• Bibliometric Research •

From descriptive observation to multimodal integration: mapping the evolution of retinal biomarkers in schizophrenia

Xin-Lei Zhou[1], Ling Wang[2], Xiao-Yan Wang[2], Chun-Yan Song[3], Ming-Ying Lai[3], Wei-Hua Yang[3]

[1]Beijing Key Laboratory of Mental Disorders, National Clinical Research Center for Mental Disorders & National Center for Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing 100191, China
[2]School of Medical Technology and Engineering, Fujian Medical University, Fuzhou 350108, Fujian Province, China
[3]Shenzhen Eye Hospital, Jinan University, Shenzhen 518040, Guangdong Province, China
Correspondence to: Wei-Hua Yang and Ming-Ying Lai. Shenzhen Eye Hospital, Jinan University, No.18 Zetian Road, Futian District, Shenzhen 518040, Guangdong Province, China. benben0606@139.com; laimydoc@163.com
Received: 2026-06-14 Accepted: 2026-07-23

Abstract

● **AIM:** To map the intellectual structure, temporal evolution, research hotspots, and emerging frontiers in the field of retinal biomarkers for schizophrenia.

● **METHODS:** The Web of Science Core Collection was searched for English-language records published from January 1, 1900 to April 7, 2026 using terms related to schizophrenia-spectrum disorders and retinal imaging or electrophysiological measures. After relevance screening, 305 of 529 retrieved records were included. Microsoft Excel 2019 and CiteSpace 6.4.R1 software were adopted to analyze annual publication trends, institutional and author collaboration networks, keyword co-occurrence, keyword clustering, and burst terms.

● **RESULTS:** The annual publication volume in this field showed an overall increasing trend. The University of Rochester and the Harvard system formed two highly productive collaborative clusters. Steven M. Silverstein was the most prolific author and a central connector. Research contents mainly focus on retinal structural abnormalities, visual electrophysiological disorders, dopaminergic dysfunction, retinal microvascular abnormalities as well as artificial intelligence and multimodal integration, which jointly confirm that the retina can act as a non-invasive window for evaluating pathological changes in the central nervous system.

● **CONCLUSION:** Research on retinal biomarkers of schizophrenia has shifted from descriptive functional observation to mechanism-oriented multimodal comprehensive research. Future work should prioritize rigorous confounder control, standardized optical coherence tomography/optical coherence tomography angiography/electroretinography protocols, large longitudinal cohorts, and externally validated artificial intelligence models for clinical translation.

● **KEYWORDS:** schizophrenia; retina; biomarker; multimodal; artificial intelligence
DOI:10.18240/ijo.2026.12.19

Citation: Zhou XL, Wang L, Wang XY, Song CY, Lai MY, Yang WH. From descriptive observation to multimodal integration: mapping the evolution of retinal biomarkers in schizophrenia. *Int J Ophthalmol* 2026;19(12):2469-2479

INTRODUCTION

Schizophrenia is a highly disabling neuro developmental disorder of unclear etiology. It affects more than 20 million people worldwide and imposes a substantial socioeconomic burden[1]. The disorder is clinically heterogeneous, and current diagnosis still relies primarily on subjective clinical symptoms defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition or International Classification of Diseases, Eleventh Revision criteria, with no objective and quantifiable biomarker available for routine use. Moreover, its symptoms overlap with those of other psychiatric disorders, further complicating diagnosis and sub-type classification. Identifying objective biomarkers that can support diagnosis and disease assessment has therefore become an urgent clinical need.

The retina, as an embryological extension of the central nervous system, offers a distinctive opportunity in this context. It shares substantial homology with the brain in embryonic origin, cell types, neurotransmitter systems, and local circuit organization. More importantly, the retina is the only part of neural tissue that can be directly assessed *in vivo* using non-invasive, high-

resolution structural and functional measurements. Abnormal retinal changes may therefore provide a direct window into the pathophysiological state of the brain[2-3].

In recent years, non-invasive technologies such as optical coherence tomography (OCT) and electroretinography (ERG) have revealed preliminary evidence of structural damage in patients with schizophrenia, including thinning of the retinal nerve fiber layer (RNFL) and abnormal ganglion-cell function[4]. These findings offer a new perspective for understanding the neurobiological mechanisms of schizophrenia and establish the retina as an important potential source of biomarkers.

However, existing reviews have largely been limited to qualitative summaries of experimental findings and have not provided a macroscopic and quantitative characterization of the field as a whole. Bibliometrics can objectively and visually reveal the developmental trajectory of a research field, its core contribution networks, shifts in research themes, and frontier burst features, thereby complementing conventional narrative reviews[5-6].

Accordingly, this study used the Web of Science Core Collection (WoSCC) as the data source and applied bibliometric methods, including co-occurrence analysis and burst detection, in combination with key literature in the field. The aim was to systematically explore the research contents of retinal-biomarker in schizophrenia from 1992 to 2026, identify key academic communities and technological inflection points that have driven the field, and detect research gaps and potential future directions. The findings may help researchers understand the internal evolutionary logic of the field, optimize pathways for the clinical translation of retinal biomarkers, inform strategic planning by research institutions, and ultimately promote the transition of retinal biomarkers from basic research to clinical psychiatric practice.

MATERIALS AND METHODS

Data Sources and Search Strategy The data were obtained from the WoSCC. The initial search was conducted from inception of the database (January 1, 1900) to December 8, 2025. To ensure timeliness, an updated final search using the identical strategy was performed on April 7, 2026, comprising two search rounds in total. We included peer-reviewed, online-first articles available up to the final search date, but did not search preprint servers. Studies first published online after April 7, 2026 were excluded.

The search strategy was as follows: Topic Search=[(schizo* OR “schizophrenia spectrum” OR psychotic disorder* OR “first episode psychosis” OR FEP) AND (retina* OR RNFL OR “ganglion cell*” OR “optical coherence tomography” OR OCT OR “OCT Angiography” OR OCTA OR electroretinograph* OR electroretinogram* OR ERG OR fundus*)]. The document type was set to “article”, and the language was restricted to “English”.

During the initial database retrieval, we did not preset any language filter, and only 13 non-English records were retrieved in total. We briefly reviewed the English abstracts of these 13 non-English literatures, and none of them fully met our predefined inclusion criteria regarding research population and retinal outcome indicators.

The restriction to English-language publications was applied due to the research team’s language proficiency and limited resources for professional translation of non-English full texts. We fully acknowledge that this may introduce language bias and potentially reduce the comprehensiveness of the evidence synthesis; this limitation is transparently addressed in the discussion.

