Clinical science

Associations between serum lipids and glaucoma: a cohort study of 400 229 UK Biobank participants

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ABSTRACT

Purpose To examine the associations of commonly-used serum lipid measures (high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and triglycerides (TG)) with glaucoma.

Methods This prospective cohort study included 400 229 participants from the UK Biobank. Cox regression and restricted cubic spline models and polygenic risk scores were employed to investigate the associations between serum lipids and glaucoma.

Results Over a mean follow-up of 14.44 years, 6868 (1.72%) participants developed glaucoma. Multivariate Cox regression revealed that higher levels of HDL-C were associated with an increased risk of glaucoma (HR for 1-SD increase in HDL-C 1.05, 95% CI 1.02 to 1.08, p=0.001), while elevated levels of LDL-C (HR 0.96, 95% CI 0.94 to 0.99, p=0.005), TC (HR 0.97, 95% CI 0.94 to 1.00, p=0.037) and TG (HR 0.96, 95% CI 0.94 to 0.99, p=0.008) were all associated with reduced risk. The analysis examining the associations between polygenic risk score of serum lipids and glaucoma showed per 1-SD increment of HDL-C genetic risk was associated with a 5% greater hazard of glaucoma (HR 1.05, 95% CI 1.00 to 1.11, p=0.031). However, the polygenic risk score of LDL-C, TC, and TG did not show a significant association with glaucoma.

Conclusions Elevated HDL-C is associated with an increased risk of glaucoma, while elevated LDL-C, TC, and TG levels are associated with a lower risk of glaucoma. This study enhances our understanding of the association between lipid profile and glaucoma and warrants further investigation of lipid-focused treatments in glaucoma management.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Glaucoma, a leading cause of blindness globally, has been associated with various risk factors including serum lipid levels. However, the specific roles of different lipids in glaucoma risk remain unclear and inconsistently reported in the studies.

WHAT THIS STUDY ADDS

⇒ This large cohort study of 400 229 UK Biobank participants reveals that elevated high-density lipoprotein cholesterol (HDL-C) is associated with an increased risk of glaucoma, contrary to its typically perceived beneficial role in cardiovascular health. Conversely, higher levels of low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG) are associated with a decreased risk of glaucoma. Additionally, these associations are influenced by age and sex, and vary between different types of glaucoma.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings challenge existing paradigms about 'good' and 'bad' cholesterol in relation to eye health. This could prompt a re-evaluation of lipid management strategies in patients at risk for glaucoma.

INTRODUCTION

Glaucoma, the most common irreversible blinding eye disease worldwide, is projected to affect approximately 112 million individuals by 2040.[1] It is characterised by progressive optic neuropathy and distinctive patterns of visual field loss. Currently identified risk factors for glaucoma include age, ethnicity, elevated intraocular pressure (IOP), and family history. Exploration of other potential risk factors may help in the development of novel interventions and reduce the global burden of glaucoma.

Dyslipidaemia has been associated with several eye diseases, including age-related macular degeneration, retinal vein occlusion, and diabetic retinopathy.[2–4] Recent studies have suggested that serum lipid levels may be associated with glaucoma, although the results have been conflicting. While several reports have found a positive association between hyperlipidaemia and glaucoma,[5 6] a cohort study of 2 182 315 participants[7] reported that individuals with hyperlipidaemia had a reduced risk of primary open-angle glaucoma (POAG) compared with those without. In addition, elevated serum lipid levels have been proposed as a risk factor for increased IOP, but published studies have also yielded inconsistent results.[8 9] Previous studies utilising cross-sectional designs may have produced inconsistent conclusions due to confounding by statin treatment,[10] and by components of the metabolic syndrome, including hypertension, diabetes, and obesity.[11]

A clearer understanding of the associations between serum lipids and glaucoma may provide valuable insights into the pathophysiology of this disease, and provide evidence for novel treatments

with widely-available agents. Hence, we conducted a comprehensive analysis using a large representative sample from the UK Biobank to examine the associations between various commonly measured serum lipids and incident glaucoma.

METHODS

Study population

The UK Biobank is a large-scale prospective cohort study of over half a million participants between 40 and 69 years of age at recruitment from 2006 through 2010.[12] All participants completed a touchscreen questionnaire, brief verbal interview, and physical measurements at one of 22 study assessment centres. The overall study protocol and protocols for individual tests (https://biobank.ndph.ox.ac.uk/ukb/index.cgi) are available online.

Assessment of serum lipid levels

A standard panel of haematological tests was performed on whole blood from all participants.[13] Serum lipid concentrations, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG), were measured by biochemical assays from non-fasting blood samples collected at baseline using a Beckman Coulter AU5800 (Beckman Coulter Inc, Brea, CA, USA). Detailed information on blood measurements and processing of samples is available in the UK Biobank online protocol.[14]

Ascertainment and exclusion of glaucoma status

Glaucoma status was determined using self-reported data (data fields 6148 and 20002) and hospital inpatient records according to International Classification of Diseases (ICD) codes for glaucoma (ICD-10 codes H401, H402, H408, H409, and ICD-9 codes 3651, 3652, and 3659).

Individuals diagnosed with any type of glaucoma at baseline or reporting a history of glaucoma surgery or laser therapy on the baseline questionnaire were excluded from the analysis. Given that self-reported data and hospital inpatient records may not fully capture all cases, we also excluded participants suspected of having glaucoma, identified by a cup-to-disc ratio ≥0.7[15] or IOP ≥21 mm Hg in either eye.

In the current study, health-related outcome data were updated to 30 June 2023 and consistent diagnostic criteria were applied to identify any new glaucoma diagnoses that occurred during the follow-up period. Follow-up time was calculated as the interval between the baseline assessment and the earliest of the following events: glaucoma diagnosis, death, or the end of the follow-up.

