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Oculomics of lipid metabolism: A scoping review across anterior and posterior segment diseases

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Abstract

Dyslipidemia comprises interacting disturbances in lipids and lipoproteins that track with metabolic status, vascular biology, and inflammation. Ocular imaging offers scalable, quantifiable phenotypes to interrogate lipid-related pathways and to develop oculomics. We conducted a scoping review to map evidence linking dyslipidemia and lipid-related biomarkers with ocular phenotypes across the ocular surface, lens, macula, retinal microvasculature, and vascular occlusive disease, and to consider implications for AI-based risk modeling. We searched PubMed, Embase, Scopus, and Web of Science, supplemented by reference screening, and charted lipid exposures such as LDL-C, non-HDL-C, apoB/apoA-I, and the triglyceride-glucose index. The biologically grounded patterns were observed in macular disease, where cholesterol- and apolipoprotein-related material within the RPE-Bruch's membrane complex and drusen-related phenotypes support lipid-handling and innate immune pathways in age-related macular degeneration. Retinal vascular phenotypes showed generally consistent signals compatible with endothelial stress and microvascular remodeling. Epidemiologic associations were apparent in metabolically co-traveling conditions such as meibomian gland dysfunction and diabetic retinopathy, in which triglyceride-rich dyslipidemia and insulin resistance markers were often more informative than LDL-C alone and associations were often nonlinear or interaction-dependent. By contrast, findings for glaucoma and cataract were modest and inconsistent, while vascular occlusive phenotypes clustered with broader atherosclerotic risk. Statin associations varied by outcome and were vulnerable to confounding. Predicting individual lipid analytes from retinal images appears limited, whereas integrated ocular signatures may support cardiovascular risk stratification. Future studies should refine phenotype definitions, model non-linearity, account for lipid-lowering therapy, and prospectively validate multimodal oculomics and AI across devices and populations.

Keywords

oculomics, dyslipidemia, cholesterol, drusen, diabetic retinopathy

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1. Introduction

Ophthalmology may provide a distinctive vantage point for studying systemic lipid biology because multiple ocular tissues are sensitive to lipid-driven oxidative and inflammatory signaling, yet remain accessible to high-resolution, noninvasive imaging.[1] Lipid handling and deposition affect the ocular surface and adnexa, including meibomian gland function and meibum composition,[2] corneal stromal lipid accumulation such as arcus, periocular lipid-laden lesions such as xanthelasma,[3] and posterior segment structures including the retinal pigment epithelium (RPE), the Bruch's membrane complex,[4] and the retinal neurovascular unit.[5] Because microvascular integrity, endothelial function, and tissue remodeling are core domains perturbed by atherogenic dyslipidemia, the eye offers a practical in vivo window into systemic vascular biology. External photography and meibography support anterior segment phenotyping, color fundus photography captures retinal structural and vascular signatures, and optical coherence tomography (OCT) or OCT angiography (OCTA) enables quantitative assessment of retinal and choroidal microarchitecture. This accessibility makes the eye a natural substrate for oculomics, in which algorithmic features extracted from ocular images are evaluated as biomarkers of local pathology and systemic health.[1] However, lipid-focused oculomics remains underdeveloped relative to other cardiometabolic exposures, and the evidence base is fragmented across phenotypes, imaging modalities, and lipid definitions.

Dyslipidemia is increasingly recognized as a heterogeneous disturbance of lipid and lipoprotein homeostasis rather than a single "high LDL cholesterol" phenotype.[6] Beyond low-density lipoprotein cholesterol (LDL-C), contemporary cardiovascular and metabolic risk assessment commonly considers non-high-density lipoprotein cholesterol (non-HDL-C) as an aggregate measure of atherogenic cholesterol, triglycerides and triglyceride-rich lipoprotein remnants, lipoprotein(a) [Lp(a)], and particle- or apolipoprotein-based metrics such as apolipoprotein B (apoB) that index the number of circulating atherogenic particles. Composite indices such as the triglyceride-glucose (TyG) index also provide pragmatic surrogates for insulin resistance and broader metabolic context.[7,8] Importantly, lipid-related risk is not fully captured by circulating concentrations alone. Qualitative dimensions, including lipoprotein modification such as oxidized LDL and small dense LDL, and functional properties of HDL such as cholesterol efflux capacity and anti-inflammatory activity, may contribute to discordant epidemiologic associations across organ systems. The etiologic landscape is similarly broad, spanning monogenic and polygenic lipid disorders as well as secondary contributors including insulin resistance, diabetes, obesity, thyroid dysfunction, chronic kidney or liver disease, dietary patterns, alcohol use, pregnancy, and medication effects.

Accordingly, we conducted a scoping review to clarify how dyslipidemia relates to ophthalmic phenotypes across the anterior and posterior segments, glaucoma-related vascular and pressure phenotypes, lens disease, and retinal vascular occlusive disorders. We also summarize evidence on lipid-lowering therapies, with emphasis on statins, and outline how oculomics and artificial intelligence can capture complex lipid–phenotype relationships in real-world settings (Figure 1). We used a scoping, evidence-based (PRISMA-ScR–guided) review approach with a comprehensive multi-database search to map evidence across ocular phenotypes and lipid-related oculomics.

2. Methods

We conducted a scoping review to map and synthesize evidence linking dyslipidemia and lipid-related biomarkers to ocular phenotypes across the anterior segment, posterior segment, lens, and retinal vascular disorders, and to summarize ocular outcomes reported in lipid-modifying interventions. A final comprehensive search was performed on 19 December 2025 without automated alerts. We searched MEDLINE (via PubMed), Embase (Elsevier), Scopus, Web of Science Core Collection, and the Cochrane Library (CENTRAL), hand-searched reference lists of key reviews and seminal mechanistic papers, and screened ClinicalTrials.gov for lipid-modifying trials reporting ocular outcomes. The full search strategy is summarized in Supplementary Table 1. Choroidal thickness and vascularity metrics were considered within the review scope; however, because these measures are not yet consistently established as distinct disease-specific phenotype categories, they were addressed as emerging biomarkers rather than mapped as a separate phenotype domain.

The search combined controlled vocabulary and free-text terms covering three concept blocks: dyslipidemia and lipid metrics (including LDL-C, non-HDL-C, triglycerides, remnant cholesterol, HDL-C and HDL function, apoB, apoA-I, lipoprotein(a), and the triglyceride–glucose index), ocular conditions (including dry eye syndromes/meibomian gland dysfunction, corneal arcus, xanthelasma, AMD and drusen-related entities including reticular pseudodrusen/subretinal drusenoid deposits, diabetic and hypertensive retinopathy, glaucoma, cataract, retinal vein/artery occlusion, NAION, and ocular ischemic syndrome), and imaging/oculomics/AI terms for targeted subqueries (fundus/CFP/UWF, OCT/OCTA, meibography, radiomics, machine learning). Boolean logic combined lipid terms AND ocular terms, with imaging/AI terms used for oculomics-focused subqueries. Where available, filters were applied for Humans and English.