Data Retrieval and Screening Studies were considered eligible if they examined retinal biomarkers in patients diagnosed with schizophrenia spectrum disorders. Biomarkers of interest encompassed retinal neural layer parameters, retinal vascular characteristics, and electrophysiological features. Only original research articles were included. We excluded animal or *in vitro* studies, case reports, conference abstracts, editorials, letters, reviews, and other non-original publications.

The screening process adhered to the PRISMA 2020 guidelines. Two investigators independently screened titles and abstracts, followed by full-text evaluation of all potentially relevant records. Disagreements typically arose when abstracts lacked sufficient detail on the study population or retinal outcome measures, or when full-text reports provided vague descriptions of the biomarker assessment protocols. All conflicts were first resolved through structured discussion with reference to the predefined eligibility criteria. When consensus could not be reached, a third senior investigator adjudicated the final decision. Inter-rater agreement was quantified using Cohen’s κ, which was 0.82 for title/abstract screening and 0.88 for full-text assessment, indicating almost perfect agreement between the two reviewers.

Statistical Analysis CiteSpace version 6.4.R1 was used to analyze institutional and author collaboration networks, keyword co-occurrence, keyword clustering, and burst terms. Additionally, Microsoft Office Excel 2019 was used for quantitative analysis of the publications. The core parameter configurations of CiteSpace 6.4.R1 were set as follows:

Time slicing: The research time span was defined as 1992–2026 with a slice length of 1y. For node screening, the g-index algorithm (k=25) was adopted, together with auxiliary filtering parameters: LRF=2.5, L/N=10, LBY=5, and e=1.0.

Network pruning: The Pathfinder pruning algorithm was implemented to simplify redundant connection lines without the minimum spanning tree.

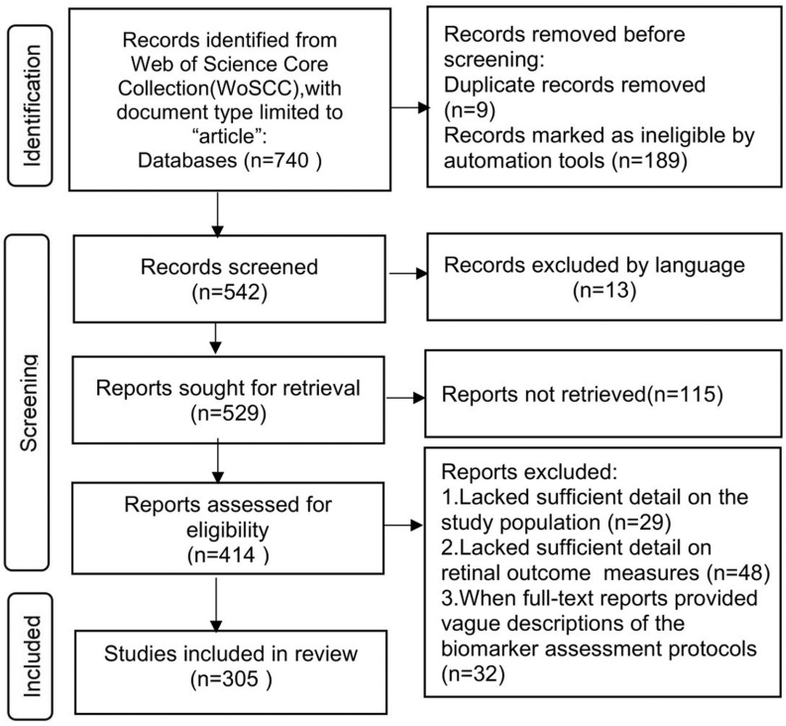


Figure 1 PRISMA flow diagram depicting the literature search and screening process.

Clustering: The log-likelihood ratio algorithm was utilized to generate cluster labels. The modularity Q of the network was 0.6467 and the weighted mean silhouette score reached 0.852, indicating reliable clustering structures.

Burst detection: The gamma coefficient was set to 1.0 for citation burst identification. Keywords with the top 25 strongest burst strengths were extracted, and the minimum duration of a valid burst was 1y.

RESULTS

Annual Publication Trends We initially retrieved 740 records from the WoSCC. After excluding 211 irrelevant records at multiple screening stages, 529 reports were retrieved for eligibility assessment, and ultimately 305 eligible studies were included for subsequent bibliometric analysis (Figure 1). The annual publication output exhibited an overall upward trend. The first original article focusing on this research field was published in 1992. Since 2018, the annual number of publications has surpassed 15, with the peak output of 35 articles recorded in 2020 (Figure 2).

Core Institutions The institutional collaboration network constructed with CiteSpace contained 338 nodes and 579 links, with a network density of only 0.0102, indicating relatively sparse inter-institutional collaboration. The modularity value was Q=0.6467 (>0.6), the weighted mean silhouette value was S=0.852 (>0.7), and the harmonic mean of Q and S was 0.7353, suggesting clear clustering and reliable network structure (Figure 3). The institutional co-occurrence map and publication counts indicated that the University of Rochester (18 publications) and the Harvard system (36 publications), including Harvard University, Harvard-affiliated medical institutions, and Harvard Medical School, formed two closely connected and consistently productive core clusters.

Core Authors The author co-occurrence network contained 328 nodes and 619 links, with a network density of only 0.0115. Twenty-eight authors had published four or more papers. Steven M. Silverstein has had the highest publication output (21 papers) and the densest collaboration links, making him a central hub with strong cross-team influence and connections across multiple research clusters. Overall, the network showed a pronounced core-periphery structure: a small number of authors controlled the main collaboration pathways, whereas most scholars collaborated only within small teams. Cross-team and cross-regional collaboration remained limited, indicating a pattern of small-group clustering with weak inter-group connectivity (Figure 4).

