Major Depressive Disorder	3	150 / 155	-0.52 [-1.00, -0.04]	75%	0.03	
Sensitivity Analysis: Leave-One-Out							
Global RNFL Thickness	**Overall Pooled SMD (k=6)**	**6**	**425 / 460**	**-0.68 [-0.95, -0.41]**	**75%**	**<0.00001**	**N/A**
	Excluding Study 1	5	375 / 405	-0.65 [-0.98, -0.32]			
	Excluding Study 2	5	380 / 410	-0.70 [-1.02, -0.38]			
	Excluding Study 3	5	365 / 395	-0.72 [-1.05, -0.39]			
	Excluding Study 4	5	355 / 380	-0.66 [-0.99, -0.33]			
	Excluding Study 5	5	370 / 400	-0.69 [-1.03, -0.35]			
	Excluding Study 7	5	260 / 305	-0.60 [-0.90, -0.30]			
Global GCL-IPL Thickness	**Overall Pooled SMD (k=6)**	**6**	**415 / 465**	**-0.75 [-1.08, -0.42]**	**80%**	**<0.0001**	**N/A**
	Excluding Study 1	5	365 / 410	-0.72 [-1.10, -0.34]			
	Excluding Study 3	5	355 / 400	-0.78 [-1.15, -0.41]			
	Excluding Study 4	5	345 / 385	-0.74 [-1.12, -0.36]			
	Excluding Study 5	5	360 / 405	-0.77 [-1.16, -0.38]			
	Excluding Study 6	5	375 / 415	-0.80 [-1.20, -0.40]			
	Excluding Study 7	5	250 / 310	-0.65 [-1.00, -0.30]			
Macular SCP Vessel Density	**Overall Pooled SMD (k=5)**	**5**	**280 / 310**	**-0.55 [-0.88, -0.22]**	**72%**	**0.001**	**N/A**
	Excluding Study 3	4	220 / 245	-0.58 [-0.95, -0.21]			
	Excluding Study 4	4	210 / 230	-0.52 [-0.90, -0.14]			
	Excluding Study 5	4	225 / 250	-0.59 [-0.98, -0.20]			
	Excluding Study 6	4	240 / 260	-0.50 [-0.85, -0.15]			
	Excluding Study 7	4	115 / 155	-0.48 [-0.88, -0.08]			

Table 9. Assessment of potential publication bias for primary outcome measures.

Outcome Parameter	Number of Studies (N) Contributing Data	Funnel Plot Visual Assessment	Egger's Regression Test Results	Interpretation & Comments
Global RNFL Thickness	6	Largely symmetrical, but visual interpretation limited by N<10.	Intercept = -1.25 (95% CI: -3.20, 0.70) p = 0.18	No statistically significant evidence of small-study effects or publication bias detected. Power of the test is low due to small N.
Global GCL-IPL Thickness	6	Possible slight asymmetry observed, interpretation limited by N<10.	Intercept = -1.40 (95% CI: -3.80, 1.00) p = 0.22	No statistically significant evidence of publication bias detected. Power of the test is low due to small N.
Central Macular Thickness (CMT)	5	Difficult to interpret reliably due to very small N.	Intercept = -0.50 (95% CI: -2.50, 1.50) p = 0.45	Assessment potentially unreliable (N<10). No significant bias detected, but result should be interpreted with extreme caution.
Macular SCP Vessel Density	5	Difficult to interpret reliably due to very small N.	Intercept = -0.95 (95% CI: -2.80, 0.90) p = 0.15	Assessment potentially unreliable (N<10). No significant bias detected, but result should be interpreted with extreme caution.
Macular DCP Vessel Density	5	Difficult to interpret reliably due to very small N.	Intercept = -0.70 (95% CI: -2.90, 1.50) p = 0.30	Assessment potentially unreliable (N<10). No significant bias detected, but result should be interpreted with extreme caution.
FAZ Area	4	Assessment unreliable due to N<5.	Not formally tested (N<5).	Insufficient number of studies to reliably assess potential publication bias using funnel plot asymmetry or Egger's test.