We included human studies reporting associations between dyslipidemia, lipid-related biomarkers, or statin therapy and ocular phenotypes, as well as studies reporting imaging or oculomics features linked to lipid biology. Because of the broad

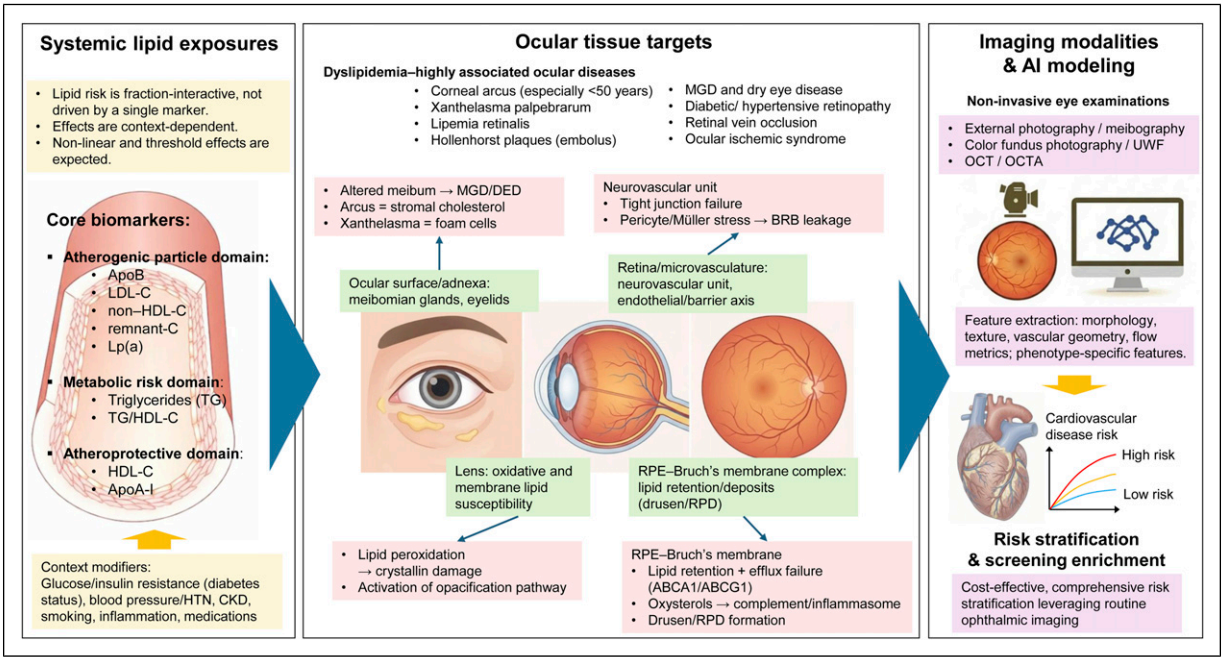

Figure 1. Schematic representation of the relationship between systemic dyslipidemia and ocular phenotypes, highlighting the potential for oculomics-based risk stratification. All original illustrations were generated by the authors.

scope of the review, the therapy-focused synthesis in the main manuscript was limited to statin-associated ocular outcomes, while fenofibrate-related evidence was discussed separately in the diabetic retinopathy section due to its disease-specific clinical relevance. Eligible designs included randomized or quasi-experimental trials, cohort/case-control studies, cross-sectional studies (particularly for imaging features), Mendelian randomization (MR) studies, and systematic reviews/meta-analyses, with inclusion of high-certainty genetic/mechanistic case series relevant to lipidopathy-associated ocular phenotypes when uniquely informative. We excluded non-human or purely in vitro studies unless indispensable for context, editorials/letters without primary data, single-case reports (except named lipidopathies), non–peer-reviewed preprints, studies lacking a defined lipid exposure or clear ocular phenotype, and non-quantitative narratives without unique evidence. The search timeframe was 1 January 1990 to 19 December 2025. The literature selection process is detailed in Supplementary Figure 1. Eligibility criteria and evidence domains were defined a priori before the literature search and screening process. Two reviewers independently screened titles/abstracts and full texts. Although inter-rater reliability statistics were not prespecified, disagreements were relatively infrequent and were resolved through discussion and consensus. Inter-rater agreement was almost perfect at the title/abstract screening stage (Cohen's $\kappa = 0.83$).

Because this study was designed as a scoping review, we did not perform a formal certainty-of-evidence assessment. Instead, we qualitatively mapped the overall pattern of evidence for each ocular phenotype, considering the direction and consistency of findings, relative study design strength, the presence or absence of higher-inference evidence such as Mendelian randomization or randomized trials, and key limitations including heterogeneity, confounding, and imprecise exposure or outcome definitions. This approach was intended to support structured evidence mapping across phenotypes rather than formal evidence grading.

Because of journal reference limits, Table 1and Table 2 provide representative examples to illustrate major evidence patterns and study types, whereas the supplementary tables provide the more complete phenotype-specific evidence base reviewed in this study. The review was conducted independently of any commercial entity, and study selection and evidence synthesis were performed using prespecified criteria to minimize potential conflicts.

3. Defining dyslipidemia: Phenotypes and biomarkers

3.1. Conceptual definition and context

Dyslipidemia is a set of quantitative and qualitative lipoprotein disturbances that often cluster with broader cardiometabolic risk.[30] For ophthalmic association studies, lipid exposures should be defined with attention to interactions between lipid

Table 1. Representative evidence linking dyslipidemia to anterior segment phenotypes.

Condition	Key lipid linkage (exposure definition)	Typical pattern of association	Representative evidence	Higher-inference support	Notable modifiers/non-linearity	Practical interpretation
DED/MGD	Dyslipidemia signals reported in DED; TC and TG-related patterns more often reported in MGD	Overall positive association, but component-level heterogeneity	Meta-analysis[2] + clinical cohorts[9]	Not established	Likely effect modification by IR/obesity	Consider cardiometabolic screening in refractory MGD/DED, particularly TG/IR patterns.
Corneal arcus (<50y/ premature)	Cholesterol deposition; early-onset dyslipidemia signal	Positive (strong age-stratified signal)	Cohorts/clinical series[10]	Not applicable	Age-dependent (stronger when early)	In younger adults, supports lipid evaluation (consider FH in marked/early arcus).
Corneal arcus (older/age-related)	Age-related deposition with weaker specificity	Mixed/attenuated	Population studies[3,11]	Not applicable	Age dominates	Contextual cue; limited specificity for systemic dyslipidemia/CVD risk.
Xanthelasma	Atherogenic lipids (higher TC/LDL/apoB; lower apoA-I) in many clinic/case-control syntheses	Positive in case-control studies; often attenuated or neutral after adjustment in population-based analyses	Meta-analysis[12] + population cohorts[3,13]	Not established	Strong confounding, selection effects	Prompt lipid testing; avoid treating as definitive cardiovascular marker.
Cataract (lens)	MetS dyslipidemia components (high TG/low HDL) frequently used	Modest, inconsistent	Cohorts/case-control[14,15]	Limited/ unclear	Possible thresholds; confounding by age, DM, lipid-lowering	Interpret cautiously because associations are modest and sensitive to age, diabetes status, medication exposure, and cataract subtype definitions.
Presbyopia	Age-related lens lipidome shifts	Biologic plausibility; direct epidemiologic evidence remains limited	Lens biophysics literature[16]	Not established	Age dominates; possible DM/ metabolic interaction	No presbyopia-specific lipid testing recommendation

Note. References listed are representative examples selected to illustrate the major evidence patterns and study types discussed in the review, not an exhaustive bibliography for each phenotype. Because this is a scoping review, the tables are intended as an evidence map rather than a formal certainty-of-evidence grading framework. Readers are referred to the supplementary tables for the more complete phenotype-specific evidence base reviewed in this study.

Abbreviations: apoA-I = apolipoprotein A-I; apoB = Apolipoprotein B; CVD = Cardiovascular disease; DED = Dry eye disease; FH = Familial hypercholesterolemia; HDL-C = High-density lipoprotein cholesterol; IR = insulin resistance; LDL-C = Low-density lipoprotein cholesterol; MetS = Metabolic syndrome; MGD = Meibomian gland dysfunction; MR = Mendelian randomization; non-HDL-C = Non–high-density lipoprotein cholesterol; TC = Total cholesterol; TG = Triglycerides; TyG = Triglyceride–glucose index.

Table 2. Representative evidence linking dyslipidemia to posterior segment phenotypes.