Keyword Co-occurrence The keyword co-occurrence network contained 277 nodes and 1075 edges, with a network density of 0.0281. The largest connected component covered 256 nodes, accounting for 92% of the network, indicating that the field has highly concentrated research themes and a structurally complete core knowledge network (Figure 5). Based on the co-occurrence analysis, four major thematic clusters were identified. The first centered on "schizophrenia-related retinal structural abnormalities", involving indices such as the RNFL, ganglion cell layer (GCL), and macular thickness, and examined their associations with disease severity. The second centered on "optical coherence tomography" and was linked to reliability and Meta-analysis,

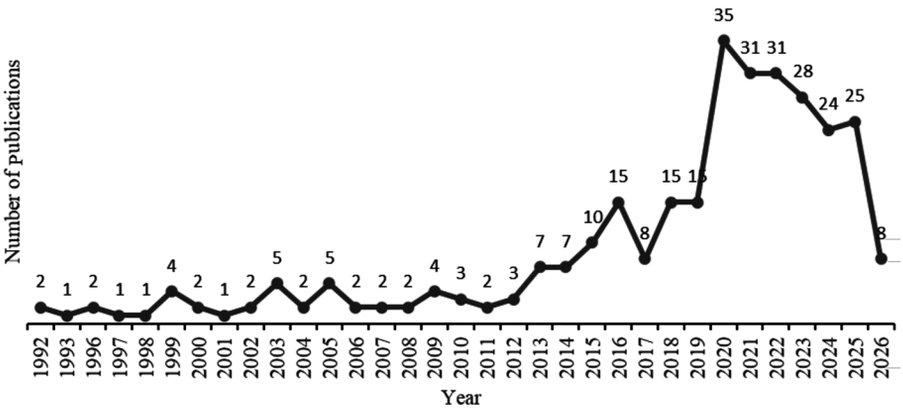


Figure 2 Annual publication output of studies on retinal biomarkers in schizophrenia from 1992 to 2026.

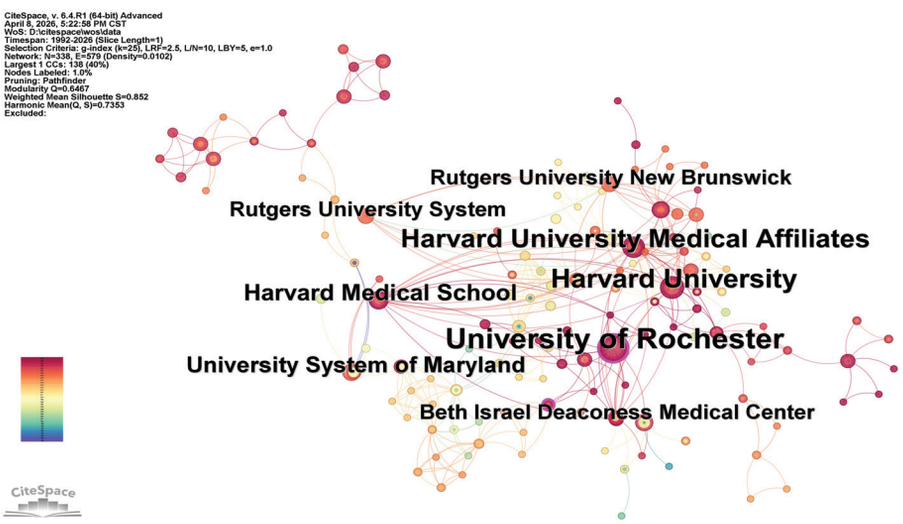


Figure 3 CiteSpace visualization of institutional cooperation network for schizophrenia retinal biomarker studies A total of 338 institutional nodes and 579 cooperative links were observed in the network, and the density of 0.0102 implies sparse inter-institutional communication. The modularity Q and silhouette coefficient meet the threshold standards, proving that the clustering distribution of this network is valid and obvious.

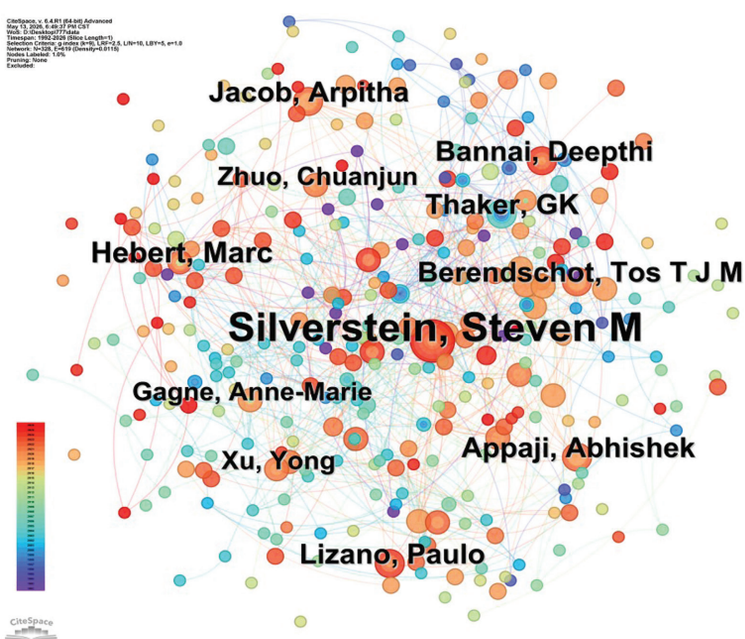


Figure 4 CiteSpace-generated author collaboration network for retinal biomarker research in schizophrenia There are 328 nodes and 619 links in the author co-occurrence network, with a density of 0.0115. Steven M. Silverstein is the most productive author with 21 papers and serves as the key collaborative hub. The network displays a typical core-periphery distribution, featuring scattered small research groups and inadequate cross-group cooperation.

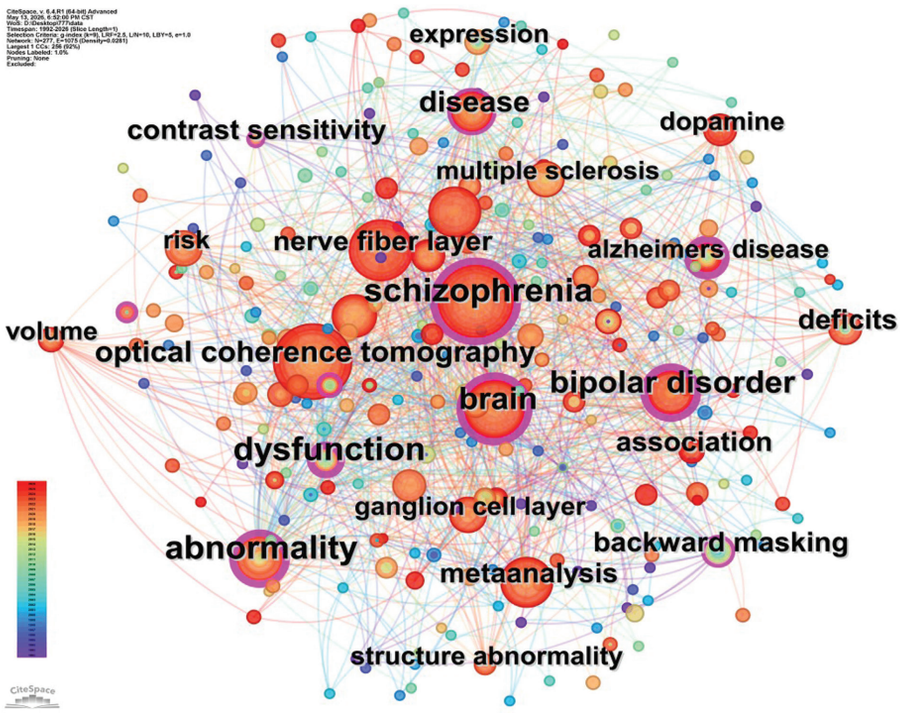


Figure 5 Keyword co-occurrence network of retinal biomarker studies in schizophrenia generated by CiteSpace The keyword network includes 277 nodes and 1075 edges, with a network density of 0.0281. The largest connected component consists of 256 nodes, occupying 92% of the whole network, which demonstrates that research themes in this field are highly concentrated and form an intact core knowledge network.

