

Serum Lipid Biomarkers and Their Associations with Age-Related Macular Degeneration: A Cross-Sectional Analysis from the Beichen Eye Study

Gang Zou

Tianjin Medical University Eye Hospital

Fei Gao

Tianjin Medical University Eye Hospital

Limin Zhang

Tianjin Medical University Eye Hospital

Xiaorong Li

xiaorli@163.com

Tianjin Medical University Eye Hospital

Research Article

Keywords: Age-related macular degeneration, Lipid metabolism, TG, HDL-c, Biomarker

Posted Date: July 3rd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10099115/v1>

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at BMC Ophthalmology on October 22nd, 2026. See the published version at <https://doi.org/10.1186/s12886-026-05413-4>.

Abstract

Background

This population-based study examined the cross-sectional associations between serum lipid biomarkers and the prevalence of age-related macular degeneration (AMD).

Methods

This cross-sectional study analyzed data from 4748 subjects aged over 50 years who were enrolled in the Beichen Eye Study. We assessed TG/HDL-c, HDL-c/LDL-c, the neutrophil/HDL-c ratio (NHR), the lymphocyte/HDL-c ratio (LHR), the monocyte/HDL-c ratio (MHR), the platelet/HDL-c ratio (PHR), the platelet/lymphocyte ratio (PLR), and the neutrophil/lymphocyte ratio (NLR). Additionally, demographic characteristics, BMI, medical history, and statin use history were collected. Logistic regression models were adjusted for age, sex, BMI, fasting glucose, diabetes, hypertension, smoking, alcohol consumption, coronary heart disease, and statin use.

Results

Among 4,748 participants, 1,245 had AMD (overall prevalence: 26.22%). Age distribution differed between AMD and non-AMD groups ($Z = -6.58$, $P < 0.001$). In univariate analysis, TG/HDL-c ($Z = -2.71$, $P = 0.007$) and HDL-c/LDL-c ($Z = -1.98$, $P = 0.047$) differed significantly between groups. In multivariable logistic regression, the highest tertile of TG/HDL-c, compared with the lowest tertile, was associated with lower odds of AMD (OR = 0.80, 95% CI: 0.69–0.95). The highest tertile of NHR showed an inverse association (OR = 0.83, 95% CI: 0.69–0.98; P for trend = 0.032). Relative to the highest TG category, participants in the middle TG category had higher odds of AMD (OR = 1.17, 95% CI: 1.01–1.34, P for trend = 0.039). HDL-c alone showed no linear association with AMD risk (P for trend = 0.269).

Conclusions

In this cross-sectional study, higher TG/HDL-c ratio was associated with lower AMD prevalence. Lower TG levels were associated with higher AMD prevalence. The NHR association was nominally significant but did not survive Bonferroni correction for multiple comparisons. HDL-c alone was not independently associated with AMD in this cohort. These cross-sectional associations are exploratory and require prospective validation before any clinical application.

Introduction

Age-related macular degeneration (AMD), the leading cause of irreversible central vision loss in people over 50 years of age, results from the interaction of genetic predisposition, aging, and metabolic risk

factors, including dyslipidemia (1–3).

Inflammation driven by abnormal lipid metabolism may contribute to AMD pathogenesis. Both lipid metabolic disorders and inflammatory responses have been implicated in AMD development (4). The relationship between dyslipidemia and the pathogenesis of AMD has been extensively studied, but epidemiological findings have been inconsistent (5–7).

Recent evidence suggests that systemic disorders associated with AMD (e.g., hypertension, atherosclerosis, hypercholesterolemia) are independently associated with accelerated retinal pigment epithelium (RPE) dysfunction across multiple cohorts (8–10). The correlation between high-density lipoprotein cholesterol (HDL-c) and AMD remains mechanistically unclear (11, 12), with contradictory observations across cohorts. Mendelian randomization studies strongly suggest high HDL-c as a risk factor for AMD in multiethnic populations (13); however, observational data exhibit marked heterogeneity, including positive correlations in European consortia (E3) (5), inverse correlations in select cohorts and null effects in others (14). This inconsistency likely stems from uncontrolled confounding factors (e.g., inflammation, oxidative stress), phenotypic heterogeneity across AMD stages, and HDL-c functional alterations under retinal microenvironment stresses (1).

Changes in neutrophil, monocyte, lymphocyte, and platelet counts in complete blood count reflect systemic inflammation (15). Since systemic dyslipidemia alone may not explain AMD pathology, systematic reviews of lipid biomarkers and AMD risk and population-based cohort epidemiological studies may show this correlation (10). New hematological parameters related to lipid indices and whole blood cells, such as the NHR (16), MHR (17), LHR (18), PHR (19), PLR (20), and NLR (21), have been proposed as new inflammatory biomarkers and may provide insight into AMD inflammation. Hence, the objective of this study was to investigate the correlations between serum lipid biomarkers and the prevalence of AMD.

Methods

1. Study population

This study is a population-based cross-sectional investigation of adults aged 50 years and older residing in Beichen District, Tianjin. The Beichen Eye Study was an epidemiological survey of eye diseases conducted by Tianjin Medical University Eye Hospital from December 2019 to February 2022. The study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of Tianjin Medical University Eye Hospital (Approval Number: 2019ky-22). All participants provided written informed consent.