4. Discussion

The observed thinning of the RNFL and GCL-IPL, representing the axons and cell bodies/dendrites of retinal ganglion cells respectively, suggests neuronal structural compromise or loss within the inner retina of psychiatric patients. This aligns with numerous neuropathological and neuroimaging studies indicating grey matter volume reduction, cortical thinning, and white matter integrity changes in the brains of individuals with schizophrenia, BD, and MDD. The retina, being developmentally and structurally linked to the CNS, appears to mirror this neuronal pathology. The central question posed by our title relates these structural changes, along with the observed vascular alterations, to neuroinflammation. While this meta-analysis provides indirect evidence, the findings are highly consistent with the potential downstream effects of chronic, low-grade inflammation within the neuro-retinal environment. Activated microglia and astrocytes in the retina, potentially triggered by systemic inflammation, CNS inflammatory signals, or local factors, release pro-inflammatory cytokines (e.g., TNF-α, IL-6) and oxidative stress mediators. These substances can directly induce neuronal apoptosis and synaptic damage (leading to GCL-IPL thinning) and axonal degeneration (leading to RNFL thinning). Thus, the inner retinal thinning observed could plausibly reflect a consequence of sustained neuroinflammatory processes shared between the brain and the eye. The retina's role as a mirror to the CNS in psychiatric disorders is underscored by the structural parallels it shares with the brain. Both the retina and the brain originate from the neural tube during embryological development, and the retina contains various neuronal and glial cell types similar to those found in the brain. This structural homology suggests that pathological processes affecting the brain, such as neurodegeneration driven by chronic inflammation, may manifest as analogous structural changes in the

retina. In this context, the thinning of the RNFL, which comprises the axons of retinal ganglion cells, and the GCL-IPL, which contains the cell bodies and dendrites of these neurons, strongly indicates a loss of neuronal integrity in psychiatric patients. This retinal neurodegeneration aligns with findings from neuroimaging studies in psychiatric patients, which frequently report grey matter volume reductions and cortical thinning in various brain regions. The implication is that similar pathological processes may be operating in both the brain and the retina, leading to neuronal damage or loss. The meta-analysis findings support the hypothesis that neuroinflammation plays a key role in driving this neuronal compromise. In the retina, resident immune cells like microglia and astrocytes can become activated in response to various pathological stimuli, leading to the release of pro-inflammatory mediators. These mediators, including cytokines and reactive oxygen species, can directly damage retinal neurons, potentially explaining the observed RNFL and GCL-IPL thinning. The time course of inflammatory events and their precise contribution to retinal damage in psychiatric disorders requires further investigation. It is possible that chronic, low-grade inflammation exerts a sustained toxic effect on retinal neurons over time, eventually leading to structural damage and neuronal loss. Alternatively, acute inflammatory episodes might trigger a cascade of events that ultimately result in neuronal death. Further longitudinal studies tracking retinal changes in relation to inflammatory markers and clinical symptoms are needed to clarify the temporal dynamics of these processes.[11-15]

Furthermore, neuroinflammation is intrinsically linked with microvascular dysfunction. Inflammatory mediators can impair endothelial function, increase vascular permeability, promote leukocyte adhesion, and potentially lead to capillary non-perfusion or rarefaction. Our finding of significantly reduced SCP vessel density, and a trend for reduced DCP vessel density, supports the presence of retinal microvascular compromise in psychiatric disorders. The SCP primarily supplies the GCL, while the DCP nourishes the inner nuclear layer. Alterations in these plexuses could further exacerbate neuronal dysfunction through hypoxia or impaired nutrient supply. These vascular changes might also reflect systemic endothelial dysfunction often reported in psychiatric populations, which itself can be driven or exacerbated by chronic inflammation. The observed reduction in retinal microvascular density, particularly in the SCP, provides further support for the role of neuroinflammation in the pathophysiology of major psychiatric disorders. Neuroinflammation and microvascular health are closely intertwined. Inflammatory processes can disrupt the delicate balance of the retinal microvasculature, leading to structural and functional changes. Pro-inflammatory mediators released during neuroinflammation can directly damage endothelial cells, the cells lining blood vessels, impairing their ability to regulate blood flow and maintain the integrity of the vessel wall. This endothelial dysfunction can manifest as increased vascular permeability, allowing leakage of fluids and molecules into the surrounding retinal tissue, and promoting the adhesion of leukocytes (white blood cells) to the vessel wall, further exacerbating inflammation. The consequences of these microvascular changes can be profound. Reduced vessel density, as observed in this meta-analysis, implies a decrease in the number of functional capillaries within the retina. This rarefaction of the capillary network can compromise the supply of oxygen and essential nutrients to retinal neurons, potentially contributing to their dysfunction and eventual degeneration. The SCP is particularly critical as it provides the primary blood supply to the GCL, the layer containing the cell bodies of retinal ganglion cells. Damage to this plexus can directly impair the function and survival of these neurons, consistent with the observed GCL-IPL thinning. Interestingly, the meta-analysis also revealed a trend towards reduced DCP vessel density, although this finding did not reach statistical significance. The DCP supplies the inner nuclear layer, which contains bipolar cells, amacrine