Condition	Key lipid linkage (exposure definition)	Typical pattern of association	Representative evidence	Higher-inference support	Notable modifiers/non-linearity	Practical interpretation
AMD (soft drusen and RPD/SDD)	Lipid-rich soft drusen; HDL-pathway genes; RPD/SDD has distinct lipid biology	Soft drusen: supportive lipid-handling and HDL-pathway signal RPD/SDD: distinct and still evolving phenotype-specific associations	Pathology[4] + large cohorts + genetics/MR[17]	Supportive at the pathway level for AMD overall; not established specifically for RPD/SDD	Yes (phenotype- and pathway-dependent)	HDL-C should not be assumed to be protective in AMD (HDL-pathway paradox); interpret lipids by AMD stage/phenotype and distinguish RPD/SDD from soft drusen.[18]
Diabetic retinopathy	Insulin resistance (TyG), remnants/non-HDL/apoB; oxidative stress	TyG generally positive; standard lipids show weak/inconsistent linear signals; apolipoprotein/remnant metrics often stronger	Multiple cohorts[19] + meta-analyses[7,20]	MR and drug-target MR support pathway-level effects beyond a simple LDL-C–only mechanism[21]	Common: non-linearity reported (U-shapes; lipids × glycemia/BP)	Follow CVD lipid guidelines; in DR-prone diabetes, target TG-rich/IR dyslipidemia and consider fenofibrate (± statin) with tight glucose and BP control.
Hypertensive retinopathy	LDL/non-HDL burden; endothelial stress	Suggestive vascular association, including reduced vessel density in imaging-based studies	Observational studies[22,23]	Not established	Likely interactions with BP/CKD	Needs longitudinal OCTA; interpret as vascular resilience signal.
POAG/IOP ↑	TC/LDL (±HDL) track IOP; TG variable	Inconsistent to modest associations across observational studies, with IOP-related signals reported more often than clear POAG causality	Observational datasets + meta-analyses[24]	Generally not supportive[25]	Limited evidence; likely effect confounding by age, BP, DM, and medication use	Manage lipids based on CVD risk, not glaucoma prevention; consider dyslipidemia as a metabolic comorbidity rather than a direct cause.
RVO	TG, non-HDL/apoB; metabolic syndrome clustering	Generally positive	Cohort/case-control + meta-analyses[26]	Not established; evidence is mainly observational	Possible	Treat as vascular-metabolic phenotype; assess remnants/apoB and systemic risks.
RAO/OIS (including Hollenhorst plaques)	Atherosclerotic dyslipidemia upstream; consider Lp(a); Hollenhorst plaques represent cholesterol emboli	Upstream-risk/trigger pattern: lipids contribute to systemic atherosclerosis; Hollenhorst plaque is a direct embolic manifestation	Vascular/clinical cohorts[27,28]	Not definitive (primarily clinical-pathway evidence)	Not primary	Treat as a high-risk vascular sign: urgent systemic vascular evaluation and aggressive risk-factor management, including lipid-lowering per ASCVD prevention.
NAION	Vascular risk clustering incl. dyslipidemia	Indirect association within broader vascular risk-factor clustering	Observational risk-factor studies + meta-analysis[29]	Not established	Possible	Manage global vascular risk (OSA/HTN/DM) rather than lipid alone.

Note. References listed are representative examples selected to illustrate the major evidence patterns and study types discussed in the review, not an exhaustive bibliography for each phenotype. Because this is a scoping review, the tables are intended as an evidence map rather than a formal certainty-of-evidence grading framework. Readers are referred to the supplementary tables for the more complete phenotype-specific evidence base reviewed in this study.

Abbreviations: AMD = age-related macular degeneration; apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; DR = diabetic retinopathy; HDL = high-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; HTN = hypertension; IOP = intraocular pressure; IR = insulin resistance; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); MR = Mendelian randomization; NAION = non-arteritic anterior ischemic optic neuropathy; OCTA = optical coherence tomography angiography; OIS = ocular ischemic syndrome; OSA = obstructive sleep apnea; POAG = primary open-angle glaucoma; RAO = retinal artery occlusion; RPD = reticular pseudodrusen; RVO = retinal vein occlusion; SDD = subretinal drusenoid deposits; TC = total cholesterol; TG = triglycerides; TyG = triglyceride-glucose.

fractions (LDL-C, TG/remnants, HDL axis), and between lipids and metabolic or vascular context (glucose/insulin resistance, blood pressure, renal function, inflammation, and vascular calcification).[6] This is important because ocular phenotypes may reflect combined insults, such as atherogenic particle burden in the setting of hyperglycemia, or triglyceride-rich dyslipidemia coupled with low HDL function.

3.2. Core lipid biomarkers for ophthalmic studies

Core quantitative biomarkers include LDL-C, non-HDL-C, triglycerides, remnant cholesterol, HDL-C, Lp(a), and apolipoproteins.[30] LDL-C remains the most familiar metric but can misrepresent risk when particle number is discordant with cholesterol content; non-HDL-C and apoB better summarize the burden of apoB-containing particles, especially in hypertriglyceridemia. Triglycerides and remnant-C capture triglyceride-rich lipoprotein biology, which may interact with microvascular stressors. HDL-C reflects the HDL axis but is an incomplete proxy for function, and Lp(a) provides a largely genetic atherothrombotic exposure that may be most relevant to vascular and occlusive ocular outcomes. Apolipoprotein A-I (apoA-I) can complement HDL-related analyses by indexing the HDL particle axis.

3.3. Emerging biomarkers and targets

Beyond conventional fractions, pathway-oriented biomarkers and targets may offer a more specific bridge to ocular microvascular disease. ApoC-III reflects triglyceride-rich lipoprotein clearance and remnant particle biology and may be more informative than triglycerides alone in insulin-resistant phenotypes.[31] Apolipoprotein profiling also supports a more granular DR risk signature, where apoC-II to apoC-III and apoE-based ratios, together with apoB indexed to non-HDL-C, have been reported as independent correlates of DR occurrence and severity after accounting for glycemia and diabetes duration. ANGPTL3 and ANGPTL4 regulate lipid trafficking through lipoprotein lipase and intersect with endothelial and permeability pathways, making them plausible candidates for retinal microvascular remodeling and exudative phenotypes.[32,33] Additional retinopathy-relevant candidates include ceramide and sphingolipid lipidomic signatures that may better reflect inflammatory and endothelial stress pathways than standard lipid panels.[34] These emerging markers provide a forward-looking framework for oculomics studies and for trials that incorporate ocular imaging endpoints.

3.4. Composite measures and interaction-aware exposure definitions

Because interactions are often clinically meaningful, composite and ratio-based measures can add context beyond single analytes. The TyG index integrates TG and glucose as a practical surrogate for insulin resistance,[7] capturing the joint metabolic milieu in which lipid effects are expressed. The atherogenic index of plasma (log [TG/HDL-C]) summarizes a triglyceride-rich, low-HDL pattern that correlates with small dense LDL and cardiometabolic risk. When feasible, studies should also consider joint exposure patterns (e.g. high apoB with high TG, or high TG with low HDL-C) and formally test effect modification by glucose status (normoglycemia, prediabetes, diabetes) and blood pressure category, rather than relying on single-variable adjustment alone.

3.5. Etiologic phenotyping and confounding structure

Etiologically, dyslipidemia should be classified as primary (familial hypercholesterolemia, familial combined hyperlipidemia, dysbetalipoproteinemia, isolated elevation of Lp(a)) or secondary (insulin resistance/diabetes, obesity, chronic kidney disease, hypothyroidism, liver disease, alcohol use, pregnancy, and medication effects).[35] These determinants can both confound and modify lipid–ocular relationships; for example, TG-rich dyslipidemia in insulin resistance may signal a different biological pathway than isolated LDL-C elevation in familial hypercholesterolemia.

3.6. Analytic considerations

Analytically, lipid–ocular associations should not be assumed to be linear. Thresholds and U-shaped patterns are plausible, and interactions can create apparent non-linearity.[8,36] These observations suggest that future studies should consider prespecifying non-linear splines for major lipid variables and reporting potential turning points. In the current literature, formal non-linear modeling was performed in only a limited number of studies, and this recommendation is therefore intended primarily as a direction for future research rather than a reflection of standard practice in the included studies. In addition, interaction terms should be prespecified for high-priority pairs, particularly LDL-related burden (non-HDL-C or apoB) with TG/remnants, and lipids with glucose/insulin resistance (e.g. TyG or diabetes status). Where available, vascular

context variables such as blood pressure, renal function, inflammatory markers, and coronary artery calcium can be used to test whether lipid–ocular associations strengthen in higher-risk strata.[37] Because ocular risk may reflect broader cardiometabolic and bone–vascular biology, interactions with glycemia and osteoporosis-related factors should be considered, and models may be strengthened by including glucose measures and bone health indicators.[38]

4. Mechanisms: From systemic dyslipidemia to local ocular damage

4.1. Conceptual overview

Systemic dyslipidemia is best treated as an interaction-driven exposure rather than a single-analyte insult. Ocular injury reflects atherogenic particle burden, triglyceride-rich remnants, and impaired HDL-mediated efflux, with downstream effects shaped by oxidative stress and inflammation. These lipid effects are frequently modified by hyperglycemia and insulin resistance, hypertension, renal dysfunction, smoking, and medication exposure, which together determine endothelial stability, barrier resilience, and local immune activation. This framework predicts non-linear or threshold effects and helps explain heterogeneous findings across populations and risk strata.