From the initial population-based cohort of 5,840 adults recruited, 4,748 eligible participants were included in the final analysis. The inclusion criteria were: age > 50 years, residing in 12 villages across 4 towns in Beichen District, Tianjin, selected via multistage random sampling. Exclusion criteria were: (1) inability to perform AMD grading (ungradable fundus photography [$n = 550$], diabetic retinopathy [$n =$

340], or non-cooperation); (2) ocular complications: glaucoma or suspected glaucoma with IOP > 21 mmHg (n = 93), retinal detachment (n = 16), and other vitreoretinal pathologies (n = 25) (note: an additional 10 participants were excluded for non-cooperation without meeting other ocular criteria; 5 participants met more than one exclusion criterion, yielding 1,029 unique ocular exclusions); and (3) missing hematological parameters (blood lipid profiles or inflammatory biomarkers; n = 63; HDL-c: n = 27; LDL-c: n = 27; TC: n = 25; monocyte count: n = 35; lymphocyte count: n = 33; neutrophil count: n = 32; platelet count: n = 32; TG: n = 11; WBC: n = 15). The final analytic cohort consisted of 1,245 AMD patients (early/intermediate AMD = 1,127; late AMD = 118) and 3,503 controls without AMD.

To assess potential selection bias, we compared the 1,092 excluded individuals with the included cohort (Supplementary Table S3). Excluded participants were slightly older (63.4 ± 7.0 vs. 62.6 ± 6.7 years, $P = 0.002$) and had a higher proportion of males (38.7% vs. 35.0%, $P = 0.026$). The prevalence of diabetes was substantially higher among excluded participants (47.2% vs. 16.5%), consistent with the primary exclusion criterion of diabetic retinopathy precluding AMD assessment. This exclusion pattern may result in a modest underestimation of AMD prevalence in the oldest age groups and in individuals with diabetes. The potential impact of this selection on the observed lipid–AMD associations is addressed through sensitivity analyses (Supplementary Tables S1–S3) and in the Discussion.

2. Ophthalmic examination

All examinations were performed at the community hospital to which the participants belonged. The protocol included comprehensive clinical assessments, blood lipid measurements, and standardized questionnaires. Clinical investigations included visual acuity assessment, optometric assays, slit-lamp examination, intraocular pressure, axial length, mydriasis, direct ophthalmoscopy of the posterior segment, fundus photography, ultrawide field retinal imaging, and swept-source optical coherence tomography (SS-OCT). The detailed methodology of the epidemiology of the Beichen Eye Study has been published previously (22). For patient screening procedures, detection methods and questionnaires, refer to the details in reference (23).

Fasting venous blood (15 mL) was collected from each participant in the morning after an 8-hour overnight fast. Blood lipid indicators included total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c). All blood samples were analyzed using an automatic blood analyzer (Sysmex, XN-9000).

3. Diagnostic criteria for AMD

AMD was defined and graded according to the Wisconsin AMD grading system (24). Early AMD was defined as the presence of drusen > 63 μm in diameter; intermediate AMD as drusen > 125 μm or retinal pigment epithelium abnormalities; and late AMD as geographic atrophy (a discrete circular area of RPE

depigmentation $\geq 175 \mu\text{m}$ in diameter) or neovascular AMD (serous or hemorrhagic detachment of the RPE or sensory retina, subretinal or sub-RPE hemorrhage, or subretinal fibrous scars).

4. Statistical Analysis

Statistical analyses were conducted using SPSS 25.0 for Windows (SPSS Inc., Chicago, USA). Continuous data with skewed distributions are presented as medians with interquartile ranges (IQR) and were compared between groups using the Mann–Whitney U test. Categorical variables are presented as frequencies and percentages and were compared using the χ^2 test. AMD prevalence is presented as a percentage with a 95% confidence interval (CI).

Logistic regression was used to estimate odds ratios (OR) and 95% CIs for the associations between serum lipid and inflammatory biomarkers and AMD. Three sequential models were fitted: Model 1 adjusted for age and sex; Model 2 additionally adjusted for BMI, fasting glucose, diabetes, hypertension, smoking, alcohol consumption, and coronary heart disease history; Model 3 additionally adjusted for history of statin use (binary variable). P for trend was determined using a multivariate regression model linear trend test, with biomarker variables entered as ordinal tertile categories.

Continuous laboratory variables (TG, HDL-c, LDL-c, TC, and derived ratios) exhibited right-skewed distributions and were therefore reported as medians with IQRs. For the composite biomarkers in Table 3 (TG/HDL-c, HDL-c/LDL-c, NHR, LHR, MHR, PHR, PLR, NLR), which lack established clinical reference ranges, variables were entered into logistic regression models after tertile categorization, which reduces the influence of extreme values. For the standard lipid panel indicators in Table 4 (TC, TG, HDL-c, LDL-c), clinically established reference ranges were used to define categories. For TG, based on prior evidence suggesting a potential inverse association at higher concentrations (5), the highest clinical category was set as the reference group to facilitate comparison with the literature. For all other biomarkers, the lowest category served as the reference group.

Variance inflation factors (VIF) were calculated for all predictors in logistic regression models. No variable exceeded a VIF threshold of 5.0 (maximum VIF: 1.29), indicating that multicollinearity did not substantially affect the stability of regression estimates. Each biomarker was modeled separately to avoid collinearity between composite markers and their constituent variables (e.g., TG/HDL-c with TG and HDL-c). Consequently, the independent association of each composite marker beyond its components cannot be determined from these models; the reported associations should be interpreted as alternative rather than independent characterizations of lipid–AMD relationships.