cells, and horizontal cells, all crucial for retinal signal processing. While the reduction in DCP density was not statistically significant, the trend suggests that microvascular compromise may extend beyond the SCP and affect deeper retinal layers. However, the quantification of DCP vessel density can be technically challenging due to its deeper location within the retina, and further research with improved imaging techniques is needed to clarify the extent of its involvement in psychiatric disorders. It is important to consider that the observed microvascular changes in the retina may not be isolated phenomena but rather reflect systemic vascular pathology. Psychiatric disorders, particularly MDD, are often associated with increased risk of cardiovascular disease, and endothelial dysfunction is a common finding in these patients. Systemic inflammation, a key feature of psychiatric disorders, can contribute to this widespread endothelial dysfunction, affecting both the cerebral and retinal microvasculature.[16-20]

5. Conclusion

This meta-analysis provides compelling evidence of retinal structural and microvascular alterations in major psychiatric disorders, specifically schizophrenia, bipolar disorder, and major depressive disorder. The findings indicate a significant thinning of the retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform layer (GCL-IPL), along with reduced superficial capillary plexus (SCP) vessel density in patients compared to healthy controls. These retinal changes are consistent with neuropathological and neuroimaging studies that have reported grey matter volume reduction, cortical thinning, and white matter integrity changes in the brains of individuals with these psychiatric conditions. The observed retinal alterations indirectly support the hypothesis of shared pathophysiological mechanisms between the eye and the brain in major psychiatric disorders, potentially involving neuroinflammation. The retinal thinning and reduced microvascular density may reflect the downstream effects of chronic, low-grade inflammation, which can lead to neuronal damage, synaptic dysfunction, and microvascular compromise. While this meta-analysis does not directly measure inflammatory markers, the consistency of the findings with the known effects of neuroinflammation strengthens the rationale for considering the retina as a valuable site for biomarker research in psychiatry. However, the study also acknowledges the limitations of the current evidence, including high heterogeneity across studies and the potential for publication bias. Further longitudinal studies correlating retinal changes with direct inflammatory markers are crucial to confirm the role of neuroinflammation in the observed retinal pathology and to fully elucidate the complex interplay between retinal and cerebral changes in psychiatric disorders.

6. References

1. Janti SS, Tikka SK. Retinal microvasculature in schizophrenia: a meta-analysis with trial sequential analysis of studies assessing vessel density using optical coherence tomography angiography. Asian J Psychiatr. 2023; 84(103570): 103570.
2. Hannaway N, Zarkali A, Leyland L-A, Bremner F, Nicholas JM, Wagner SK, et al. Visual dysfunction is a better predictor than retinal thickness for dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2023; 94(9): 742–50.
3. Domagała A, Domagała L, Kopiś-Posiej N, Harciarek M, Krukow P. Differentiation of the retinal morphology aging trajectories in schizophrenia and their associations with cognitive dysfunctions. Front Psychiatry. 2023; 14: 1207608.
4. Kılıç OHT, Kartı Ö, Kıyat P, Bayram ZN, Kırcı Dallıoğlu Ç. Can retinal nerve fiber layer (RNFL) thickness be a marker for distinguishing bipolar depression from unipolar depression? Nord J Psychiatry. 2024; 78(7): 610–5.
5. Al-Mazidi S. Molecular physiology unlocks the mystery that relates cognitive impairment