focusing on measurement reproducibility and evidence synthesis. The third covered "multiple disorders, including schizophrenia, bipolar disorder, and multiple sclerosis, and was connected with disease association and risk factors", aiming to compare retinal biomarkers across diseases and provide evidence for differential diagnosis. The fourth focused on concepts such as "brain, dopamine, perception, dysfunction, and abnormality", emphasizing the relationship between retinal changes and brain structure/function, dopaminergic pathways, and cognitive-perceptual disturbances, thereby explaining biomarker mechanisms from a pathophysiological perspective.

Keyword Clustering The keyword co-occurrence timeline network contained 573 nodes and 1950 edges, with a density of 0.0119. Its modularity was Q=0.6467, the weighted mean silhouette was S=0.852, and the harmonic mean was 0.7353, indicating a significant cluster structure, high internal consistency, and good reliability (Figure 6). The evolution of the field can be divided into three stages.

The evolution of this research field can be divided into three consecutive stages. From 1992 to 2005, core research clusters mainly contained #3 smooth pursuit, #7 vision, #11 electroretinography and #12 attention deficit hyperactivity disorder. Relevant studies centered on neurobiological mechanisms and visual function impairments of mental disorders, predominantly exploring smooth pursuit eye movement, contrast sensitivity and dopamine system abnormalities. Ophthalmic detection approaches were tentatively applied in related investigations, while large-scale interdisciplinary integration remained absent.

From 2006 to 2015, driven by the popularization of OCT technology, cluster #4 optical coherence tomography gradually grew into a pivotal research node. Clusters #1 retinal ganglion cells, #2 fundus, and #9 ganglion cells also gained rapid research attention. The research priority transferred to quantitative detection of retinal structural variations, and relevant studies expanded from schizophrenia to bipolar disorder and Alzheimer's disease, eventually constructing a stable research framework linking mental disorders with retinal morphological changes.

From 2016 to 2026, the number of research nodes and correlations kept rising, with cluster #0 machine learning, #6 biomarker, and #1 Meta-analysis becoming mainstream research hotspots. Retinal structural parameters including macular thickness and GCL thickness were widely verified as potential non-invasive biomarkers for mental diseases. Machine learning algorithms were extensively adopted for image analysis, biomarker screening and disease risk assessment. Accumulated Meta-analysis further validated the stability of correlations between retinal indicators and mental disorders. The emergence of cluster #16 resonance Raman spectroscopy also implied that multimodal detection techniques would become promising developing trends in this domain.

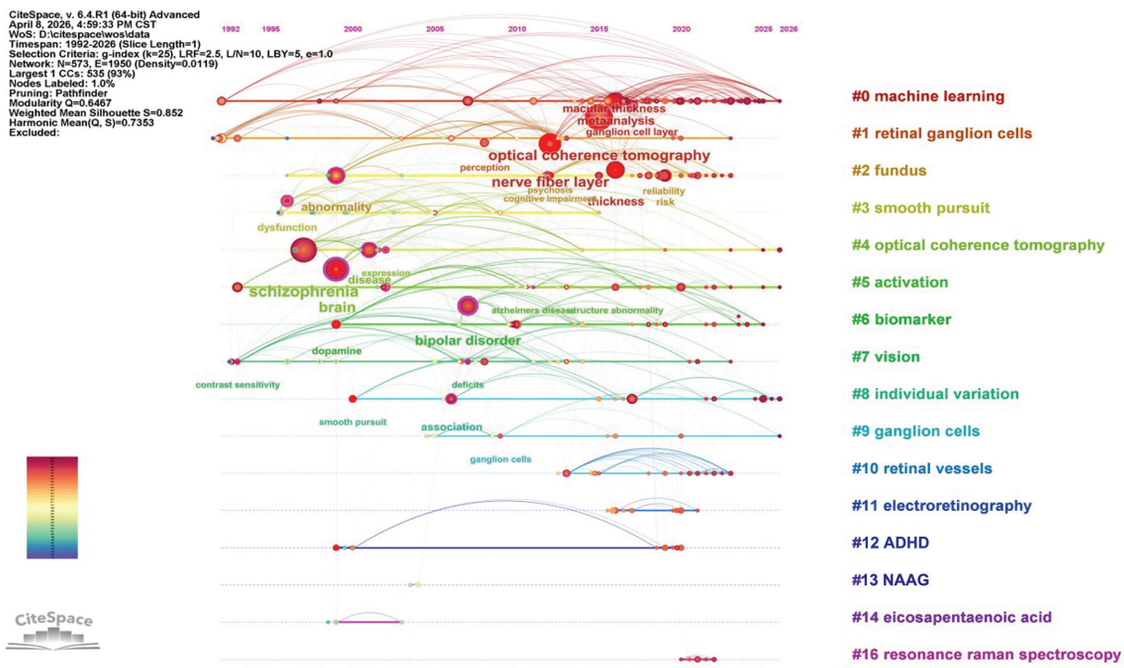


Figure 6 CiteSpace-generated keyword co-occurrence timeline network for schizophrenia retinal biomarker research With 573 nodes and 1950 edges, the network density is 0.0119. The values of modularity, silhouette coefficient and their harmonic mean all meet credible thresholds, showing prominent clusters and stable internal consistency. The research evolution of this field is divided into three phases. ADHD: Attention deficit hyperactivity disorder; NAAG: N-Acetylaspartylglutamate.