Given that eight composite biomarkers (Table 3) constituted the primary hypothesis, we note that applying a Bonferroni correction would set the significance threshold at $P < 0.00625$ ($0.05/8$). The four standard lipid indicators in Table 4 represent secondary analyses of established biomarkers. If all 12 biomarkers were considered, the adjusted threshold would be $P < 0.0042$ ($0.05/12$). We report nominal P

values throughout and indicate which associations survive these thresholds, while acknowledging that formal multiple comparison correction was not applied in the primary analysis.

The relatively small number of late AMD cases ($n = 118$; 9.5%) precluded statistically robust stratified analyses between early/intermediate and late AMD. Consequently, the main analyses compared all AMD (early/intermediate and late AMD) with controls. To assess the robustness of this approach, two sensitivity analyses were conducted: restricting the outcome to early/intermediate AMD alone (Supplementary Table S1) and excluding participants with laboratory values beyond 3 standard deviations from the mean (Supplementary Table S2). Both yielded results consistent with the primary analysis.

Results

1. Basic characteristics of the study population

A total of 4748 participants were included in this study, of whom 1245 were diagnosed with AMD on the basis of fundus photography and macular SS-OCT. A comparison of included and excluded participants is presented in Supplementary Table S3. Excluded participants were older, had a higher prevalence of diabetes and hypertension, and had higher blood leukocyte and neutrophil counts (all $P < 0.05$), consistent with the exclusion of participants with diabetic retinopathy and other ocular conditions precluding AMD grading. The prevalence of AMD was 26.22%, while the non-AMD group consisted of 3503 individuals (73.78%). Among the 1245 AMD patients, 1127 (90.5%) were classified as early/intermediate AMD and 118 (9.5%) as late AMD. The median age was 64 years in early/intermediate AMD and 68 years in late AMD. The participant selection process is detailed in Fig. 1. No significant differences were observed between the AMD and non-AMD participants for any blood cell parameter (Supplementary Table S4). The age distribution significantly differed between the case and control groups, with the median age in the AMD group being 64 years compared with 62 years in the non-AMD group ($P < 0.001$). The prevalence of AMD increased markedly with age and was considerably higher in older adults ($Z = -6.58$, $P < 0.001$) (Table 1). Compared with that in the non-AMD group, the median level of TG in the AMD group was significantly lower ($Z = -2.70$, $P = 0.007$). This difference suggests that TG may be associated with AMD risk. No significant differences were observed between the two groups with respect to other confounding factors, including BMI, diabetes, hypertension, fasting blood glucose, smoking history, alcohol consumption, coronary heart disease history, and statin use ($P > 0.05$).

Table 1
Baseline cohort characteristics ^{a, b}

Variables	Total (n = 4748)	Non-AMD (n = 3503)	AMD (n = 1245)	Statistic	p-value
Age, M (Q₁, Q₃)	63.00 (57.00, 67.00)	62.00 (57.00, 67.00)	64.00 (59.00, 68.00)	Z=-6.58	< 0.001**
BMI, M (Q₁, Q₃)	25.95 (23.83, 28.35)	25.95 (23.81, 28.36)	25.97 (23.88, 28.33)	Z=-0.14	0.892
GLU, M (Q₁, Q₃)	4.60 (4.30, 5.20)	4.60 (4.30, 5.20)	4.60 (4.30, 5.30)	Z=-0.41	0.684
TC, M (Q₁, Q₃)	5.30 (4.60, 5.90)	5.30 (4.60, 5.90)	5.30 (4.60, 6.00)	Z=-0.16	0.872
TG, M (Q₁, Q₃)	1.42 (1.04, 1.93)	1.43 (1.05, 1.96)	1.38 (1.02, 1.86)	Z=-2.70	0.007**
LDL-c, M (Q₁, Q₃)	3.01 (2.49, 3.52)	3.02 (2.49, 3.52)	3.00 (2.46, 3.50)	Z=-0.87	0.383
HDL-c, M (Q₁, Q₃)	1.11 (0.96, 1.31)	1.11 (0.95, 1.30)	1.12 (0.97, 1.32)	Z=-1.71	0.087
Sex, n (%)				$\chi^2=0.34$	0.561
Male	1665 (35.07)	1220 (34.83)	445 (35.74)		
Female	3083 (64.93)	2283 (65.17)	800 (64.26)		
DM, n (%)				$\chi^2=0.21$	0.644
No	3900 (82.14)	2872 (81.99)	1028 (82.57)		
Yes	848 (17.86)	631 (18.01)	217 (17.43)		
HBP, n (%)				$\chi^2=0.97$	0.324
No	1506 (31.72)	1125 (32.12)	381 (30.60)		
Yes	3242 (68.28)	2378 (67.88)	864 (69.40)		

^a Continuous and categorical variables are presented as medians (interquartile ranges) and numbers (%), respectively. The age distribution was skewed, with negative Z scores indicating an older age in the AMD group.

^b Abbreviations: Z: Mann–Whitney test; χ^2 : chi–square test; M: median; Q₁: 1st quartile; Q₃: 3rd quartile. AMD: age-related macular degeneration; BMI: body mass index; GLU: fasting plasma glucose; TC: total cholesterol; TG: triglyceride; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; DM: diabetes mellitus; HBP: hypertension; CHD: coronary heart disease.

* P < 0.05; ** P < 0.01.