Polygenic risk score

UK Biobank has released a set of polygenic risk scores for 28 diseases and 25 traits specifically designed for use on individuals within the UK Biobank cohort. These polygenic risk scores have demonstrated superior predictive performance compared with 81 previously published polygenic risk scores. The enhanced polygenic risk score set, which has the advantage of being trained on external data as well as additional training data from UK Biobank, was calculated using data from 104 231 individuals in the UK Biobank.[16] In this study, we used the enhanced polygenic risk score for HDL-C, LDL-C, TC, and TG to examine the associations between genetic determinants of serum lipid and glaucoma.

Assessment of covariates

A wide range of potential confounders collected at the baseline assessment visit were adjusted for in this analysis. Ethnicity was self-reported and categorised as white and non-white. Townsend Deprivation Index was derived from the postal code of residence and calculated based on the employment status, home and car ownership, and household condition, with a higher score representing a greater degree of deprivation.[17] Smoking status, frequency of alcohol drinking, and statin use were determined by self-report. The waist-to-hip ratio, considered a more accurate indicator of health and risk of illness than body mass index,[18] was also measured and included in the current analysis. Waist and hip circumference were measured using a non-elastic SECA 200 tape measure. Waist circumference ≥88 cm for women and ≥102 cm for men was used to define central obesity.[19] Blood pressure was measured using a digital sphygmomanometer (Omron 705 IT), and the average of the two measurements was used in the analysis. Fasting time and season of blood collection were recorded when blood samples were taken. Participants were asked if a doctor had ever told them that they suffered from conditions including heart attack, angina, stroke, high blood pressure, and diabetes. Heart attack, angina, and stroke were categorised as cardiovascular diseases. Systemic conditions at baseline were identified using hospital inpatient (ICD-10) records and self-reported data (codes for each condition are listed in online supplemental table 1).

Statistical analyses

Baseline data from the UK Biobank are presented as mean (SD) for continuous variables and number (%) for categorical variables. Pearson correlation coefficients were calculated for associations between the various serum lipids (online supplemental figure 1). Because of the high correlations, Cox proportional hazard models were used to assess associations between individual serum lipid levels and glaucoma. Each serum lipid and its corresponding polygenic risk score were included in the analysis as continuous variables and quartiles. Linear trends were tested by entering the median value of each category of serum lipid as a continuous variable in the models.[20] Multivariate models were adjusted for age, sex, ethnicity, Townsend deprivation index, smoking status, alcohol intake, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, hypertension, diabetes and heart disease, statin use, season of blood collection, and fasting time. Potential non-linear relationships between serum lipid and glaucoma were fit to restricted cubic splines, with prespecified knots placed at the 10th, 50th, and 90th percentiles of the exposure distribution.[21]

We conducted additional analyses of the associations of glaucoma with apolipoprotein A and B and with lipid ratios commonly used in clinical practice (TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C).[22] Stratified analyses in subgroups based on age, sex, and glaucoma type were performed, and their interactions were tested. Finally, we performed three sensitivity analyses to assess the robustness of our results: adjusting for multiple lipid components in a single model, excluding users of statins, and including IOP in the multivariable model for participants with available IOP data. All data analyses were performed using R software version 4.3.1 (R Core Team, Vienna, Austria).

RESULTS

Baseline characteristics

In total, 502 364 participants were initially enrolled from the UK Biobank database. After excluding participants with missing values, the final analysis included 400 229 participants (79.7%)