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1992 - 2026
confocal microscopy	2008	2.04	**2008**	2009	
association	2006	3.04	**2014**	2017	
smooth pursuit	2005	3.91	**2015**	2017	
abnormality	1999	1.73	**2015**	2016	
schizophrenia	1997	2.8	**2017**	2018	
multiple sclerosis	2016	2.57	**2018**	2020	
contrast sensitivity	1993	1.62	**2018**	2019	
risk	2019	3.26	**2019**	2023	
ganglion cell layer	2019	2.41	**2019**	2020	
reliability	2019	2.3	**2019**	2020	
psychosis	2020	3.48	**2020**	2022	
perception	2013	2.46	**2020**	2021	
ganglion cells	2018	1.94	**2020**	2021	
volume	2020	1.94	**2020**	2021	
metaanalysis	2016	1.54	**2020**	2021	
thickness	2016	4.34	**2021**	2023	
brain	1999	2.58	**2021**	2022	
illness	2021	2.49	**2021**	2023	
stress	2021	2.07	**2021**	2022	
nerve fiber layer	2016	2.1	**2022**	2023	
gray matter	2022	2.02	**2022**	2023	
deficits	2007	1.44	**2023**	2024	
optical coherence tomography	2015	3.34	**2024**	2026	
dopamine	1999	3.17	**2024**	2026	
optical coherence tomography angiography	2024	2.32	**2024**	2026	

Figure 7 Visualization of burst keywords in schizophrenia retinal biomarker research Twenty-five high-intensity burst keywords were recognized *via* burst analysis, uncovering a three-stage evolution of research hotspots. Studies between 2008 and 2017 predominantly explored visual functional abnormalities. Multiple burst keywords reflected broad focus on visual defects and pathological changes, with confocal microscopy and association analysis serving as early research methodologies.

Keyword Burst Analysis Keyword burst analysis identified 25 high-strength burst terms, revealing a clear three-stage evolution of research hotspots (Figure 7). From 2008 to 2017, research mainly focused on functional abnormalities of the visual system. Burst keywords including “smooth pursuit” (3.91, 2015–2017), “abnormality” (1.73, 2015–2016), and “schizophrenia” (2.80, 2017–2018) demonstrated widespread concern over visual function defects and pathological changes of psychiatric disorders, while confocal microscopy and association analysis laid early methodological foundations.

From 2018 to 2020, research hotspots shifted from visual function to retinal microstructure. Representative burst terms such as “multiple sclerosis” (2.57, 2018–2020), “ganglion cell layer” (2.41, 2019–2020), and “reliability” (2.30, 2019–

2020) illustrated expanding research objects across central nervous diseases and growing emphasis on the stability and repeatability of retinal morphological indicators.

From 2021 to 2023, "thickness" (4.34, 2021–2023) presented the highest burst intensity. Burst words covering "nerve fiber layer", "risk", and "Meta-analysis" indicated intensive exploration of retinal structural biomarkers, disease risk assessment and systematic evidence verification. Three terms maintained sustained burst until 2026. "Optical Coherence Tomography" (3.34, 2024–2026) represented continuous upgrading and wide application of core imaging technology. "Optical Coherence Tomography Angiography" (2.32, 2024–2026) promoted research from simple structural measurement to retinal vascular perfusion evaluation. "Dopamine" (3.17, 2024–2026) reflected the return to neurobiological pathogenesis, further revealing the intrinsic correlation between retinal morphological variation and central nervous neurotransmitter disorder.

DISCUSSION

Overall Publication Output, Research Institutions, and Researchers Over the past three decades, publication output in this field has continued to rise, indicating increasing academic attention, growing research investment, and the gradual formation of a stable research direction. The institutional landscape is characterized by leadership from European and North American institutions and a marked rise in participation from Asian academic communities. Research capacity remains relatively dispersed, and no monopolistic high-output institution has emerged. Future work should strengthen collaboration between Eastern and Western institutions to accelerate progress in retinal biomarkers for schizophrenia. In terms of academic leadership, Steven M. Silverstein and colleagues have used high-resolution structural imaging technologies such as OCT and OCTA, integrated large cohorts, genetic association analyses, machine learning, and longitudinal prediction, and moved the field from single functional measures toward a multimodal structure-function-vascular assessment framework. This work has advanced early warning, differential diagnosis, mechanistic interpretation, and the clinical translation of oculomics as a precision diagnostic tool in schizophrenia.

Evolution of Research Content Research on retinal biomarkers in schizophrenia has progressed from early single-modality electrophysiological exploration to current systematic studies integrating multimodal imaging and artificial intelligence. In this study, RNFL, OCT technology, and the dopaminergic system emerged as three central topics. Around the broader themes of structure, function, vasculature, and multimodal integration, the evidence base now extends from descriptive abnormalities to mechanistic interpretation and clinical translation.

Retinal structural abnormalities: from RNFL thinning to core macular ganglion cell-inner plexiform layer damage Early studies of retinal structural abnormalities produced highly inconsistent findings until 2015 a Meta-analysis began to integrate these discrepancies and confirmed reduced mean RNFL thickness in patients, particularly in the nasal, inferior, and temporal quadrants[7-8]. However, after strictly excluding cardiometabolic comorbidities such as diabetes and hypertension, Steven M. Silverstein and colleagues found that group differences in RNFL and macular thickness disappeared, whereas abnormalities in optic-disc parameters such as cup volume and cup-to-disc ratio appeared more specific[9-10]. This finding suggests that the high burden of cardiometabolic comorbidity in schizophrenia may contribute secondarily to retinal ganglion cell axonal loss through microvascular ischemia and chronic inflammation, thereby confounding the attribution of RNFL thinning specifically to schizophrenia[11].

With the improved capacity of spectral-domain OCT for fine-layer segmentation of the macula, the research focus has gradually shifted from peripapillary RNFL to deeper inner macular structures. Retinal segmentation studies show that patients with schizophrenia have lower overall RNFL thickness, GCL volume, and inner plexiform layer (IPL) volume than controls, with more pronounced damage in treatment-resistant patients. Importantly, GCL and IPL volumes show stronger associations with Positive and Negative Syndrome Scale (PANSS) scores, illness duration, and number of hospitalizations than RNFL[12]. This suggests that atrophy of inner macular structures, represented by the GCL and IPL, may reflect disease progression and clinical severity more sensitively than RNFL thinning[13]. More critically, bidirectional Mendelian randomization has identified a positive causal association between RNFL thinning and schizophrenia, without evidence of reverse causality, providing genetic evidence that retinal thinning is not merely secondary to disease or medication but is related to inherited susceptibility[14]. Polygenic risk score analyses further indicate that macular ganglion cell–IPL (mGC-IPL) thinning is associated with genetic susceptibility to schizophrenia independently of confounders such as age, potentially reflecting intrinsic neurodevelopmental and/or neurodegenerative processes in schizophrenia[15]. A large real-world study reported significant thinning of the mGC-IPL, and this difference persisted after excluding patients with diabetes and after restricting the analysis to individuals younger than 55y, supporting its role as a marker of intrinsic neuronal damage[16]. By contrast, abnormalities in retinal vascular fractal dimension disappeared after adjustment for diabetes, suggesting that microvascular changes are largely secondary to the cardiometabolic

comorbidities common in this population. Together, these findings support mGC-IPL thinning as a core structural marker that is relatively independent of metabolic confounding[17]. Thus, the field has moved from asking whether the retina becomes thinner to asking where, why, and under what mechanisms thinning occurs. The mGC-IPL complex has become one of the most robust candidate structural biomarkers and provides a new anatomical anchor for understanding the neurodegenerative dimension of schizophrenia.