Variables	Total (n = 4748)	Non-AMD (n = 3503)	AMD (n = 1245)	Statistic	p-value
CHD, n (%)				$\chi^2=3.66$	0.056
No	3788 (79.78)	2818 (80.45)	970 (77.91)		
Yes	960 (20.22)	685 (19.55)	275 (22.09)		
Statin use, n (%)				$\chi^2=0.54$	0.464
No	4397 (92.63)	3238 (92.46)	1159 (93.09)		
Yes	350 (7.37)	264 (7.54)	86 (6.91)		
Smoke, n (%)				$\chi^2=2.70$	0.260
No smoking	3513 (73.99)	2613 (74.59)	900 (72.29)		
Quit smoking	285 (6.00)	208 (5.94)	77 (6.18)		
Smoking	950 (20.01)	682 (19.47)	268 (21.53)		
Drink, n (%)				$\chi^2=2.70$	0.259
No drinking	3680 (77.51)	2720 (77.65)	960 (77.11)		
Quit drinking	150 (3.16)	102 (2.91)	48 (3.86)		
Drinking	918 (19.33)	681 (19.44)	237 (19.04)		
^a Continuous and categorical variables are presented as medians (interquartile ranges) and numbers (%), respectively. The age distribution was skewed, with negative Z scores indicating an older age in the AMD group.					
^b Abbreviations: Z: Mann–Whitney test; χ^2 : chi–square test; M: median; Q ₁ : 1st quartile; Q ₃ : 3rd quartile. AMD: age-related macular degeneration; BMI: body mass index; GLU: fasting plasma glucose; TC: total cholesterol; TG: triglyceride; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; DM: diabetes mellitus; HBP: hypertension; CHD: coronary heart disease.					
* P < 0.05; ** P < 0.01.					

2. Univariate Analysis of Serum Lipid and Inflammatory Biomarkers

This study revealed a median triglyceride-to-HDL ratio (TG/HDL-c) of 1.28 (IQR: 0.84–1.91) and HDL-c/LDL-c ratio of 0.37 (IQR: 0.30–0.47). Mann-Whitney U tests revealed significant differences in the TG/HDL-c and HDL-c/LDL-c ratios between the AMD and non-AMD groups, with the AMD group exhibiting lower TG/HDL-c ratios (Z = -2.71, P = 0.007) but higher HDL-c/LDL-c ratios (Z = -1.98, P = 0.047) (Table 2). No significant intergroup differences were detected for the NHR (Z = -1.50, P = 0.134), LHR (Z = -1.37, P = 0.171), or inflammatory markers including the PLR (Z = -0.31, P = 0.755), NLR (Z =

-0.42, $P = 0.674$), and MHR ($Z = -0.81$, $P = 0.420$). The PHR showed borderline significance ($Z = -1.71$, $P = 0.087$).

Table 2
Serum lipid and inflammatory level biomarkers ^{a, b}

Variables	Total (n = 4748)	Non-AMD (n = 3503)	AMD (n = 1245)	Statistic	p-value
TG/HDL-c, M (Q ₁ , Q ₃)	1.28 (0.84, 1.91)	1.30 (0.85, 1.94)	1.21 (0.82, 1.80)	Z=-2.71	0.007**
HDL-c/LDL-c, M (Q ₁ , Q ₃)	0.37 (0.30, 0.47)	0.37 (0.30, 0.47)	0.38 (0.31, 0.48)	Z=-1.98	0.047*
NHR, M (Q ₁ , Q ₃)	2.88 (2.14, 3.87)	2.89 (2.15, 3.89)	2.85 (2.09, 3.77)	Z=-1.50	0.134
LHR, M (Q ₁ , Q ₃)	1.75 (1.35, 2.25)	1.76 (1.36, 2.27)	1.73 (1.34, 2.21)	Z=-1.37	0.171
PHR, M (Q ₁ , Q ₃)	219.81 (178.26, 272.08)	220.91 (178.79, 273.07)	216.51 (176.67, 268.07)	Z=-1.71	0.087
PLR, M (Q ₁ , Q ₃)	126.23 (102.69, 155.95)	125.84 (102.47, 156.16)	126.85 (103.87, 155.77)	Z=-0.31	0.755
NLR, M (Q ₁ , Q ₃)	1.63 (1.28, 2.10)	1.63 (1.29, 2.10)	1.64 (1.28, 2.10)	Z=-0.42	0.674
MHR, M (Q ₁ , Q ₃)	0.37 (0.28, 0.49)	0.37 (0.28, 0.49)	0.36 (0.28, 0.48)	Z=-0.81	0.420
^a Data are presented as medians with interquartile ranges (IQRs). Statistical significance was evaluated by the Mann–Whitney U test (* $P < 0.05$, ** $P < 0.01$).					
^b Abbreviations: Z: Mann–Whitney test; M: median; Q ₁ : 1st quartile; Q ₃ : 3rd quartile. TG/HDL-c: triglyceride/HDL-c; triglyceride/HDL-c ratio; HDL-c/LDL-c: high-density lipoprotein cholesterol/low-density lipoprotein cholesterol ratio; NHR: neutrophil/HDL-c ratio; LHR: lymphocyte/HDL-c ratio; PHR: platelet/HDL-c ratio; PLR: platelet/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; MHR: monocyte/HDL-c ratio.					
* $P < 0.05$; ** $P < 0.01$.					