Importantly, many retinal conditions evolve gradually rather than presenting abruptly. Even in the absence of a diagnosable ophthalmic disease, cumulative lipid-related vascular and tissue stress may drive subclinical retinal remodeling over time; therefore, oculomics studies should consider continuous retinal changes and early biomarkers, not only overt clinical endpoints.

4.2. Vascular endothelium: Oxidative lipoproteins and microthrombi

A core vascular pathway is endothelial injury induced by oxidized and remnant lipoproteins. Oxidized LDL can activate lectin-like oxidized LDL receptor-1 (LOX-1) on endothelial cells, reducing nitric oxide bioavailability and increasing reactive oxygen species generation.[39] Reduced nitric oxide impairs vasodilation and endothelial repair, while reactive oxygen species promotes adhesion molecule expression and leukocyte recruitment.[40] This combination supports a proinflammatory, prothrombotic endothelium that can favor microthrombi, capillary nonperfusion, and increased vascular permeability. Triglyceride-rich remnants and lipoprotein(a) may further potentiate endothelial activation and fibrinolytic imbalance, creating conditions conducive to retinal and choroidal ischemia and occlusive disease, particularly in the presence of hypertension, diabetes, and smoking.

4.3. Barrier dysfunction and the neurovascular unit

Barrier breakdown provides a second mechanistic axis. The inner blood–retinal barrier depends on tight junction integrity in retinal endothelial cells and on pericyte-mediated stabilization. Oxidative stress and inflammatory signaling can weaken junctional proteins, increase transcytosis, and impair pericyte survival, producing vascular leakage and tissue edema.[40] Once leakage begins, a feed-forward loop can emerge in which extravasated mediators activate Müller glia and other retinal immune-like cells, increasing cytokines and vascular endothelial growth factor and further destabilizing the barrier. In parallel, dyslipidemia-related bioactive lipid signaling, especially the ceramide versus sphingosine-1-phosphate rheostat, can tilt tissues toward mitochondrial stress and proapoptotic pathways, reducing resilience of both vascular and neuronal compartments.[5] These processes offer a coherent bridge between lipid stress and microvascular retinopathies, ischemic injury patterns, and broader neurovascular vulnerability.

4.4. RPE–Bruch's membrane complex: Lipid retention, oxysterols, and innate immune activation

The RPE–Bruch's membrane complex is a key site where systemic lipid biology intersects with age-related lipid deposition.[4] Bruch's membrane accumulates neutral lipids with age, reducing hydraulic conductivity and impairing exchange of nutrients and waste products. Drusen and subretinal drusenoid deposits (reticular pseudodrusen) contain cholesterol esters, phospholipids, and apolipoprotein-associated material, reflecting local lipid retention and remodeling. Protective cholesterol efflux depends on transporters such as ABCA1 and ABCG1, coordinated by liver X receptor signaling; reduced efflux capacity promotes accumulation and oxidative modification of lipids.[41] Oxysterols, including 7-ketocholesterol, can serve as potent inflammatory stimuli, promoting RPE stress and local innate immune activation. Complement activation and inflammasome signaling can reinforce each other, sustaining chronic para-inflammation at the macula and converting lipid-rich deposits into active immunometabolic niches rather than inert byproducts.

4.5. Ocular surface and adnexa: Meibomian lipid biology, arcus, and xanthelasma

The ocular surface represents a clinically accessible interface for lipid-related pathology. Meibomian gland function depends on regulated lipogenesis and meibocyte differentiation, in which peroxisome proliferator–activated receptor gamma signaling plays a central role.[9] Dyslipidemia and insulin resistance can shift meibum composition toward higher viscosity and melting point, promoting duct obstruction, gland dropout, tear film instability, and evaporative dry eye disease. Oxidized lipid species at the lid margin may further amplify local inflammation. Beyond glandular dysfunction, peripheral corneal arcus reflects stromal cholesterol deposition,[10] while periocular xanthelasma reflects dermal foam-cell infiltration and local macrophage lipid handling, providing visible manifestations of systemic lipid burden and inflammatory recruitment.[12]

4.6. Lens: Membrane lipid balance, lipid peroxidation, and crystallin cross-linking

The crystalline lens offers an additional pathway linking lipid stress to opacity. Lens fiber cell membranes are enriched in cholesterol and sphingomyelin to preserve stability and transparency. Disturbance of this lipid balance, combined with oxidative stress, can promote membrane dysfunction and protein modification.[41] Lipid peroxidation generates reactive aldehydes such as malondialdehyde and 4-hydroxynonenal that can form adducts with crystallins and drive cross-linking, reducing solubility and increasing light scattering. While cataractogenesis is multifactorial and strongly age-driven, these oxidative lipid pathways provide a plausible mechanism by which systemic dyslipidemia and lipid oxidation states could contribute to lens opacification, especially with coexisting diabetes and smoking.

5. Disease-specific evidence

This evidence map summarizes the major patterns linking dyslipidemia to ocular phenotypes across the anterior and posterior segments. Across diseases, associations are rarely explained by a single lipid analyte in a linear fashion. Instead, risk often reflects interaction patterns, such as apoB-containing particle burden in the setting of hypertriglyceridemia, impaired HDL function under oxidative stress, and lipid effects that are modified by glycemia, blood pressure, kidney function, smoking, and medication exposure.

5.1. Anterior segment (including lens)

Table 1 summarizes the major evidence patterns linking dyslipidemia to anterior segment phenotypes, including dry eye disease (DED) and meibomian gland dysfunction (MGD), corneal arcus, xanthelasma palpebrarum, and cataract.

5.1.1. Dry eye disease and meibomian gland dysfunction

Observational studies and pooled syntheses generally indicate that dyslipidemia co-travels with DED and worse MGD, although effect sizes are modest and heterogeneous across definitions and populations.[2,9] The most consistent pattern is effect modification by insulin resistance and obesity, with triglyceride-rich and insulin-resistant phenotypes appearing more clinically relevant than isolated LDL-C elevation. Overall, the literature is generally supportive, although heterogeneous across definitions and populations, and it supports consideration of cardiometabolic screening in refractory DED or MGD, particularly when triglyceride-rich or insulin resistance–related patterns are suspected.

5.1.2. Corneal arcus

Corneal arcus is strongly age-dependent in interpretation. In younger adults, particularly premature arcus before 50 years, it is a strong signal of early-onset dyslipidemia and should prompt lipid evaluation, with consideration of familial hypercholesterolemia when arcus is marked or early.[10] In older adults, the association is heterogeneous across study settings because age dominates, so arcus is best treated as a contextual cue with limited specificity for systemic dyslipidemia or cardiovascular risk.[3,11]

5.1.3. Xanthelasma palpebrarum

Clinic-based and case-control syntheses often show atherogenic lipid patterns in xanthelasma,[3] but population cohort analyses that adjust for confounding frequently report neutral or weaker associations, suggesting strong confounding and selection effects.[13] Taken together, the evidence is inconsistent across study settings, although xanthelasma may still serve as a practical clinical cue for broader lipid and cardiometabolic evaluation.[12] Clinically, xanthelasma should trigger lipid testing and broader cardiometabolic risk review, but it should not be interpreted as a definitive surrogate for cardiovascular events.

5.1.4. Cataract

Cataract is an important source of bias in oculomics because lens opacity can reduce fundus image quality (e.g. blur, haze, reduced contrast), leading to measurement error or systematic misclassification. In epidemiologic studies of age-related cataract, dyslipidemia is typically assessed in a metabolic-syndrome pattern, most often elevated triglycerides and lower HDL-C; however, reported associations are modest and inconsistent.[14,15] The available evidence is modest and inconsistent, with likely threshold effects and substantial confounding by age, diabetes, and lipid-lowering therapy. Interpretation should therefore be cautious, and analyses should explicitly account for diabetes status and medication exposure.