From the perspective of differential diagnosis across psychiatric disorders, patients with major depressive disorder do not show RNFL thinning, suggesting that retinal structural damage is not a universal feature of psychiatric illness[14,18]. Retinal structural damage in schizophrenia and bipolar disorder shows both shared and disorder-specific features. Both conditions are associated with peripapillary RNFL thinning and reduced macular GCL volume, and both are negatively associated with illness duration, indicating progressive neurodegenerative characteristics[19-20]. However, retinal involvement in schizophrenia appears broader and more severe, affecting multiple RNFL subregions, the full macular thickness, and mGCL-IPL structures, whereas thinning in bipolar disorder is relatively restricted. This difference may support the use of retinal structural characteristics for differential diagnosis[12,21-22].

Longitudinal evidence also suggests that retinal structural damage may be partially reversible. A comparative study of young individuals at clinical high risk and patients with first-episode psychosis found that retinal regions and layers showed different patterns of involvement across disease stages[23]. In another study, patients with first-episode psychosis showed significant thickening of the total retina, IPL, outer plexiform layer, and inner nuclear layer after electroconvulsive therapy, indicating that short-term effective treatment may improve or even reverse neurodegenerative alterations in specific retinal layers[24]. These findings suggest that retinal structural indices may serve both as state markers of disease progression and as potential tools for monitoring treatment response.

Visual electrophysiological abnormalities and dopaminergic dysfunction: a bridge from phenomenon to mechanism Beyond retinal structure, ERG may have dual value for early risk detection and differential diagnosis. It is relatively less affected by medication confounding and may therefore serve as a robust functional biomarker spanning the preclinical and clinical stages of illness. Among unaffected and unmedicated offspring at high genetic risk, ERG shows a selective and significant reduction in maximal rod b-wave amplitude, with an effect size of -1.47, independent of parental diagnosis and age subgroup. This finding indicates that rod-system dysfunction may already exist before disease onset, making it a potential early and relatively specific risk marker for psychosis while minimizing biases related to medication exposure and illness duration[25-26]. In diagnosed patients, ERG parameters distinguished schizophrenia from bipolar disorder with an accuracy of 0.86, and performance remained 0.83 in a medication-matched subgroup. Waveform parameters were unrelated to antipsychotic dose, suggesting that retinal electrophysiological signatures may support differential diagnosis even in the context of stable medication treatment[27].

Among these functional abnormalities, dopaminergic findings are particularly important. Retinal dopamine is synthesized and released mainly by amacrine cells and is a key neuromodulator of light-dark adaptation, contrast sensitivity, and center-surround antagonism[28]. Because central dopaminergic dysfunction is a core pathological feature of schizophrenia, the retinal dopaminergic system may provide a direct window into monoaminergic states in the brain[29]. Existing analyses show that patients have significantly reduced oscillatory potential (OP) total indices and subwave amplitudes reflecting dopaminergic amacrine-cell activity, suggesting reduced retinal dopaminergic function[30]. OP-related synaptic activity is concentrated mainly in the IPL, corresponding closely to the region of prominent mGC-IPL thinning and thereby linking function with structure. Psychophysical evidence of reduced dynamic contrast sensitivity is also consistent with impaired dopaminergic modulation of the magnocellular pathway. A multilayer evidence chain can therefore be proposed: central dopaminergic dysregulation–retinal amacrine-cell hypofunction reflected by OPs abnormalities–mGC-IPL structural thinning–visual behavioral deficits such as reduced contrast sensitivity. Retinal dopaminergic indices are therefore not merely auxiliary diagnostic values; they may reflect disease pathophysiology and provide an accessible window for evaluating brain dopaminergic function.

Retinal microvascular abnormalities: dual interpretations based on cerebrovascular homology and metabolic comorbidity Given the homology between retinal and cerebral vasculature, OCTA and fundus photography studies have identified several microvascular abnormalities in patients with schizophrenia, including venular widening, increased arterial tortuosity, altered vascular fractal dimension, and reduced peripapillary vessel density. Greater decreases have been observed in patients with longer illness duration, suggesting a progressive pattern[31-32]. Some machine-learning models based solely on vascular trajectory parameters have achieved classification accuracies of up to 86%, indicating potential screening utility[33]. However, from a differential-diagnostic perspective, both schizophrenia and bipolar disorder are associated with increased retinal arterial tortuosity and lower trajectory values, indicating flatter vascular curves. The

similarity of these vascular changes across the two disorders suggests that retinal vascular morphology may reflect a shared degenerative pathway[34].

In the AlzEye study[15-16], differences in vascular fractal dimension disappeared after adjustment for metabolic factors, whereas mGC-IPL thinning persisted. This suggests that microvascular abnormalities may be more closely linked to the cardiometabolic comorbidities prevalent among patients, whereas neuronal-layer damage may better reflect the intrinsic features of schizophrenia. However, findings from the Dunedin birth cohort and related studies indicate that retinal microvascular abnormalities cannot be fully explained by cardiovascular comorbidity and are associated with psychotic symptoms in childhood, suggesting that vascular mechanisms may participate early in the disease process[35-36]. Future studies should jointly analyze OCTA vascular parameters and OCT neuronal-layer indices in prospective designs with rigorous metabolic control, thereby clarifying the relationship between primary neurodegeneration and secondary vascular change and exploring their value for cardiovascular risk stratification.

Artificial intelligence and multimodal integration: from single biomarkers to multidimensional prediction systems Artificial intelligence is moving retinal research in schizophrenia from the detection of group differences toward individualized prediction[37]. Convolutional neural network models based on fundus photographs have distinguished schizophrenia from healthy controls with an accuracy of up to 95% and an area under curve (AUC) of 0.98[38]. OCT-based retinal-age prediction models have further shown that patients are a retinal age approximately 5.9–7.4y older than their chronological age, and this acceleration is associated with antipsychotic dose and symptom severity, introducing the concept of accelerated retinal aging[39-42].