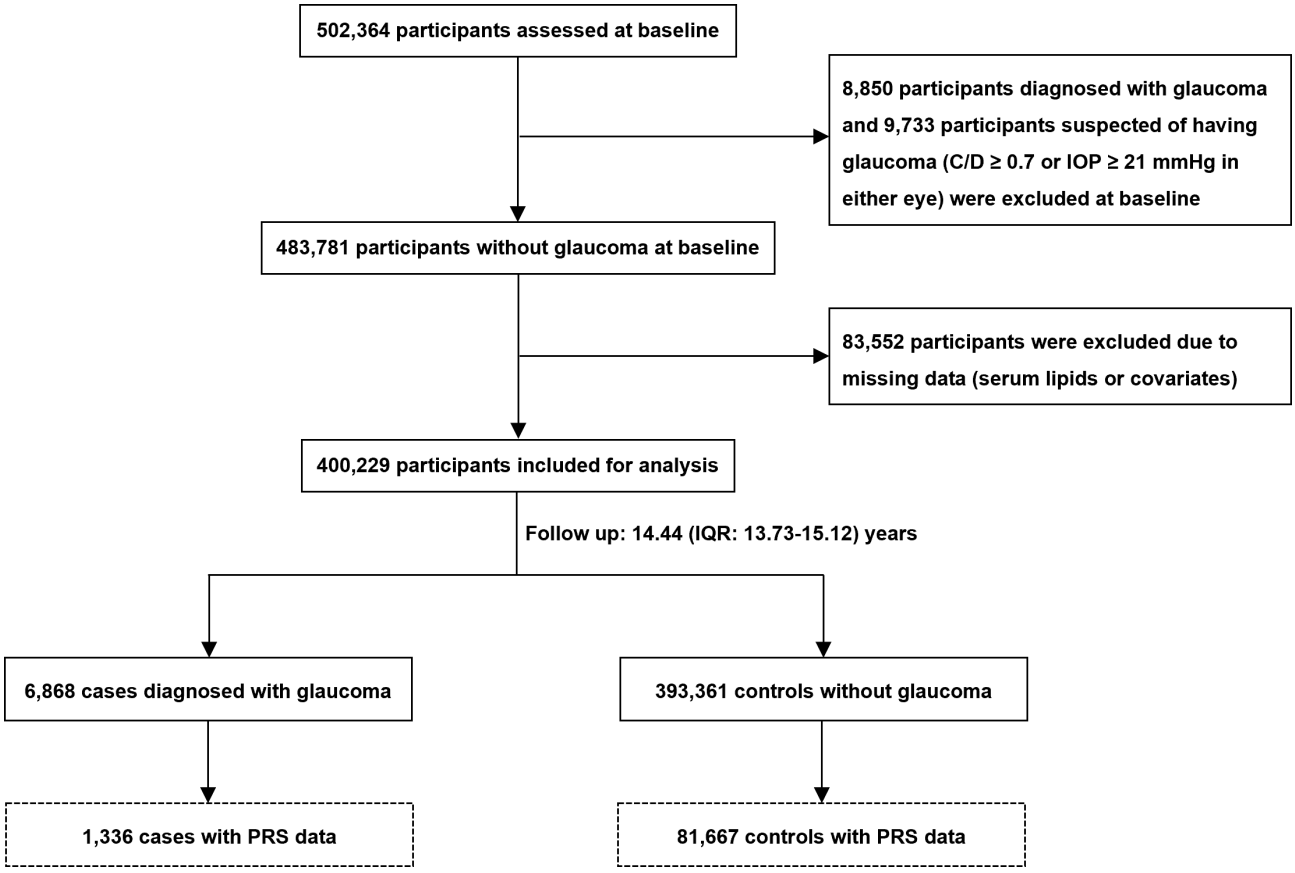

Figure 1 Flowchart outlining eligible participants for this study in the UK Biobank. This flow diagram summarises the number of participants available for each analysis. C/D, cup-to-disc ratio; IOP, intraocular pressure; PRS, polygenic risk score.

who did not have glaucoma at baseline. A detailed comparison of included and excluded participants is provided in online supplemental table 2. Notably, the variable values between the study group and the total population are similar. However, due to the large sample size, even minimal group differences achieved statistical significance. Over a mean (IQR) 14.44 (13.73–15.12) years of follow-up, 6868 (1.72%) individuals were diagnosed with glaucoma (figure 1).

Compared with participants without incident glaucoma, those with glaucoma were older, more likely to be non-white, had a lower Townsend deprivation index, higher HDL-C but lower LDL-C, higher waist-to-hip ratio (indicative of central obesity), and were more likely to be prior smokers who never drank alcohol (all $p<0.05$) (table 1). Additionally, participants with incident glaucoma were more likely to use statins and had a higher prevalence of diabetes, hypertension, and cardiovascular disease.

Associations between serum lipids and the risk of glaucoma

The findings from the multivariate Cox regression analysis revealed that higher levels of HDL-C were associated with an increased risk of glaucoma (p for trend=0.002), while higher LDL-C levels were associated with a decreased risk (p for trend=0.019), consistent with the results of the univariate model. In the univariate analysis, TC and TG did not show significant associations with glaucoma, but the associations became significantly negative after adding age and sex into multivariate models. Age- and sex-stratified analyses confirmed these results (online supplemental table 3).

In the multivariate models (table 2 and figure 2), participants with HDL-C levels in the highest quartile demonstrated a higher risk of glaucoma than those in the lowest quartile (HR 1.10, 95% CI 1.02 to 1.20, p=0.014). A 1-SD increment in HDL-C was associated with a 5% greater hazard of glaucoma (HR 1.05, 95% CI 1.02 to 1.08, p=0.001). Participants with LDL-C (HR 0.92, 95% CI 0.85 to 0.99, p=0.030) and TG (HR 0.86, 95% CI 0.80 to 0.93, p<0.001) levels in the highest quartile showed a lower risk of glaucoma than those in the lowest quartile, but this association was not significant for TC. The hazard for incident glaucoma was lower by 4% (HR 0.96, 95% CI 0.94 to 0.99, p=0.005) for each 1-SD increase in LDL-C and was 3% (HR 0.97, 95% CI 0.94 to 1.00, p=0.037) and 4% (HR 0.96, 95% CI 0.94 to 0.99, p=0.008) lower for each 1-SD increase in TC and TG, respectively.

Restricted cubic spline modelling was used to examine a potential non-linear relationship between serum lipid levels and glaucoma (figure 3). Higher HDL-C linearly increased the risk of glaucoma (p for non-linear relationship=0.229). The risk of glaucoma was relatively flat until around an LDL-C of 3.50 mmol/L and declined thereafter (p for non-linear=0.399). An inverted U-shaped relationship was observed between glaucoma and TC level (p for non-linear=0.154), with the highest risk occurring at around 5.28 mmol/L with decreasing risk in both directions away from this value. In contrast, a significant non-linear U-shaped association was observed between glaucoma and TG (p for non-linear <0.001), with the lowest risk occurring at 2.45 mmol/L.