3. Multivariable associations between lipid profiles and AMD

The results of the multivariable-adjusted logistic regression models are shown in Tables 3 and 4. After adjusting for age, sex, BMI, fasting glucose, diabetes mellitus, hypertension, smoking, alcohol consumption, coronary heart disease history, and statin use (Model 3), lipid profiles showed distinct patterns of association with AMD. The TG/HDL-c ratio was inversely associated with AMD prevalence (P for trend = 0.010). Compared with those in the lowest tertile, participants in the highest tertile of

TG/HDL-c ratio (≥ 1.7) had 20% lower odds of AMD (OR=0.80, 95% CI: 0.69–0.95). Similarly, the neutrophil-to-HDL-c ratio (NHR) showed an inverse association (p for trend = 0.032), with the highest tertile (≥ 3.5) associated with lower odds of AMD (OR=0.83, 95% CI: 0.69–0.98). Sex-stratified analysis of HDL-c levels revealed no significant association with AMD risk across categories (middle category: OR=1.04, 95% CI: 0.89–1.22; P for trend=0.269). The overlapping confidence intervals and absence of a linear trend indicate that HDL-c alone, as measured by standard lipid panels, does not demonstrate a robust independent correlation with AMD in this cohort. Total cholesterol (TC) and LDL-c were not significantly associated with AMD risk according to the fully adjusted models.

Table 3
OR with 95% CI of biomarkers of serum lipid and inflammatory level for AMD risk analyzed by logistic models^{a, b}

TG/HDL-c	Model 1	Model 2	Model 3
	OR(95%CI)	OR(95%CI)	OR(95%CI)
	P for trend = 0.101	P for trend = 0.009*	P for trend = 0.010*
Bottom tertile (≤ 1.0)	Reference	Reference	Reference
Middle tertile (1.0–1.7)	0.93 (0.79 ~ 1.09)	0.93 (0.79 ~ 1.09)	0.93 (0.79 ~ 1.09)
Top tertile (≥ 1.7)	0.81 (0.69 ~ 0.95) *	0.80 (0.68 ~ 0.94) *	0.80 (0.69 ~ 0.95) *
HDL-c/LDL-c	P for trend = 0.185	P for trend = 0.120	P for trend = 0.131
Bottom tertile (≤ 0.3)	Reference	Reference	Reference
Middle tertile (0.3–0.4)	1.17 (1.00 ~ 1.37)	1.17 (0.99 ~ 1.37)	1.17 (0.99 ~ 1.37)
Top tertile (≥ 0.4)	1.14 (0.97 ~ 1.34)	1.14 (0.96 ~ 1.34)	1.14 (0.97 ~ 1.35)
NHR	P for trend = 0.058	P for trend = 0.027*	P for trend = 0.032*
Bottom tertile (≤ 2.4)	Reference	Reference	Reference
Middle tertile (2.4–3.5)	0.93 (0.80 ~ 1.09)	0.93 (0.80 ~ 1.10)	0.94(0.80 ~ 1.10)
Top tertile (≥ 3.5)	0.84 (0.71 ~ 0.99) *	0.82 (0.69 ~ 0.98) *	0.83 (0.69 ~ 0.98) *
LHR	P for trend = 0.479	P for trend = 0.390	P for trend = 0.411
Bottom tertile (≤ 1.5)	Reference	Reference	Reference
Middle tertile (1.5–2.1)	1.04 (0.89 ~ 1.21)	1.04 (0.89 ~ 1.22)	1.04 (0.89 ~ 1.22)
Top tertile (≥ 2.1)	0.93 (0.79 ~ 1.10)	0.93 (0.78 ~ 1.09)	0.93 (0.79 ~ 1.10)
MHR	P for trend = 0.353	P for trend = 0.249	P for trend = 0.264
Bottom tertile (≤ 0.3)	Reference	Reference	Reference
Middle tertile (0.3–0.4)	0.95 (0.81 ~ 1.11)	0.95 (0.81 ~ 1.12)	0.95 (0.81 ~ 1.12)
Top tertile (≥ 0.4)	0.91 (0.77 ~ 1.08)	0.90 (0.76 ~ 1.07)	0.90 (0.76 ~ 1.08)
^a Tertile cutoffs were derived from the sample distribution. The lowest tertile served as the reference group for all biomarkers. P for trend was determined by entering tertile categories as an ordinal variable.			
^b Abbreviations: TG/HDL-c, triglyceride/HDL-c ratio; HDL-c/LDL-c, HDL-c/LDL-c ratio; NHR, neutrophil/HDL-c ratio; LHR, lymphocyte/HDL-c ratio; MHR, monocyte/HDL-c ratio; PHR, platelet/HDL-c ratio; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio.			
* P < 0.05.			