Deeper integration has emerged from multimodal eye-brain studies. By combining OCT, ERG, and brain magnetic resonance imaging data and applying multivariate algorithms such as sparse partial least squares, researchers have established phenotype-eye-brain association patterns and demonstrated that retinal abnormalities are closely linked to polygenic risk for schizophrenia, cognitive impairment, and brain structural alterations[28]. Nevertheless, artificial intelligence models commonly face risks of overfitting, reliance on small single-center samples, and lack of independent external validation. The operational complexity and cost of multimodal studies also limit large-scale implementation. Future work should build standardized multimodal databases, conduct cross-center and cross-ethnic validation, and integrate structural, vascular, functional, genetic, and clinical data into unified models to achieve true translation from group-level difference description to individualized precision stratification and prognosis prediction.

Limitations and Future Directions Despite substantial progress, the field still faces several challenges. First, antipsychotic medication, particularly differential effects of drug generations on D2 receptors, and cardiometabolic comorbidity remain the most important confounders. Their independent and interactive effects are still difficult to disentangle. In some studies, structural differences disappear after adjustment, and the causal role of medication in retinal structural change remains uncertain. Second, heterogeneity in OCT/OCTA devices, scanning protocols, segmentation algorithms, and ERG stimulus parameters severely limits direct comparability across studies and reduces the quality of meta-analytic evidence. Third, differences between acute and chronic phases and between first-episode unmedicated patients and long-term treated patients suggest that the timing of involvement across retinal structures may vary, but existing cross-sectional designs cannot answer this question. Another limitation is that only English articles were analyzed. Exclusion of non-English literature may cause language bias and affect the overall picture of the field. Future research should therefore pursue four priorities: 1) Large longitudinal cohorts tracking individuals from the clinical high-risk stage to chronic illness, to define the dynamic trajectories of retinal structural and functional indices and their temporal relationships with disease progression and treatment response; 2) Consensus standards for OCT and ERG acquisition and analysis to enable multicenter collaboration and clinical validation; 3) Deep integration of multimodal data using artificial intelligence to develop composite indices such as a retinal dopamine index and retinal biological age, enabling precise characterization of disease state; 4) Future studies may adopt multi-language retrieval strategies to obtain a more comprehensive understanding of the research landscape in this field.

In summary, over the past three decades, research on retinal biomarkers for schizophrenia has gradually established a mature research system, while research resources remain relatively fragmented. Scholars represented by Steven M. Silverstein have provided important academic leadership, driving the field to evolve from the assessment of single functional indicators toward a multimodal framework integrating structure, function and vasculature. Remarkable progress has been achieved in early warning, differential diagnosis, mechanistic interpretation and clinical translation.

Early studies in this field mainly focused on electrophysiological exploration with a single modality, which has now developed into systematic research combining multimodal imaging techniques and artificial intelligence. RNFL, OCT technology and the dopaminergic system stand as the three dominant research topics. The research scope has expanded continuously covering retinal structure, function, vascular characteristics,

and multimodal integration, and the research focus has shifted from mere description of abnormal phenotypes to the elucidation of pathological mechanisms and the translation of clinical applications.

Going forward, substantial collaborations between Eastern and Western research institutions should be further strengthened to integrate large-scale longitudinal cohorts across multiple centers and ethnic groups, and promote the sharing of research data and methodologies. Based on the existing "structure-function-vasculature" framework, multi-omics information including genomics and proteomics should be incorporated. Combined with artificial intelligence algorithms, novel models for early warning and stratified diagnosis of schizophrenia can be constructed to accelerate the translation of research findings into practical use and give full play to the value of oculomics in the precision diagnosis and treatment of schizophrenia.

ACKNOWLEDGEMENTS

Authors' Contributions: Zhou XL: Writing–original draft, resources; Wang L: Writing–review & editing; Wang XY: Writing–review & editing; Song CY: Writing–review & editing; Lai MY: Writing–review & editing; Yang WH: Writing–review & editing, conceptualization.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

AI-Generated Content Disclosure: AI-assisted tools were used solely for language polishing and grammar improvement during manuscript preparation. All modifications were reviewed and approved by the authors, who take full responsibility for the scientific content and integrity of the manuscript.

Foundation: Supported by Sanming Project of Medicine in Shenzhen (No.SZSM202411009).

Conflicts of Interest: Zhou XL, None; **Wang L,** None; **Wang XY,** None; **Song CY,** None; **Lai MY,** None; **Yang WH,** None.

REFERENCES

1 World Health Organization. Schizophrenia. [EB/OL]. (2024-10-06) [2026-05-20]. https://www.who.int/zh/news-room/fact-sheets/detail/schizophrenia.

2 Almonte MT, Capellàn P, Yap TE, *et al*. Retinal correlates of psychiatric disorders. *Ther Adv Chronic Dis* 2020;11:2040622320905215.

3 Kang HH, Shu YQ, Yang L, *et al*. Measuring abnormal intrinsic brain activities in patients with retinal detachment using amplitude of low-frequency fluctuation: a resting-state fMRI study. *Int J Neurosci* 2019;129(7):681-686.

4 Jurišić D, Ćavar I, Sesar A, *et al*. New insights into schizophrenia: a look at the eye and related structures. *Psychiatr Danub* 2020;32(1): 60-69.

5 Feng H, Chen J, Zhang Z, *et al*. A bibliometric analysis of artificial intelligence applications in macular edema: exploring research hotspots and Frontiers. *Front Cell Dev Biol* 2023;11:1174936.

6 Zhao JQ, Lu Y, Zhu SJ, *et al*. Systematic bibliometric and visualized analysis of research hotspots and trends on the application of artificial intelligence in ophthalmic disease diagnosis. *Front Pharmacol* 2022;13:930520.

7 Lee WW, Tajunisah I, Sharmilla K, *et al*. Retinal nerve fiber layer structure abnormalities in schizophrenia and its relationship to disease state: evidence from optical coherence tomography. *Invest Ophthalmol Vis Sci* 2013;54(12):7785.

8 Pan JR, Zhou YY, Xiang Y, *et al*. Retinal nerve fiber layer thickness changes in Schizophrenia: a meta-analysis of case-control studies. *Psychiatry Res* 2018;270:786-791.

9 Blose BA, Lai A, Crosta C, *et al*. Retinal neurodegeneration as a potential biomarker of accelerated aging in schizophrenia spectrum disorders. *Schizophr Bull* 2023;49(5):1316-1324.