Table 1 Baseline characteristics of participants included in the study

Variables	Total	Without glaucoma	With glaucoma	P value
N	400 229	393 361	6868	
Age in years, mean (SD)	56.40 (8.10)	56.32 (8.10)	60.85 (6.47)	<0.001
Sex, n (%)				0.462
Females	216 291 (54.0)	212 610 (54.0)	3681 (53.6)	
Males	183 938 (46.0)	180 751 (46.0)	3187 (46.4)	
Ethnicity, n (%)				0.008
Others	20 577 (5.1)	20 175 (5.1)	402 (5.9)	
White	379 652 (94.9)	373 186 (94.9)	6466 (94.1)	
Townsend deprivation index, n (%)				0.01
Quantile 1 (≤ −3.66312)	100 059 (25.0)	98 269 (25.0)	1790 (26.1)	
Quantile 2 (−3.66312 to −2.16878)	100 114 (25.0)	98 338 (25.0)	1776 (25.9)	
Quantile 3 (−2.16878 to 0.47742)	99 999 (25.0)	98 379 (25.0)	1620 (23.6)	
Quantile 4 (≥0.47742)	100 057 (25.0)	98 375 (25.0)	1682 (24.5)	
HDL-C in mmol/L, mean (SD)	1.44 (0.37)	1.44 (0.37)	1.45 (0.37)	0.009
Females	1.58 (0.36)	1.58 (0.36)	1.59 (0.37)	0.393
Males	1.28 (0.30)	1.28 (0.30)	1.30 (0.32)	<0.001
LDL-C in mmol/L, mean (SD)	3.56 (0.86)	3.56 (0.86)	3.54 (0.87)	0.01
Females	3.63 (0.86)	3.62 (0.86)	3.66 (0.87)	0.022
Males	3.49 (0.86)	3.49 (0.86)	3.40 (0.86)	<0.001
TC in mmol/L, mean (SD)	5.69 (1.13)	5.69 (1.13)	5.67 (1.16)	0.133
Females	5.86 (1.11)	5.86 (1.11)	5.92 (1.13)	0.002
Males	5.49 (1.12)	5.49 (1.12)	5.38 (1.12)	<0.001
TG in mmol/L, mean (SD)	1.74 (0.99)	1.74 (0.99)	1.75 (0.98)	0.328
Females	1.55 (0.85)	1.54 (0.84)	1.63 (0.89)	<0.001
Males	1.96 (1.10)	1.96 (1.10)	1.88 (1.07)	<0.001
Fasting time in hours, mean (SD)	3.80 (2.45)	3.80 (2.45)	3.80 (2.37)	0.973
Season of blood collection, n (%)				<0.001
Spring	117 400 (29.3)	115 522 (29.4)	1878 (27.3)	
Summer	104 899 (26.2)	102 929 (26.2)	1970 (28.7)	
Autumn	95 628 (23.9)	93 990 (23.9)	1638 (23.8)	
Winter	82 302 (20.6)	80 920 (20.6)	1382 (20.1)	
Smoking status, n (%)				<0.001
Never/previous	357 774 (89.4)	351 505 (89.4)	6269 (91.3)	
Current	42 455 (10.6)	41 856 (10.6)	599 (8.7)	
Alcohol drinking frequency, n (%)				<0.001
Never	31 880 (8.0)	31 226 (7.9)	654 (9.5)	
Special occasions only	45 939 (11.5)	45 069 (11.5)	870 (12.7)	
One to three times a month	44 854 (11.2)	44 138 (11.2)	716 (10.4)	
Once or twice a week	104 107 (26.0)	102 502 (26.1)	1605 (23.4)	
Three or four times a week	92 833 (23.2)	91 299 (23.2)	1534 (22.3)	
Daily or almost daily	80 616 (20.1)	79 127 (20.1)	1489 (21.7)	
Waist-to-hip ratio, mean (SD)	0.87 (0.09)	0.87 (0.09)	0.88 (0.09)	<0.001
Central obesity, n (%)				<0.001
No	266 159 (66.5)	261 805 (66.6)	4354 (63.4)	
Yes	134 070 (33.5)	131 556 (33.4)	2514 (36.6)	
SBP in mm Hg, mean (SD)	137.70 (18.56)	137.65 (18.56)	140.77 (18.57)	<0.001
DBP in mm Hg, mean (SD)	82.26 (10.13)	82.26 (10.13)	82.05 (10.01)	0.087
Hypertension, n (%)				<0.001
No	293 035 (73.2)	288 459 (73.3)	4576 (66.6)	
Yes	107 194 (26.8)	104 902 (26.7)	2292 (33.4)	
Diabetes, n (%)				<0.001
No	386 400 (96.5)	379 902 (96.6)	6498 (94.6)	
Yes	13 829 (3.5)	13 459 (3.4)	370 (5.4)	
Heart disease, n (%)				<0.001
No	387 214 (96.7)	380 673 (96.8)	6541 (95.2)	
Yes	13 015 (3.3)	12 688 (3.2)	327 (4.8)	
Statin use, n (%)				<0.001
Non-user	339 014 (84.7)	333 533 (84.8)	5481 (79.8)	
Atorvastatin	11 738 (2.9)	11 457 (2.9)	281 (4.1)	
Fluvastatin	188 (<0.1)	184 (<0.1)	4 (0.1)	
Pravastatin	1889 (0.5)	1833 (0.5)	56 (0.8)	
Rosuvastatin	2389 (0.6)	2330 (0.6)	59 (0.9)	
Simvastatin	44 984 (11.2)	43 998 (11.2)	986 (14.4)	
Multiple statins	27 (<0.1)	26 (<0.1)	1 (<0.1)	

DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Associations between polygenic risk score of serum lipid and the risk of glaucoma

After adjusting for confounders, a 1-SD increment in HDL-C genetic risk was associated with a 5% greater hazard of glaucoma (HR 1.05, 95% CI 1.00 to 1.11, p=0.031). As HDL-C genetic risk increased, there was a significant upward trend in glaucoma incidence (p for trend=0.025). However, the polygenic risk score of LDL-C, TC, and TG did not show a significant association with glaucoma (online supplemental table 4).