5.1.5. Presbyopia

Presbyopia is predominantly age-driven, but lens lipidomics suggests a plausible mechanistic link.[16] Age-related increases in cholesterol and sphingolipid content of lens membranes may increase membrane order and stiffness, which could contribute to reduced accommodation. Direct epidemiologic evidence relating circulating lipid fractions to presbyopia remains limited, and causality is not established. Therefore, presbyopia should be framed as biological plausibility rather than a clinical dyslipidemia marker.

5.2. Posterior segment

Table 2 summarizes the major evidence patterns linking dyslipidemia to posterior segment phenotypes, including age-related macular degeneration (AMD), diabetic retinopathy (DR), hypertensive retinopathy, primary open-angle glaucoma (POAG), and retinal occlusive and ischemic phenotypes.

5.2.1. Age-related macular degeneration, drusen, and reticular pseudodrusen

Drusen and Bruch's membrane are enriched with cholesterol and apolipoprotein-associated material, supporting a lipid-handling framework for AMD.[4] Genetic and MR evidence suggests an "HDL–AMD paradox," where higher HDL-C–related pathways may associate with higher AMD risk, emphasizing that HDL-C concentration is not equivalent to HDL function and that HDL-related genetics may act through local retinal lipid trafficking and innate immune pathways.[17] Importantly, this should not be interpreted to mean that higher measured HDL-C levels are necessarily harmful in clinical practice; rather, these findings implicate HDL-related biological pathways that may influence AMD through retinal lipid handling and immune mechanisms. Additionally, reticular pseudodrusen (subretinal drusenoid deposits) should be distinguished from soft drusen because their risk architecture and biological underpinnings may differ.[18] Reticular pseudodrusen also implicates lipid biology at the tissue level (local lipid trafficking and remodeling), although a direct, independent association with systemic dyslipidemia has not been firmly established. Overall, the evidence is generally supportive, particularly for drusen-related and lipid-handling pathways, but interpretation should remain stage- and phenotype-specific.

5.2.2. Diabetic retinopathy

Across cohorts and meta-analyses, insulin-resistance-related dyslipidemia shows the most coherent signal.[7,19,20] TyG is generally positively associated with DR risk, while standard lipid fractions often show weak or inconsistent linear associations; remnant metrics and apoB-based measures may be more informative. MR and drug-target MR suggest pathway-level effects rather than a simple LDL-only mechanism.[21] Non-linearity and interactions are common (including U-shapes and lipid by glycemia or blood pressure effects), supporting interaction modeling and medication-aware analyses.[8,36] Overall, the evidence is supportive but heterogeneous, with the practical implication that lipid management should follow cardiovascular disease guidelines and, in DR-prone diabetes, should pay particular attention to triglyceride-rich and insulin resistance–related phenotypes, alongside tight glucose and blood pressure control. Fenofibrate is discussed separately in the DR context because of its disease-specific relevance. Among lipid-modifying therapies, fenofibrate has the strongest randomized evidence for DR benefit. In the FIELD study, fenofibrate reduced the need for first retinal laser treatment over approximately 5 years.[42] In ACCORD Eye, adding fenofibrate to statin therapy reduced retinopathy worsening over 4 years, with the largest benefit in participants with pre-existing retinopathy and without clear dependence on baseline triglycerides or LDL-C.[43] These findings support effects beyond conventional lipid lowering, consistent with PPARα-mediated anti-inflammatory and microvascular mechanisms. More recent ocular-outcome trials further support fenofibrate for DR endpoints and reinforce the value of standardized retinal imaging outcomes in cardiometabolic trials targeting triglyceride-rich lipoprotein pathways.[44] Trials suggest DR benefits are not fully explained by standard lipid profile changes, supporting pathway-level microvascular mechanisms.

5.2.3. Hypertensive retinopathy and microvasculature

Current evidence suggests a link between LDL or non-HDL burden and reduced retinal vessel density on OCTA,[22] but most studies are observational and cross-sectional.[23] Interactions with blood pressure and chronic kidney disease are likely, so dyslipidemia may be better interpreted as a vascular resilience modifier rather than a standalone driver. Overall, the available evidence remains limited and largely observational, and longitudinal OCTA studies with robust adjustment for antihypertensive and lipid-lowering therapy remain a key gap.

5.2.4. Primary open-angle glaucoma and ocular hypertension

Observational datasets and meta-analyses suggest a modest tendency for total cholesterol or LDL (and sometimes HDL) to track higher IOP or POAG risk, with variable triglyceride patterns.[24] However, genetic causality signals for POAG attributable to standard lipid fractions are mostly not supportive, implying substantial confounding by age, diabetes, blood pressure, and medication use.[25] Overall, the evidence remains inconsistent and susceptible to confounding, and the practical implication is to manage lipids based on cardiovascular risk rather than glaucoma prevention, treating dyslipidemia primarily as a metabolic comorbidity signal. Normal-tension glaucoma merits separate consideration because vascular dysregulation may be more prominent than pressure-driven mechanisms. Observational evidence links glaucoma to atherogenic lipid patterns, and normal-tension glaucoma has been associated with lower HDL that may track with disease severity, supporting a vascular-context interpretation.[45]

5.2.5. Retinal occlusive and ischemic phenotypes

Retinal vein occlusion (RVO) commonly clusters with metabolic syndrome, and the most consistent lipid links involve triglycerides and broader atherogenic burden (non-HDL or apoB), although the evidence remains predominantly observational.[26] Retinal artery occlusion (RAO) and ocular ischemic syndrome (OIS), including Hollenhorst plaques, are best framed as downstream manifestations of systemic atherosclerosis or embolic disease in which dyslipidemia contributes upstream.[27,28] RAO and OIS should be regarded as high-risk vascular signs that warrant urgent systemic vascular evaluation and aggressive risk-factor management, including lipid-lowering in accordance with ASCVD prevention principles. For non-arteritic anterior ischemic optic neuropathy (NAION), dyslipidemia typically acts as part of broader vascular risk clustering, so management should prioritize global risk control (hypertension, diabetes, obstructive sleep apnea) rather than lipids alone.[29]

5.3. Rare lipidopathies and confirmed lipid-handling disorders

Rare disorders provide clear causal examples that help clarify how specific lipid pathways generate distinct ocular phenotypes. Schnyder corneal dystrophy due to UBIAD1 variants demonstrates that disturbed intracellular cholesterol handling can directly produce corneal crystalline deposits and stromal haze, and the ocular finding may precede systemic recognition, supporting lipid screening and family evaluation.[46] LCAT deficiency, including fish-eye disease, shows that impaired HDL maturation and lipid trafficking can cause corneal clouding, making lipid phenotyping and systemic workup clinically actionable. In contrast, Bietti crystalline dystrophy caused by CYP4V2 variants is a tissue-level fatty-acid metabolism retinopathy with crystalline deposits and progressive chorioretinal degeneration, and serum lipid profiles may be normal, underscoring that ocular lipid phenotypes can reflect local lipid metabolism not fully captured by circulating measures.[47] Finally, lipemia retinalis represents a direct, reversible ocular sign of extreme hypertriglyceridemia from chylomicronemia, and it should prompt urgent systemic evaluation for secondary causes and pancreatitis risk.[35] Collectively, these entities support biological plausibility for subtler, interaction-driven lipid effects in common dyslipidemia states while emphasizing phenotype-specific clinical actions.

6. Statins and eye disease

Because statins are prescribed at scale for cardiovascular prevention, any observed association with ocular outcomes is difficult to interpret causally. Across outcomes in Table 3, the evidence base is predominantly observational and therefore vulnerable to confounding by indication, healthy-user effects, and surveillance or detection bias. Many studies also use simplified exposure definitions such as ever versus never, despite a more plausible biological relation to intensity, cumulative duration, adherence, and achieved lipid levels. Accordingly, the most defensible synthesis is that statin signals are small and context dependent, and future analyses should prioritize time-updated exposure, cumulative dose or intensity, and effect modification by diabetes status, renal disease, smoking, and baseline cardiovascular risk.

For AMD, pooled estimates suggest at most a small protective signal for early AMD (relative risk [RR] 0.83, confidence interval [CI] 0.66 to 0.99) and exudative AMD (RR 0.90, CI 0.80 to 0.99), while late AMD overall is neutral (RR 0.92, CI

Table 3. Summary of evidence on statin exposure and ocular outcomes.