TG/HDL-c	Model 1	Model 2	Model 3
	OR(95%CI)	OR(95%CI)	OR(95%CI)
	P for trend = 0.101	P for trend = 0.009*	P for trend = 0.010*
PHR	P for trend = 0.211	P for trend = 0.084	P for trend = 0.093
Bottom tertile (≤ 191.7)	Reference	Reference	Reference
Middle tertile (191.7–252.1)	0.95 (0.81 ~ 1.11)	0.95 (0.81 ~ 1.11)	0.95 (0.81 ~ 1.12)
Top tertile (≥ 252.1)	0.87 (0.74 ~ 1.02)	0.86 (0.73 ~ 1.02)	0.87 (0.74 ~ 1.02)
PLR	P for trend = 0.904	P for trend = 0.884	P for trend = 0.888
Bottom tertile (≤ 110.7)	Reference	Reference	Reference
Middle tertile (110.7–144)	1.13 (0.96 ~ 1.32)	1.13 (0.97 ~ 1.33)	1.14 (0.97 ~ 1.33)
Top tertile (≥ 144)	1.01 (0.86 ~ 1.19)	1.01 (0.86 ~ 1.19)	1.01 (0.86 ~ 1.19)
NLR	P for trend = 0.687	P for trend = 0.243	P for trend = 0.257
Bottom tertile (≤ 1.4)	Reference	Reference	Reference
Middle tertile (1.4–1.9)	0.96 (0.82 ~ 1.12)	0.96 (0.81 ~ 1.12)	0.96 (0.82 ~ 1.12)
Top tertile (≥ 1.9)	0.91 (0.77 ~ 1.07)	0.91 (0.77 ~ 1.07)	0.91 (0.77 ~ 1.07)
^a Tertile cutoffs were derived from the sample distribution. The lowest tertile served as the reference group for all biomarkers. P for trend was determined by entering tertile categories as an ordinal variable.			
^b Abbreviations: TG/HDL-c, triglyceride/HDL-c ratio; HDL-c/LDL-c, HDL-c/LDL-c ratio; NHR, neutrophil/HDL-c ratio; LHR, lymphocyte/HDL-c ratio; MHR, monocyte/HDL-c ratio; PHR, platelet/HDL-c ratio; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio.			
* P < 0.05.			

Table 4

OR with 95% CI of lipidemia level indicators for AMD risk analyzed by logistic models ^b

	Model 1	Model 2	Model 3
	OR(95%CI)	OR(95%CI)	OR(95%CI)
TC	P for trend = 0.744	P for trend = 0.693	P for trend = 0.748
≤ 2.8	Reference	Reference	Reference
2.8–5.16	1.09 (0.48 ~ 2.46)	1.11 (0.49 ~ 2.52)	1.12 (0.49 ~ 2.55)
≥ 5.16	1.11 (0.49 ~ 2.52)	1.14 (0.50 ~ 2.59)	1.14 (0.50 ~ 2.60)
TG ^a	P for trend = 0.030*	P for trend = 0.034*	P for trend = 0.039*
≤ 0.56	1.22 (0.75 ~ 1.97)	1.21 (0.74 ~ 1.97)	1.20 (0.73 ~ 1.97)
0.56–1.69	1.17 (1.02 ~ 1.34) *	1.17 (1.01 ~ 1.35) *	1.17 (1.01 ~ 1.34) *
≥ 1.69	Reference	Reference	Reference
LDL-c	P for trend = 0.483	P for trend = 0.545	P for trend = 0.491
≤ 1.59	Reference	Reference	Reference
1.59–3.0	0.87 (0.62 ~ 1.23)	0.89 (0.63 ~ 1.26)	0.88 (0.62 ~ 1.25)
≥ 3.0	0.86 (0.61 ~ 1.21)	0.87 (0.62 ~ 1.24)	0.86 (0.61 ~ 1.22)
HDL-c	P for trend = 0.097	P for trend = 0.100	P for trend = 0.269
≤ 0.96 in male/ ≤ 0.9 in female	Reference	Reference	Reference
0.96–1.14 in male/ 0.91–1.54 in female	1.24 (1.04 ~ 1.49) *	1.25 (1.04 ~ 1.50) *	1.04 (0.89 ~ 1.22)
≥ 1.14 in male/ ≥ 1.54 in female	1.18 (0.96 ~ 1.45)	1.19 (0.96 ~ 1.47)	1.18 (0.95 ~ 1.47)
^a TG: the highest category was used as the reference group (see Methods). For all other biomarkers, the lowest category served as the reference group. Categories were defined using clinically established reference ranges.			
^b Abbreviations: TC, total cholesterol; TG, triglyceride; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol.			
* P < 0.05.			

Triglycerides (TGs) showed a significant linear trend ($P = 0.039$). Relative to the highest TG category (≥ 1.69 mmol/L), participants in the lowest category (≤ 0.56 mmol/L) showed a non-significant elevation in AMD odds (OR = 1.20, 95% CI: 0.73–1.97), while those in the middle category (0.56–1.69 mmol/L) had 17% higher odds of AMD (OR = 1.17, 95% CI: 1.01–1.34, P for trend = 0.039). This suggests an inverse relationship between elevated TG levels and AMD risk.

Discussion

In this community-based cross-sectional study of 4,748 Chinese adults aged 50 years and older, we examined associations between eight composite lipid–inflammatory markers and AMD. The TG/HDL-c ratio and NHR were associated with lower AMD prevalence, while TG level showed an inverse association with AMD (lower TG associated with higher AMD prevalence). HDL-c alone was not independently associated with AMD risk. We found that the TG/HDL-c ratio may be more reliable than either TG or HDL-c alone.

The overall AMD prevalence of 26.22% in this cohort is higher than that reported in several other Asian population-based studies (e.g., Beijing Eye Study: ~5% in adults ≥ 40 years (25); Handan Eye Study: ~4% in adults ≥ 30 years (26)). The higher prevalence likely reflects the older age distribution of our cohort (≥ 50 years, median 63 years), the inclusion of drusen > 63 μm as the minimum AMD criterion per the Wisconsin grading system (which captures early drusen that some grading schemes exclude), and the use of SS-OCT in addition to fundus photography, which improves detection sensitivity. Notably, distinct discrepancies in lipid profile signatures emerged between the AMD and non-AMD groups, particularly concerning the TG/HDL-c and HDL-c/LDL-c ratios (Table 2). These findings are consistent with growing evidence that lipid dysregulation contributes to AMD pathogenesis. Previous studies have emphasized the importance of maintaining a dynamic balance between TG and HDL-c/LDL-c in AMD pathophysiology (11).