Additional analyses

Additional analyses (table 2) revealed a positive association between apolipoprotein A and the risk of glaucoma, while apolipoprotein B showed a negative association with the risk of glaucoma. For each 1-SD increase in apolipoprotein A, the hazard rose by 6% (HR 1.04, 95% CI 1.02 to 1.07, p=0.002), whereas for each 1-SD increase in apolipoprotein B, the hazard decreased by 5% (HR 0.95, 95% CI 0.93 to 0.98, p<0.001). Additionally, lower risk of glaucoma was associated with higher TC to HDL, LDL to HDL, and TG to HDL-C ratios (p<0.005).

Stratified analyses based on age, sex, and glaucoma type

Stratified analyses based on age found that the associations mentioned above between blood lipids and glaucoma only persisted among those older than 55 years, with no significant association observed in participants aged 40–55 years (all p>0.05) (online supplemental tables 5 and 6).

Among participants older than 55 years (online supplemental table 3), higher levels of HDL-C and lower levels of TG were associated with a higher risk of glaucoma in males (p for trend <0.001) but not in female participants (p for trend >0.05). In contrast, higher levels of LDL-C and TC were associated with a lower risk of glaucoma, with statistical significance observed only in female participants (p for trend <0.05).

Stratified analyses of patients with POAG versus primary angle closure glaucoma (PACG) indicated that TG was only associated with glaucoma in participants with POAG (p<0.001). LDL-C and

Table 2 Associations between serum lipid levels and glaucoma

Serum lipid levels (mmol/L)	Crude HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
HDL-C per 1-SD increase	1.03 (1.01 to 1.06)	0.006	1.05 (1.02 to 1.08)	0.001
HDL-C in quartiles				
1 (≤1.171)	Reference		Reference	
2 (1.171–1.397)	0.95 (0.89 to 1.02)	0.135	0.98 (0.91 to 1.05)	0.537
3 (1.397–1.669)	1.04 (0.97 to 1.11)	0.282	1.08 (1.01 to 1.16)	0.036
4 (≥1.669)	1.06 (1.00 to 1.14)	0.070	1.10 (1.02 to 1.20)	0.014
P for trend		0.010		0.002
LDL-C per 1-SD increase	0.97 (0.95 to 0.99)	0.009	0.96 (0.94 to 0.99)	0.005
LDL-C in quartiles				
1 (≤2.952)	Reference		Reference	
2 (2.952–3.522)	0.92 (0.86 to 0.98)	0.013	0.99 (0.92 to 1.06)	0.699
3 (3.522–4.121)	0.93 (0.87 to 0.99)	0.028	0.96 (0.89 to 1.03)	0.275
4 (≥4.121)	0.94 (0.88 to 0.99)	0.041	0.92 (0.85 to 0.99)	0.030
P for trend		0.018		0.019
TC per 1-SD increase	0.98 (0.96 to 1.00)	0.046	0.97 (0.94 to 1.00)	0.037
TC in quartiles				
1 (≤4.910)	Reference		Reference	
2 (4.910–5.648)	0.91 (0.85 to 0.97)	0.006	0.99 (0.92 to 1.06)	0.782
3 (5.648–6.416)	0.92 (0.86 to 0.98)	0.016	0.96 (0.89 to 1.03)	0.238
4 (≥6.416)	0.97 (0.90 to 1.03)	0.296	0.93 (0.86 to 1.01)	0.069
P for trend		0.391		0.044
TG per 1-SD increase	1.01 (0.99 to 1.03)	0.370	0.96 (0.94 to 0.99)	0.008
TG in quartiles				
1 (≤1.046)	Reference		Reference	
2 (1.046–1.483)	1.06 (0.99 to 1.14)	0.079	0.91 (0.85 to 0.97)	0.006
3 (1.483–2.142)	1.11 (1.04 to 1.19)	0.002	0.90 (0.84 to 0.96)	0.002
4 (≥2.142)	1.05 (0.98 to 1.13)	0.130	0.86 (0.80 to 0.93)	<0.001
P for trend		0.211		<0.001
Apolipoprotein A per 1-SD increase	1.06 (1.04 to 1.09)	<0.001	1.04 (1.02 to 1.07)	0.002
Apolipoprotein A in quartiles				
1 (≤1.347)	Reference		Reference	
2 (1.347–1.511)	1.05 (0.98 to 1.13)	0.132	1.04 (0.97 to 1.12)	0.235
3 (1.511–1.698)	1.11 (1.04 to 1.19)	0.002	1.09 (1.01 to 1.17)	0.025
4 (≥1.698)	1.17 (1.09 to 1.25)	<0.001	1.11 (1.03 to 1.20)	0.007
P for trend		<0.001		0.005
Apolipoprotein B per 1-SD increase	0.97 (0.95 to 1.00)	0.020	0.95 (0.93 to 0.98)	<0.001
Apolipoprotein B in quartiles				
1 (≤0.863)	Reference		Reference	
2 (0.863–1.017)	0.97 (0.91 to 1.04)	0.353	0.99 (0.92 to 1.06)	0.685
3 (1.017–1.182)	0.98 (0.91 to 1.04)	0.496	0.96 (0.89 to 1.03)	0.256
4 (≥1.182)	0.95 (0.89 to 1.02)	0.138	0.90 (0.84 to 0.97)	0.008
P for trend		0.175		0.005
Serum lipids in same model per 1-SD increase				
HDL-C†	1.03 (1.01 to 1.06)	0.006	1.05 (1.02 to 1.08)	0.001
LDL-C‡	0.97 (0.95 to 0.99)	0.009	0.96 (0.93 to 0.99)	0.003
TC§	0.98 (0.96 to 1.00)	0.046	0.98 (0.95 to 1.00)	0.039
TG¶	1.01 (0.99 to 1.03)	0.370	0.97 (0.94 to 1.00)	0.031
Clinical serum lipid ratios				
LDL-C/HDL-C	0.93 (0.91 to 0.96)	<0.001	0.93 (0.90 to 0.96)	<0.001
TC/HDL-C	0.95 (0.93 to 0.97)	<0.001	0.94 (0.92 to 0.97)	<0.001
TG/HDL-C	1.00 (0.97 to 1.02)	0.718	0.96 (0.94 to 0.99)	0.005