with the retina in schizophrenia and autism spectrum disorders: a perspective review. Front Psychiatry. 2024; 15: 1495017.
6. Lizano P, Velez-Perez E. Multimodal retinal imaging findings in schizophrenia spectrum disorders. Biol Psychiatry. 2024; 96(10): 769–71.
7. Boudriot E, Gabriel V, Popovic D, Pingen P, Yakimov V, Papiol S, et al. Signature of altered retinal microstructures and electrophysiology in schizophrenia spectrum disorders is associated with disease severity and polygenic risk. Biol Psychiatry. 2024; 96(10): 792–803.
8. Kuchler T, Hausinger R, Braunisch MC, Günthner R, Wicklein R, Knier B, et al. All eyes on PCS: analysis of the retinal microvasculature in patients with post-COVID syndrome-study protocol of a 1 year prospective case-control study. Eur Arch Psychiatry Clin Neurosci. 2024; 274(8): 1847–56.
9. Ashour AS, El Serafy O, El Fayoumy NM, Hassan A, El Gendy NS, Heikal ES, et al. Unveiling the retinal secrets of neuromyelitis optica spectrum disorder. Egypt J Neurol Psychiatr Neurosurg. 2024; 60(1).
10. Alba-Arbalat S, Solana E, Lopez-Soley E, Camos-Carreras A, Martinez-Heras E, Vivó F, et al. Predictive value of retinal atrophy for cognitive decline across disease duration in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2024; 95(5): 419–25.
11. Jerotic S, Maric N. Attention flexibility is associated with retinal cup-to-disk ratio in patients with schizophrenia spectrum disorders. Eur Psychiatry. 2024; 67(S1): S288–9.
12. Komatsu H, Onoguchi G, Silverstein SM, Jerotic S, Sakuma A, Kanahara N, et al. Retina as a potential biomarker in schizophrenia spectrum disorders: a systematic review and meta-analysis of optical coherence tomography and electroretinography. Mol Psychiatry. 2024; 29(2): 464–82.
13. Baykara S, Kazğan A, Yıldırım H, Tabara MF, Kaşıkcı HÖ, Danacı Keleş D. Retinal changes in generalized anxiety disorder patients. Int J Psychiatry Med. 2024; 59(3): 270–86.
14. Krukow P, Domagała A, Silverstein SM. Specific association between retinal neural layer thinning and neurological soft signs in schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2024; 274(5): 1237–40.
15. Carriello MA, Costa DFB, Alvim PHP, Pestana MC, Bicudo DDS, Gomes EMP, et al. Retinal layers and symptoms and inflammation in schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2024; 274(5): 1115–24.
16. Blose BA, Silverstein SM, Stuart KV, Keane PA, Khawaja AP, Wagner SK. Association between polygenic risk for schizophrenia and retinal morphology: a cross-sectional analysis of the United Kingdom Biobank. Psychiatry Res. 2024; 339(116106): 116106.
17. Fuyi Q, Xiang C, Xinling Z, Zeyi G, Liu Y, Jia W, et al. Association between retinal nerve fiber layer thickness and psychiatric disorders: a mendelian randomization study. BMC Psychiatry. 2024; 24(1):640.
18. Boudriot E, Stephan M, Rabe F, Smigielski L, Schmitt A, Falkai P, et al. Genetic analysis of retinal cell types in neuropsychiatric disorders. JAMA Psychiatry. 2025; 82(3): 285–95.
19. Chart-Pascual JP, Cano-Escalera G, Graña M, Zorrilla I, Lopez-Peña P, Requena CM, et al. Retinal thickness: a window into cognitive impairment in bipolar disorder. Span J Psychiatry Ment Health. 2025.
20. Zhu J, Wang Z, Chen T, Zhou Y, Xu F, Du J, et al. Thinning of central foveal thickness in the retina of patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2025; 275(3): 839–49.