Category	Outcome	Direction	Best evidence	Effect size (95% CI range)	Notes on confounding/dose–duration
AMD	AMD (early AMD)	Potential protective association	Meta-analysis[48]	RR 0.83 (0.66–0.99)	Signals may depend on phenotype definition and residual healthy-user bias; not consistently reproduced in newer syntheses.
	AMD (late AMD overall)	No clear association	Meta-analysis[48]	RR 0.92 (0.77–1.07)	Subtype signals diverge (e.g. CNV vs GA), supporting phenotype-stratified reporting.
	AMD (CNV/exudative)	Small protective association in some analyses	Meta-analysis[48]	RR 0.90 (0.80–0.99)	Subtype-specific effect; cohort-only subtype estimates may be less stable.
Diabetic retinopathy	Diabetic retinopathy (incident DR)	Protective association reported in some cohorts	Large cohort[49]	HR 0.60 (0.54–0.66)	Strong potential for time-varying confounding (lipid control, diabetes duration/severity, medication changes).
	Diabetic retinopathy (need for intervention/progression surrogate)	Protective association reported in some observational syntheses	Meta-analysis (observational)[50]	HR 0.72 (0.64–0.80)	Progression definitions vary; adjustment often incomplete for glycemia/BP and treatment intensity.
POAG/ocular hypertension	Open-angle glaucoma (OAG) onset	Small protective association	Systematic review/meta-analysis[51]	Pooled RR 0.95 (0.93–0.98)	Evidence largely observational; progression outcomes inconsistent; selection/confounding bias common.
	OAG onset (null findings in some populations)	No clear association	Large observational study[52]	aOR 0.98 (0.93–1.03)	Suggests heterogeneity by population, baseline risk, and exposure definition.
	Ocular hypertension/glaucoma signals (subsets)	Potential adverse association in some datasets	Large observational study[53]	aOR 1.12 (≈1.0–1.2)	Potential surveillance bias and confounding by cardiometabolic profile; may vary by statin type and duration.
Cataract	Cataract (any/cataract surgery)	Small adverse association overall, but inconsistent	Systematic reviews/meta-analyses (observational)[54]	OR 1.11 (1.02–1.21) and RR 1.13 (1.01–1.25)	High heterogeneity; strong confounding by age/DM/smoking and healthcare contact; outcome definitions differ.
	Cataract (recent large cohort example)	Adverse association	Large cohort[55]	HR 1.56 (1.43–1.70)	Likely sensitive to detection and residual confounding; use time-updated exposure and negative-control checks if feasible.

(continued)

Table 3. (continued)

Category	Outcome	Direction	Best evidence	Effect size (95% CI range)	Notes on confounding/dose–duration
RVO	After RVO (systemic CV events: stroke/MI)	Protective association	Population-based nested case-control[56]	aOR 0.604 (0.557–0.655)	Strongest and most consistent benefit is systemic secondary prevention; ocular recurrence outcomes less directly studied.

Note. References listed are representative examples selected to illustrate key evidence types, not an exhaustive bibliography for each phenotype. Readers are referred to the supplementary tables for the more complete phenotype-specific evidence base reviewed in this study.
Abbreviations: aOR = adjusted odds ratio; CI = confidence interval; CNV = choroidal neovascularization; DM = diabetes mellitus; DR = diabetic retinopathy; GA = geographic atrophy; HR = hazard ratio; MI = myocardial infarction; OAG = open-angle glaucoma; OR = odds ratio; RR = relative risk; RVO = retinal vein occlusion.

0.77 to 1.07).[48] The divergence by subtype supports phenotype-stratified reporting (choroidal neovascularization versus geographic atrophy, and ideally drusen phenotype including reticular pseudodrusen), and it raises the possibility that residual confounding or phenotype misclassification contributes to heterogeneous findings rather than a consistent class effect.

For DR, some observational cohorts have reported an apparent protective association for incident DR, including an HR of 0.60 (95% CI 0.54 to 0.66).[49] Observational meta-analyses suggest fewer progression or intervention surrogates (HR 0.72, CI 0.64 to 0.80).[50] However, these estimates are highly susceptible to time-varying confounding, including changes in glycemic control, blood pressure, diabetes duration and severity, and concurrent therapies.[5] Accordingly, effect sizes of this magnitude from non-randomized data should not be interpreted as definitive evidence of a causal protective effect. Overall, the DR literature is better regarded as suggestive rather than conclusive, with a need for consistent endpoint definitions and more rigorous analytic strategies.

For POAG and ocular hypertension signals, results are discordant and effect sizes are small. A meta-analysis suggests a modest reduction in POAG onset (pooled RR 0.95, CI 0.93 to 0.98),[51] while another large observational study reports null (adjusted odds ratio [aOR] 0.98, CI 0.93 to 1.03),[52] and some datasets report a potential adverse association in subsets (aOR 1.12, CI approximately 1.0 to 1.2).[53] These discrepancies likely reflect differences in phenotype definition (POAG, ocular hypertension, glaucoma suspect, or normal-tension glaucoma), statin exposure modeling (ever use, duration, or intensity), and residual confounding related to cardiometabolic comorbidity and healthcare utilization. Overall, the evidence supports uncertainty rather than a stable protective or harmful effect.

For cataract, observational syntheses show a small increased risk overall (odds ratio [OR] 1.11, CI 1.02 to 1.21; RR 1.13, CI 1.01 to 1.25),[54] and a recent cohort example reports a larger association (HR 1.56, CI 1.43 to 1.70).[55] The cataract literature is particularly sensitive to confounding by age, diabetes, smoking, and healthcare contact, and to outcome definition differences (any cataract versus surgery).[41] Thus, cataract findings should be interpreted cautiously and should not be treated as causal without study designs that better address detection bias and residual confounding. The heterogeneity of cataract estimates likely reflects differences in outcome definition (incident cataract, subtype-specific cataract, or cataract surgery), detection bias related to healthcare contact, and confounding by age, diabetes, smoking, and indication for lipid-lowering therapy.

Finally, regardless of direct ocular effects, statins are clinically relevant after ocular vascular events due to systemic secondary prevention. In patients with RVO, statin treatment is associated with reduced subsequent stroke or myocardial infarction risk (aOR 0.604, CI 0.557 to 0.655),[56] which supports statin optimization as part of cardiovascular risk management after RVO even when ocular recurrence or visual outcomes are less directly studied.

7. Oculomics and AI models

Retinal and ocular changes attributable to dyslipidemia are unlikely to be acute "lipid fingerprints." Instead, they plausibly accumulate over years through vascular remodeling, endothelial dysfunction, oxidative stress, and lipid deposition, producing gradual and heterogeneous signatures across ocular tissues. This retinal change helps explain why single-analyte prediction from color fundus photographs is often limited. In representative fundus-based deep learning studies, lipid biomarkers frequently show low explained variance (e.g. $R^2 \leq 0.05$ in a biobank setting),[57] and weak external performance across datasets in multi-cohort validation,[58] while some settings report only moderate discrimination for triglyceride-defined

dyslipidemia (AUC ~0.70)[59] or moderate accuracy for total cholesterol (MAE ~0.63 mmol/L; R^2 ~0.29).[60] Similarly, metabolic syndrome component analyses show modest discrimination for dyslipidemia (AUC ~0.6–0.7), with minimal incremental gain from adding retinal to clinical features.[61] In contrast, fundus-based models can perform strongly for composite cardiometabolic endpoints such as elevated 10-year atherosclerotic cardiovascular disease (ASCVD) risk, which is computed using lipid inputs, with AUC ~0.89 in UK Biobank and sensitivity 94% and specificity 72% in EyePACS 10K using a diabetes modifier.[62] An OCTA pilot study reported promising results for dyslipidemia (AUC 0.81, accuracy 0.79), specifically using high-resolution 3 × 3 mm scans. This indicates that small-field microvascular imaging may outperform broader-field approaches in identifying retinal lipid signatures.[63] Collectively, Table 4 suggests that fundus AI may capture a broad cardiometabolic context rather than reliably recovering individual lipid fractions. Interpretation of these AI studies requires attention to the specific analyte definition, imaging modality, sample size, and validation design, because performance estimates are not directly comparable across fundus- and OCTA-based studies.