Continued

Table 2 Continued

*Adjusting for age, sex, ethnicity, Townsend deprivation index, smoking status, alcohol drinking frequency, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, hypertension, diabetes, heart disease, statin use, season of blood collection and fasting time.
†Additionally adjusted for LDL-C.
‡Additionally adjusted for HDL-C.
§Additionally adjusted for TG.
¶Additionally adjusted for TC.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

TC showed no significant association with the risk of POAG or PACG, but significant positive associations were found between HDL-C and both glaucoma types (all $p<0.05$) (online supplemental table 7). Further analysis of secondary glaucoma revealed no significant associations between serum lipid levels and the risk of secondary glaucoma (all $p>0.05$) (online supplemental table 8). Significant interactions were observed between serum lipid levels and stratified variables such as age, sex, and glaucoma type, except for LDL-C with age (p for interaction=0.039) and TG with glaucoma type (p for interaction=0.869), as detailed in online supplemental table 9.

Sensitivity analyses

Sensitivity analyses were performed to assess the association between HDL-C and glaucoma after adjusting for LDL-C. The results showed HDL-C remained positively associated with glaucoma (HR 1.05, 95% CI 1.02 to 1.08, p=0.001). Similarly, LDL-C was still associated with a lower risk of glaucoma, when adjusting for HDL-C (HR 0.96, 95% CI 0.93 to 0.99, p=0.003). The sensitivity analyses for TC and TG also demonstrated that both TC (HR 0.98, 95% CI 0.95 to 1.00, p=0.039) and TG (HR 0.97, 95% CI 0.94 to 1.00, p=0.031) remained negatively associated with glaucoma when adjusting for each other. The magnitude and direction of all associations were largely unchanged in multivariate-adjusted models of sensitivity analysis, whether excluding users of statins or including IOP in the multivariable model (online supplemental tables 10 and 11).

DISCUSSION

By using a large, population-representative sample from the UK Biobank with long-term follow-up, this study identified that elevated HDL-C was associated with an increased risk of glaucoma, consistent with the polygenic risk score analysis, whereas higher LDL-C, TC, and TG levels were associated with lower risk of glaucoma. Non-linear analyses indicated a U-shaped association between glaucoma and TG and an inverted U-shaped relationship between glaucoma and TC. Notably, further stratified analyses indicated that these associations between serum lipids and glaucoma only persisted among participants over 55 years of age. In this age group, HDL-C was positively associated with glaucoma, and TG was negatively associated with glaucoma only in male participants, while LDL-C and TC only were significantly negatively associated with glaucoma in female participants. Regarding different glaucoma types, TG only increased risk among participants with POAG, while HDL-C was positively associated with the risk of both POAG and PACG. None of the serum lipid levels showed a significant association with secondary glaucoma.