Multivariable logistic regression analysis indicated that individuals in the highest tertile of TG/HDL-c (≥ 1.7) had 20% lower odds of AMD compared with those in the lowest tertile (P for trend = 0.010). This finding reinforces the previously reported paradoxical inverse correlation of TG with AMD risk observed in multivariable Mendelian randomization studies (13). The inverse association of TG/HDL-c ratio with AMD may reflect the opposing effects of HDL-c dysfunction (inflammation and oxidative stress) and TG on RPE. Recent studies suggest oxidized phospholipid derivatives from systemic TG metabolism may help reduce complement-mediated retinal inflammation in AMD models (27). In this study, the median triglyceride (TG) level in the AMD group was lower than that in the non-AMD group (Table 1), suggesting that specific mechanisms may contribute to higher risk of AMD in individuals with low TG levels.

We did not find a significant independent association between HDL-c and AMD in this cohort, which is consistent with several population-based studies (14) but apparently conflicts with Mendelian randomization findings (13). This discrepancy likely reflects the functional heterogeneity of HDL particles: standard HDL-c measurements do not capture particle size distribution, oxidative

modifications, or inflammatory remodeling that may alter HDL function in the retinal microenvironment. In particular, HDL-c may shift from anti-inflammatory to pro-inflammatory under conditions of chronic oxidative stress, as observed in AMD pathogenesis (28). The borderline correlation observed in the middle category (OR = 1.04, 95% CI: 0.89–1.22) may reflect unmeasured HDL subfraction effects and should not be interpreted as a causal association without further subfraction analysis. Future studies incorporating HDL particle profiling (e.g., HDL2, HDL3) are needed to clarify these relationships.

The inverse association between the NHR and AMD prevalence (OR = 0.83, 95% CI: 0.69–0.98, for the top tertile) provides novel insight into the interplay between neutrophils and lipid metabolism(16, 29). The NHR serves as a proxy marker reflecting the balance between the anti-inflammatory properties of HDL-c and the pro-inflammatory activity of neutrophils; its association with AMD risk observed here warrants confirmation in independent cohorts. Other markers, such as PLR, NLR, and MHR are not associated but the inverse association of NHR further shows the role of neutrophils in chronic inflammation processes associated with AMD.

These findings suggest that lipid profile ratios, particularly TG/HDL-c and NHR ratios, are associated with AMD prevalence and warrant further investigation as potential biomarkers. Model 2 and Model 3 yielded very consistent effect estimates, with less than 5% change in odds ratios between the two models. The inverse associations of TG/HDL-c and NHR with AMD remained nominally significant after adjusting for statin use (P for trend = 0.010 and 0.032, respectively). The consistency of these findings after statin adjustment suggests that statin use is unlikely to fully account for the observed lipid–AMD relationships. These candidate biomarkers could eventually complement emerging multimodal AMD risk prediction frameworks (30), and may be particularly relevant in the context of anti-VEGF treatment response heterogeneity modified by systemic metabolic status (31).

The limitations of this study include the following: (1) its cross-sectional design, which limits causal inference; (2) the lack of follow-up data to differentiate between dry and wet AMD subtypes; and (3) selection bias, since the 1,092 individuals excluded because of ungradable fundus images were older than those in our study. Thus, prevalence estimates and risk associations may not apply to older populations with advanced cataracts or other media opacities, (4) The limited number of late AMD cases (n = 118) precluded powered stratified analyses by AMD subtype. Early AMD (drusen, RPE abnormalities) and late AMD (neovascular AMD, geographic atrophy) are pathophysiologically distinct, and lipid-inflammatory associations may differ between subtypes. Future studies with larger samples of late AMD will need to explore these associations independently. We recommend using nested case-control designs to improve exposure measurements and assess protective mechanisms of specific lipid species through lipidomics. Although this is a limited study, to our knowledge, this is the first systematic study of lipid-inflammatory composite markers and their association with AMD in a Chinese community cohort.

In conclusion, our population-based cross-sectional data support the hypothesis that TG/HDL-c ratio and NHR are associated with a lower prevalence of AMD. Higher TG levels showed a dose-dependent inverse association with AMD prevalence. The association between HDL-c and AMD risk appeared non-linear

and may be modified by inflammatory and oxidative stress conditions. Future longitudinal studies need to validate the temporal associations and explore the potential use of these biomarkers for risk stratification.