These observations argue for a shift in modeling targets and feature scope. To our knowledge, fully integrated oculomics models that jointly combine posterior segment structure, retinal microvasculature, neural tissue, and anterior or external ocular signals for systemic risk prediction are not yet widely established or validated.[38] Current multimodal work remains more fragmented, with most published models combining retinal modalities, whereas anterior and external ocular features are usually assessed separately rather than within a unified systemic-risk framework. Rather than optimizing models to predict LDL-C, TG, or total cholesterol in isolation, oculomics should integrate multi-structure signals that reflect the downstream burden of chronic dyslipidemia: (1) retinal vasculature (caliber, tortuosity, branching geometry, and perfusion surrogates), (2) RPE–Bruch's membrane and outer retinal changes (drusen- and deposit-related patterns, pigmentary alteration, and atrophy trajectories), (3) neural tissue integrity (retinal nerve fiber layer and ganglion cell complex features where OCT is available), and (4) lens phenotypes (cataract type and severity when imaging or clinical labels permit). External photography and meibography can add complementary information on visible lipid deposition and glandular lipid handling (e.g. corneal arcus, xanthelasma, meibomian gland morphology), while OCT and OCTA can quantify deposits and microvascular flow metrics with higher specificity than color fundus alone. The goal is not to infer lipids directly, but to model the cumulative biological consequences of dyslipidemia across ocular compartments.

Accordingly, the most defensible clinical objective for AI-based oculomics is cardiovascular risk prediction or risk enrichment, where lipid-related ocular signals are integrated with other ocular and systemic correlates of vascular risk. In this framing, "lipid prediction" is a supporting component within a broader cardiometabolic model reflecting interactions with age, blood pressure, glycemia, kidney function, and inflammation. Large-scale cardiovascular oculomics provides a proof of principle. A deep-learning model that estimated coronary artery calcium risk from retinal photographs showed external validation across multiple international datasets and predicted cardiovascular events, adding information beyond established risk scores.[64] Model development should emphasize patient-level partitioning, explicit handling of lipid-lowering therapies, external validation across devices and populations, and reporting of calibration and clinical utility when used for stratification.

8. Discussion

This scoping review suggests that dyslipidemia relates to ocular phenotypes through compartment-specific mechanisms and interaction-driven risk patterns, rather than simple linear effects of a single lipid fraction. The most biologically anchored evidence concerns the macula, where the RPE–Bruch's membrane complex and drusen or subretinal drusenoid deposits contain cholesterol and apolipoprotein-related constituents, supporting lipid-handling and innate immune pathways in AMD. Importantly, retinal vascular phenotypes also show consistent signals across the literature, with lipid-related metabolic context plausibly contributing to microvascular remodeling and endothelial stress reflected in vascular caliber, geometry, and perfusion metrics. Epidemiologic associations are strongest for metabolically co-traveling conditions such as MGD/DED and DR, in which triglyceride-rich dyslipidemia and insulin resistance may be more informative than LDL-C alone, and where inconsistent findings often reflect heterogeneity in phenotype definitions and covariate adjustment. Corneal arcus and xanthelasma remain clinically useful markers, but their interpretation is context dependent, with arcus in younger adults more suggestive of systemic dyslipidemia and xanthelasma showing stronger clinic-based associations than fully adjusted population estimates. Evidence for hypertensive retinopathy and OCTA-derived microvascular metrics is emerging as potential intermediate phenotypes of lipid-related endothelial stress, although much of the literature is cross-sectional. Associations with glaucoma and cataract are generally small and inconsistent, implying that shared cardiometabolic context and medication patterns may contribute substantially to observed effects. Retinal vascular occlusions cluster with broader atherosclerotic and metabolic syndrome risk, reinforcing the need for systemic cardiovascular evaluation. Finally, oculomics and AI approaches provide a complementary pathway to integrate multi-structure ocular and vascular signals into cardiometabolic risk stratification, although stronger external validation and longitudinal designs are needed.

Table 4. Representative studies using AI-based oculomics to predict or associate with lipid measures.

First author (year)	Design & sample	Ocular phenotype & definition	Lipid exposure definition	Main result
Gerrits (2020) [57]	Fundus-based deep learning study in a population biobank setting using 3,000 participants; person-level prediction from optic disc-centered and macula-centered fundus photographs from both eyes	Color fundus photographs used for systemic biomarker prediction rather than lesion-specific ophthalmic classification	Lipid-related biomarkers within a broader cardiometabolic panel, including cholesterol fractions and triglycerides	Reported very low explained variance for lipid-related biomarkers in summary analyses (R^2 generally ≤ 0.05), indicating limited recovery of individual lipid analytes from fundus images alone in this setting. The study also emphasized that age and sex substantially influenced prediction performance, suggesting strong demographic mediation or confounding.
Rim (2020) [58]	Deep learning development with external validation across multiple datasets using 236,257 retinal photographs from 72,890 participants	Retinal fundus photographs used in an oculomics-style systemic biomarker prediction framework	Broad systemic biomarker panel including lipid profiles among laboratory biomarkers	External performance for many biomarkers was limited; the study reported that lipid-related biomarkers were not predicted well, with $R^2 \leq$ 0.14 across all external test datasets. This supports the interpretation that generalizability for several laboratory biomarkers, including lipid-related measures, was modest under external validation.
Zhang (2020) [59]	Cross-sectional deep learning study from central China with 625 participants	Color fundus photographs used for image-based classification without manual lesion annotation	Dyslipidemia defined as triglycerides > 1.71 mmol/L	Deep learning prediction of triglyceride-defined dyslipidemia achieved AUC 0.703, indicating modest discrimination for a binary TG-based dyslipidemia definition rather than precise estimation of continuous lipid values.
Huang (2023) [63]	Cross-sectional pilot study with 247 participants	OCTA retinal microvasculature, with scan-size-specific image-based prediction and emphasis on small-field high-resolution scans	Dyslipidemia treated as a clinically defined cardiometabolic risk factor according to the study definition	The model achieved AUC 0.81 and accuracy 0.79 for dyslipidemia classification. This suggests that high-resolution small-field OCTA may capture lipid-related microvascular signatures better than standard fundus photography, although interpretation should remain cautious given the pilot design, limited sample size, and lack of a reported 95% CI in the source report.
Basit (2025) [60]	Deep learning on fundus photographs from Qatar Biobank; 5,653 participants and 15,802 images	Color fundus photographs analyzed using a CNN-based oculomics pipeline	Cardiometabolic biomarker panel including total cholesterol	For total cholesterol, the model reported MAE $\approx$ 0.63 mmol/L and $R^2 \approx 0.29$. This was better than many earlier fundus-only studies but still indicates only moderate prediction performance for an individual lipid analyte.

(continued)

Table 4. (continued)

First author (year)	Design & sample	Ocular phenotype & definition	Lipid exposure definition	Main result
Vaghefi (2024) [62]	Development and testing in UK Biobank with additional testing in EyePACS 10K; 89,894 images from 44,176 UK Biobank participants and 18,900 images from 8,969 EyePACS participants	Color fundus photographs used to predict elevated 10-year ASCVD risk rather than a single lipid analyte	10-year ASCVD risk score defined as PCE $\geq$ 7.5%; the PCE includes total cholesterol and HDL-C as key inputs	Achieved AUC 0.89 in UK Biobank for elevated ASCVD risk. In EyePACS 10K, use of a diabetes modifier yielded sensitivity 94% and specificity 72%. These findings support stronger retinal AI performance for composite cardiometabolic risk prediction than for isolated lipid analytes.
Lee (2025) [61]	Health check-up cohort with 3,000 individuals and 6,000 retinal images; RETFound-based Vision Transformer with 5-fold cross-validation	Color fundus photographs used for metabolic syndrome classification with interpretable heatmap visualization	Metabolic syndrome, including an atherogenic dyslipidemia component rather than a single lipid analyte	Retinal-image-only performance for metabolic syndrome classification was AUC 0.7752 (95% CI 0.7719-0.7786); when retinal features were combined with basic clinical variables, performance improved to AUC 0.8725 (95% CI 0.8669-0.8781). This supports the view that retinal AI is more informative for composite metabolic risk states than for isolated dyslipidemia prediction.