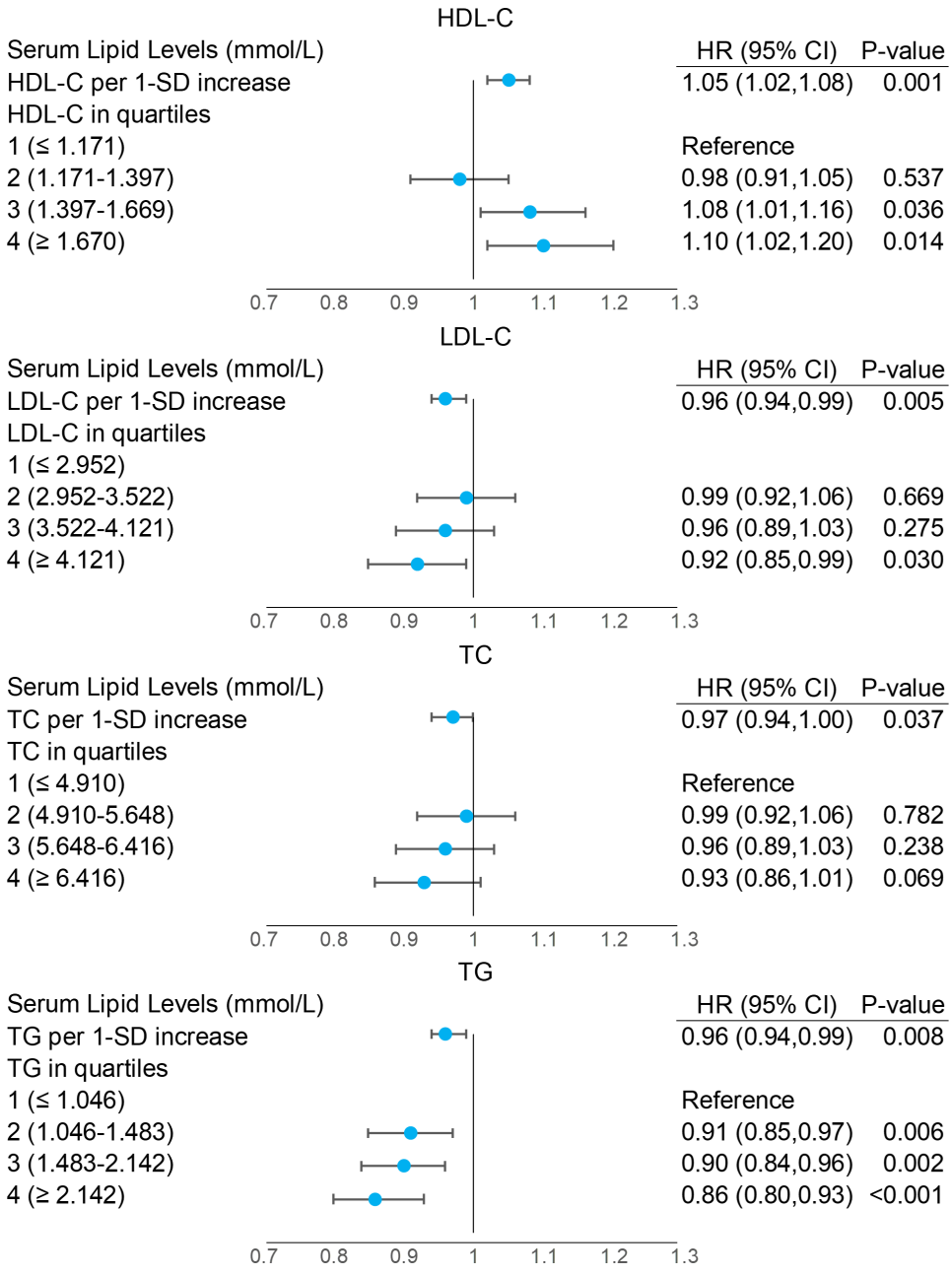

Figure 2 Associations between serum lipid levels and glaucoma, adjusting for age, sex, ethnicity, Townsend deprivation index, smoking status, alcohol drinking frequency, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, hypertension, diabetes, heart disease, statin use, season of blood collection, and fasting time. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

A previous study in the UK Biobank reported a positive association between HDL-C and IOP,[9] consistent with our finding of an association between HDL-C and risk of glaucoma. Similar results were found in a case-control study of 320 Chinese participants with PACG and 242 controls,[23] where high HDL-C levels were significantly associated with PACG (OR 11.01, 95% CI 5.616 to 21.587). Traditionally, high HDL-C levels were considered the 'good cholesterol' due to their association with a reduced risk of cardiovascular disease.[24] However, recent studies have challenged this notion, as high HDL-C levels have been associated with adverse outcomes such as cardiovascular and infectious diseases, age-related macular degeneration, and increased mortality.[25–28] These findings have prompted a reconsideration of the HDL-C hypothesis and have raised doubts about its widely-recognised 'good cholesterol' label.

Our findings contradict previously reported positive associations between LDL-C, TC, and TG levels and glaucoma. Wang *et al*[29] performed multiple meta-analyses and found a significant association between hyperlipidaemia and glaucoma (OR 1.37, 95% CI 1.16 to 1.61). However, this association was significant in cross-sectional and case-control studies but not in prospective cohort studies, suggesting that the association is likely due to unmeasured confounders. The pooled results showed that a 10 mg/dL increase in LDL-C, TC, and TG would increase the IOP by 0.050 mm Hg, 0.032 mm Hg, and 0.016 mm Hg, respectively. Although all the associations were statistically significant,