10 Wang RY, Zuo GX, Li KK, *et al*. Systematic bibliometric and visualized analysis of research hotspots and trends on the application of artificial intelligence in diabetic retinopathy. *Front Endocrinol (Lausanne)* 2022;13:1036426.

11 Lin YW, Xu J, Huang QB, *et al*. Unraveling the role of microglial activation and immune regulation in glaucomatous neurodegeneration: insights into its dynamic interactions with retinal cells. *Vis Neurosci* 2025;42:e011.

12 Lizano P, Bannai D, Lutz O, *et al*. A meta-analysis of retinal cytoarchitectural abnormalities in schizophrenia and bipolar disorder. *Schizophr Bull* 2020;46(1):43-53.

13 Celik M, Kalenderoglu A, Sevgi Karadag A, *et al*. Decreases in ganglion cell layer and inner plexiform layer volumes correlate better with disease severity in schizophrenia patients than retinal nerve fiber layer thickness: findings from spectral optic coherence tomography. *Eur Psychiatry* 2016;32:9-15.

14 Qin FY, Cao X, Zhao XL, *et al*. Association between retinal nerve fiber layer thickness and psychiatric disorders: a Mendelian randomization study. *BMC Psychiatry* 2024;24(1):640.

15 Blose BA, Silverstein SM, Stuart KV, *et al*. Association between polygenic risk for schizophrenia and retinal morphology: a cross-sectional analysis of the United Kingdom Biobank. *Psychiatry Res* 2024;339:116106.

16 Wagner SK, Cortina-Borja M, Silverstein SM, *et al*. Association between retinal features from multimodal imaging and schizophrenia. *JAMA Psychiatry* 2023;80(5):478-487.

17 Zhu JY, Wang ZJ, Chen TZ, *et al*. Thinning of central foveal thickness in the retina of patients with schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2025;275(3):839-849.

18 Sönmez İ, Köşger F, Aykan Ü. Retinal nerve fiber layer thickness measurement by spectral-domain optical coherence tomography in patients with major depressive disorder. *Noro Psikiyatr Ars* 2017;54(1):62-66.

19 Kalenderoglu A, Sevgi-Karadag A, Celik M, *et al*. Can the retinal ganglion cell layer (GCL) volume be a new marker to detect

neurodegeneration in bipolar disorder *Compr Psychiatry* 2016;67: 66-72.

20 Mehraban A, Samimi SM, Entezari M, *et al*. Peripapillary retinal nerve fiber layer thickness in bipolar disorder. *Graefes Arch Clin Exp Ophthalmol* 2016;254(2):365-371.

21 Polo V, Satue M, Gavin A, *et al*. Ability of swept source OCT to detect retinal changes in patients with bipolar disorder. *Eye* (*Lond*) 2019;33(4):549-556.

22 Sheehan N, Bannai D, Silverstein SM, *et al*. Neuroretinal alterations in schizophrenia and bipolar disorder: an updated meta-analysis. *Schizophr Bull* 2024;50(5):1067-1082.

23 Demirlek C, Arslan B, Eyuboglu MS, *et al*. Retina in clinical high-risk and first-episode psychosis. *Schizophr Bull* 2026;52(1):sbae189.

24 Velez-Perez E, Demirlek C, Zeng V, *et al*. Retinal cytoarchitectural alterations across the psychosis spectrum and their correlates with cognition: a UK biobank nested case-control study. *Mol Psychiatry* 2026;31(4):1923-1932.

25 Hébert M, Gagné AM, Paradis ME, *et al*. Retinal response to light in young nonaffected offspring at high genetic risk of neuropsychiatric brain disorders. *Biol Psychiatry* 2010;67(3):270-274.

26 Boudriot E, Gabriel V, Popovic D, *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.

27 Hébert M, Mérette C, Gagné AM, *et al*. The electroretinogram may differentiate schizophrenia from bipolar disorder. *Biol Psychiatry* 2020;87(3):263-270.

28 Masson G, Mestre D, Blin O. Dopaminergic modulation of visual sensitivity in man. *Fundam Clin Pharmacol* 1993;7(8):449-463.

29 Chu EM, Kolappan M, Barnes TRE, *et al*. A window into the brain: an *in vivo* study of the retina in schizophrenia using optical coherence tomography. *Psychiatry Res* 2012;203(1):89-94.

30 Bernardin F, Schwitzer T, Schwan R, *et al*. Altered central vision and amacrine cells dysfunction as marker of hypodopaminergic activity in treated patients with schizophrenia. *Schizophr Res* 2022;239:134-141.

31 Hanifi Kokaçya M, İdil Çakmak A. Optical coherence tomography angiography in schizophrenia. *Alpha Psychiatry* 2022;23(5):253-261.

32 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.

33 Appaji A, Nagendra B, Chako DM, *et al*. Examination of retinal vascular trajectory in schizophrenia and bipolar disorder. *Psychiatry Clin Neurosci* 2019;73(12):738-744.

34 Appaji A, Nagendra B, Chako DM, *et al*. Retinal vascular tortuosity in schizophrenia and bipolar disorder. *Schizophr Res* 2019;212:26-32.

35 Meier MH, Shalev I, Moffitt TE, *et al*. Microvascular abnormality in schizophrenia as shown by retinal imaging. *Am J Psychiatry* 2013;170(12):1451-1459.

36 Bannai D, Adhan I, Katz R, *et al*. Quantifying retinal microvascular morphology in schizophrenia using swept-source optical coherence tomography angiography. *Schizophr Bull* 2022;48(1):80-89.

37 Massoda S, Rakkay H, Émond C, *et al*. High-density retinal signal deciphering in support of diagnosis in psychiatric disorders: a new paradigm. *Biomed Signal Process Control* 2025;102:107373.

38 Appaji A, Harish V, Korann V, *et al*. Deep learning model using retinal vascular images for classifying schizophrenia. *Schizophr Res* 2022;241:238-243.

39 Antaki F, Kerexeta-Sarriegi J, Reis APR, *et al*. The association of retinal age gap with schizophrenia: a cross-sectional analysis. *Schizophr Res* 2025;283:180-187.

40 Ayyildiz D. Central choroidal thickness in children and adolescents with anxiety disorders: enhanced depth imaging optical coherence tomography findings. *Int J Ophthalmol* 2020;13(10):1580-1585.

41 Krukow P, Domagała A, Kiersztyn A, *et al*. The retinal age gap as a marker of accelerated aging in the early course of schizophrenia. *Schizophr Bull* 2026;52(1):sbaf038.

42 Liu S, Chen RY, Hu WY, *et al*. Ocular ageing biomarkers and their clinical utility: a review. *Vis Neurosci* 2025;42:e009.