Note. References listed are representative examples selected to illustrate key evidence types, not an exhaustive bibliography for each phenotype. Performance metrics should be interpreted in light of differences in target definition, sample size, imaging modality, and internal versus external validation design. 95% confidence intervals are shown only where reported in the original study.
Abbreviations: AI = artificial intelligence; ASCVD = atherosclerotic cardiovascular disease; AUC = area under the receiver operating characteristic curve; DL = deep learning; MAE = mean absolute error; OCTA = optical coherence tomography angiography; PCE = Pooled Cohort Equation; TG = triglycerides; R^2 = coefficient of determination.

Beyond fundus photography, OCT, and OCTA, retinal hyperspectral imaging and adaptive optics can extend oculomics from structural vasculature to metabolic and cellular-scale signals. Hyperspectral retinal imaging captures spatial and spectral information that can support oxygenation and biochemical proxy measures and has been proposed as a non-invasive way to detect early vascular and metabolic dysfunction before overt structural change.[65] Adaptive optics provides micrometer-scale transverse resolution that can visualize fine capillary morphology and cellular features that are not resolved by conventional OCTA, enabling sensitive phenotyping of early microvascular alteration in diabetic retinopathy and related microvascular disease.[66] Choroidal structure can be quantified noninvasively using enhanced depth imaging OCT or swept-source OCT, enabling assessment of a vascular bed that complements retinal OCTA signatures. Choroidal structure and vascular indices provide an additional tissue-level readout of lipid-associated vascular biology that is not captured by retinal vasculature alone. Recent studies in dyslipidemia, including treatment-naïve hypercholesterolemia, report alterations in choroidal vascularity metrics such as a lower choroidal vascularity index,[67] suggesting stromal–vascular imbalance and microvascular remodeling. In diabetic eye disease, lipid profiles have also been associated with subfoveal choroidal thickness, supporting the choroid as a relevant compartment for lipid-linked vascular phenotyping.[68] Although choroidal thickness and choroidal blood flow metrics are increasingly measurable with modern OCT-based imaging,[69,70] they are not yet consistently established as distinct disease-specific phenotypes in common ophthalmic conditions such as macular degeneration or retinopathy, and the current literature remains limited. For this reason, they were discussed as emerging oculomic biomarkers rather than mapped as a separate phenotype category.

Given the gradual, cumulative nature of dyslipidemia-related retinal changes and the strong influence of cardiometabolic context, predicting individual lipid analytes from retinal images alone is often limited, whereas estimating integrated atherosclerotic or cardiovascular risk is a more clinically coherent objective. A consistent theme across conditions is non-linearity, and historical null or conflicting results may reflect U-shaped or threshold relationships, particularly for composite metabolic markers such as the TyG index and for lipid measures strongly shaped by treatment and disease severity.[8,36] Future

observational studies should therefore prespecify and report appropriate non-linear modeling, identify turning points, and avoid default linear assumptions that can obscure clinically meaningful patterns, especially when both low and high lipid values may represent different risk states and when competing risks or survival bias are plausible. Medication confounding is another major limitation because statins, fibrates, ezetimibe, and PCSK9 inhibitors both modify lipid levels and indicate higher baseline vascular risk, making on-treatment lipid values an imperfect proxy for etiologic exposure.[50] Designs should incorporate time-updated medication variables, consider stratification by treatment exposure and intensity, and, when feasible, apply causal inference methods to mitigate indication bias.

Lipid–ocular associations can vary by ethnicity because baseline lipid distributions and cardiometabolic phenotypes differ across populations, particularly triglyceride-rich and low-HDL patterns that often track with insulin resistance and medication exposure.[71,72] Importantly, the current literature is heavily weighted toward East Asian and European populations, with relatively limited representation from African-descent and Latin American cohorts. These differences affect both the level and duration of lipid exposure and can change the apparent direction or magnitude of associations if studies pool heterogeneous groups without testing effect modification. We therefore recommend reporting ancestry composition, performing stratified analyses when feasible, and explicitly modeling lipid-by-ethnicity interactions for key exposures such as apoB and remnant-related metrics. Future oculomics consortium efforts should move beyond ancestry reporting alone and actively expand inclusion of underrepresented populations, including African-descent and Latin American groups, through multi-ancestry biobank resources, external validation cohorts, and dedicated cross-population collaboration.

A life-course framework is essential because ocular outcomes likely reflect cumulative lipid burden rather than a single contemporaneous measurement. Midlife or long-duration exposure to atherogenic particles may better capture the relevant window for vascular remodeling and chronic inflammation that precede late-onset ocular disease,[73] whereas late-life cholesterol can be distorted by treatment initiation, reverse causation, and survivor bias.[74] Accordingly, future studies should distinguish midlife versus late-life lipid measurements, quantify exposure duration or cumulative exposure using repeated measures, and evaluate whether longer-term apoB or remnant burden predicts ocular outcomes more consistently than single time-point lipid fractions.

Compared with prior narrative reviews on lipid metabolism disorders and ocular disease,[75] this review uses a reproducible search strategy and structured evidence mapping across anterior segment, lens, posterior segment, and vascular occlusive phenotypes. We move beyond descriptive associations by specifying lipid exposures and plausible mechanisms, emphasizing interactions and non-linearity, and separating confounding-prone observational findings from higher-inference evidence such as MR and trial data. We also extend the discussion into an oculomics framework by integrating imaging-derived biomarkers and fundus-based AI studies for cardiometabolic risk modeling, and we propose methodological standards and future directions to support more comparable and clinically actionable research.

This review has limitations inherent to scoping methods. We aimed to map the evidence rather than provide pooled causal estimates, and our conclusions are constrained by heterogeneous phenotype definitions, potential publication bias, and the predominance of observational evidence for many ocular endpoints. A prior oculomics review likewise highlighted important heterogeneity and multiple sources of bias, supporting cautious interpretation of this literature.[76] Another limitation is that the review protocol was not prospectively registered. Prospective registration was not undertaken because this work was developed as a broad scoping and evidence-mapping review across heterogeneous ocular phenotypes, lipid-related exposures, imaging-based oculomics, and lipid-modifying therapies, and the final synthesis framework was refined during the early design phase rather than fixed in a registry-ready format before study initiation. However, to reduce post hoc decision-making, the eligibility criteria, screening procedures, literature sources, core evidence domains, and evidence-mapping categories were defined before formal screening and were applied consistently throughout study selection and synthesis. These elements were maintained through reviewer discussion and consensus rather than modified in response to the direction of the retrieved findings. Accordingly, the absence of prospective registration should be considered a limitation that reduces external auditability of the review process. Nonetheless, the mapped literature supports a coherent framework in which dyslipidemia shapes ocular biology through interactions among lipid fractions, metabolic context, and vascular resilience, motivating more rigorous, non-linear, medication-aware, and multimodal future studies.

9. Conclusion

Dyslipidemia is a heterogeneous disturbance of lipid and lipoprotein homeostasis whose ocular associations are shaped by metabolic context, vascular biology, and inflammation rather than a uniform effect of any single lipid fraction. Across phenotypes, associations vary by definition, disease stage, and treatment status, and may also reflect non-linear or interaction-dependent patterns. Rare lipidopathies and other monogenic lipid-handling disorders provide clear causal examples that reinforce the biological plausibility of subtler, interaction-driven ocular changes in common dyslipidemia states. Oculomics

and AI offer a framework to integrate these signals, but current evidence suggests limited reliability for recovering individual lipid analytes from retinal photographs alone. Future work should use standardized phenotypes, longitudinal and device-robust validation, and explicit accounting for lipid-lowering therapy, with emphasis on calibration and clinical utility for risk stratification.

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Ethical considerations

This study was a scoping review of published literature and did not involve the collection of new data from human participants or animals. Therefore, institutional review board approval was not required.

Author contributions

H.K. and T.K.Y. conceived the study and performed the main analyses. H.K. drafted the manuscript. B.H.J. and D.N. provided clinical consultation and contributed to writing and revising relevant subsections. T.K.Y. supervised the study and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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Data Availability Statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Supplemental material

Supplemental material for this article is available online.

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