Abbreviations

AMD: Age-related macular degeneration

BMI: Body mass index

CHD: Coronary heart disease

CI: Confidence interval

DM: Diabetes mellitus

DR: Diabetic retinopathy

GA: Geographic atrophy

GLU: Fasting plasma glucose

HBP: Hypertension

HDL-c: High-density lipoprotein cholesterol

HDL-c/LDL-c: HDL-c to LDL-c ratio

IOP: Intraocular pressure

IQR: Interquartile range

LDL-c: Low-density lipoprotein cholesterol

LHR: Lymphocyte to HDL-c ratio

MHR: Monocyte to HDL-c ratio

MR: Mendelian randomization

NHR: Neutrophil to HDL-c ratio

NLR: Neutrophil to lymphocyte ratio

OR: Odds ratio

PHR: Platelet to HDL-c ratio

PLR: Platelet to lymphocyte ratio

RBC: Red blood cell

RPE: Retinal pigment epithelium

SD: Standard deviation

SS-OCT: Swept-source optical coherence tomography

TC: Total cholesterol

TG: Triglyceride

TG/HDL-c: Triglyceride to HDL-c ratio

VIF: Variance inflation factor

WBC: White blood cell

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Tianjin Medical University Eye Hospital (Approval Number: 2019ky-22). Written informed consent was obtained from each participant.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by Tianjin Key Medical Discipline Construction Project (grant No. TJYXZDXK-3-004A-2)

Author Contribution

G.Z. and F.G. conceived and planned the study. G.Z. and F.G. planned the statistical analyses. G.Z. wrote the manuscript. F.G. and L.M.Z. participated in the interpretation of the data and provided feedback on the manuscript. X.R.L. reviewed and provided feedback on the manuscript. All authors reviewed and approved the final manuscript.

Acknowledgment

We would like to express our gratitude to the doctors, nurses, statisticians and all other contributors of the Beichen Eye Hospital research team. The authors acknowledge the use of DeepSeek V3.2 for language refinement and proofreading purposes only. All generated suggestions were critically reviewed and approved by the authors.

Data Availability

All data generated or analyzed during this study are included in this published article. Further inquiries can be directed to the authors.

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Figures

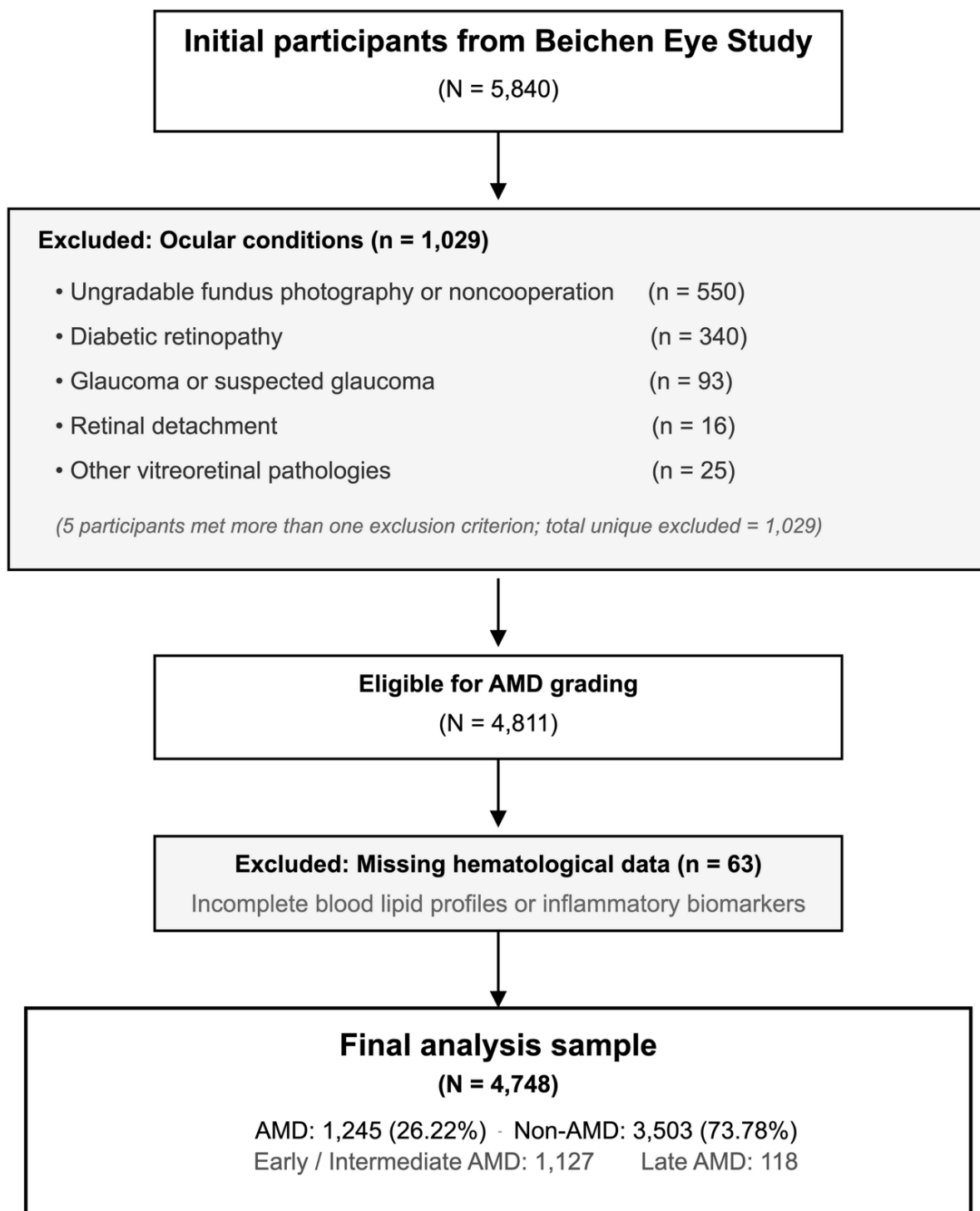


Figure 1

Processing flowchart for selecting participant data

Supplementary Files

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