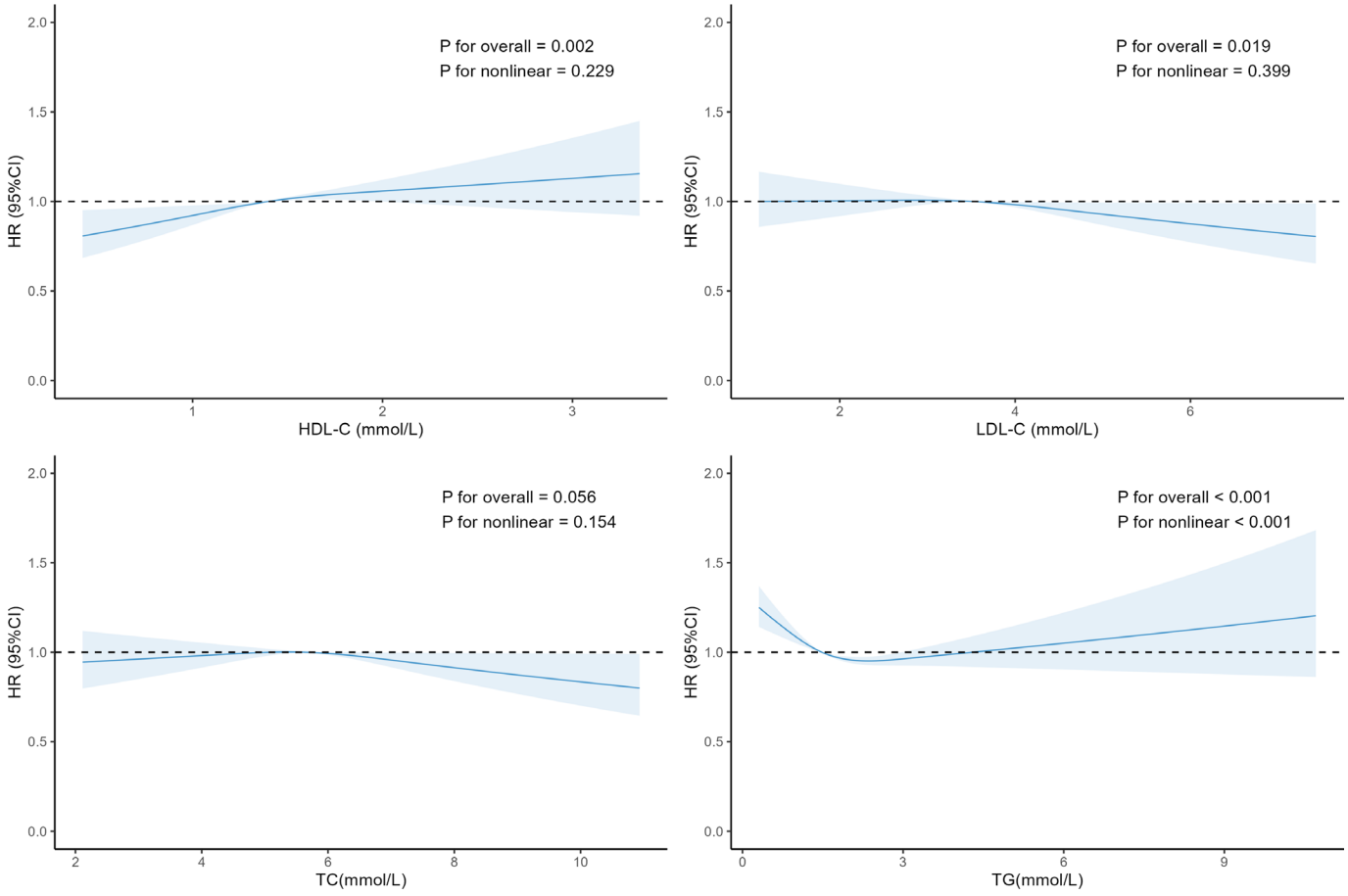

Figure 3 Restricted cubic spline models for associations between serum lipid levels and glaucoma, adjusting for age, sex, ethnicity, Townsend deprivation index, smoking status, alcohol drinking frequency, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, hypertension, diabetes, heart disease, statin use, season of blood collection, and fasting time. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

they were not clinically significant because the changes were much smaller than the clinical measurement error. After adjusting for important confounding variables, a longitudinal study of 2 182 315 participants[7] demonstrated that individuals with hyperlipidaemia had a 5% reduced hazard of POAG, posited to be an effect of lipid-lowering drugs. However, in our analyses excluding users of cholesterol-lowering medications, TG, TC, and LDL-C levels remain associated with reduced risk of glaucoma.

Recent studies have demonstrated that lipid ratios, such as LDL/HDL, are more predictive of cardiovascular disease than individual lipoproteins. These ratios reflect more accurately the complex interactions of lipoprotein metabolism.[30 31] Therefore, further analyses were conducted in the current study to examine associations between glaucoma and clinically relevant lipid ratios. The results showed that higher TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C ratios were associated with a lower risk of glaucoma. A prior cross-sectional study of 94 323 participants from the UK Biobank suggested similar associations between IOP and these lipid ratios, where higher TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C were significantly associated with lower IOP.[9] This observation suggests that elevated lipid ratios may be associated with a reduction in IOP, potentially impacting glaucoma risk. The Early Manifest Glaucoma Trial supports this, showing that each millimetre of mercury increase in baseline IOP was associated with a 5% increase in the risk of glaucoma progression (HR 1.05, 95% CI 1.01 to 1.10).[32] Further research is warranted to explore the mechanisms that directly link high lipid ratios with beneficial changes in aqueous humour dynamics or IOP reduction.

As lipid levels are known to differ by age and sex, age- and sex-stratified analyses were performed. We found that the associations between blood lipids and glaucoma only persisted in participants over 55 years of age, and exhibited sex-based disparities. For example, higher levels of HDL-C were associated with a higher risk of glaucoma only in male participants. Additional analysis of apolipoproteins showed that apolipoprotein A, the major protein component of HDL-C, was also positively associated with glaucoma risk only in male participants. This aligns with previous findings that higher levels of apolipoprotein A were associated with higher IOP in male patients.[33] Sex-specific associations between lipids are supported by extensive studies. This difference may be due to a genetic susceptibility to dyslipidaemia in men and changes in hormonal status in postmenopausal women.[34] For example, lipoprotein metabolism is more accelerated in women due to the stimulating effect of oestrogen.[35] The exact physiological mechanisms underlying these sex differences remain speculative, but an animal study has suggested sex differences could be related to a difference in LDL receptors.[36] Therefore, it may be important to develop different strategies for men and women based on these findings.

Previous studies, including metabolomic analyses of aqueous humour in rat glaucoma models and phospholipid profiling of the trabecular meshwork in humans with glaucoma, have

documented significant differences in lipid levels between glaucoma group and control group, underscoring a potential association between serum lipid levels and glaucoma.[37 38] However, the mechanisms underlying these associations are still unclear. Genetic predisposition may partially explain this association, as genes involved in lipid metabolism, such as *ABCA1* and *Caveolin-1*, appear to be significantly associated with glaucoma risk.[39 40]

Polygenic risk scores provide a personalised measure of the genetic liability of diseases by combining genetic risk information from across the genome.[41] Polygenic risk score analysis in our study revealed a significant relationship between elevated HDL-C genetic risk and a higher risk of glaucoma. Furthermore, in the stratified analysis of glaucoma types and the two sensitivity analyses, only the relationship between HDL-C and glaucoma always remained significant. Based on these findings, we hypothesise that the associations between increased TC, TG, and LDL-C levels and reduced glaucoma risk may be mediated by the interplay between HDL-C and these lipid fractions. HDL-C has been shown to exhibit an inverse relationship with TC, TG, and LDL-C, and one possible mechanism for this interaction is the reverse cholesterol transport pathway, where HDL-C plays a crucial role in removing excess cholesterol from peripheral tissues and transporting it back to the liver for clearance.[42] These findings have implications for clinical practice, as genetic factors, in addition to known general risk factors, could inform more tailored treatment choices to prevent glaucoma. Further research is needed to elucidate the underlying molecular mechanisms and confirm these findings, which may provide valuable insights into the pathogenesis of glaucoma and potential therapeutic targets.

One of the major strengths of our study is that the UK Biobank is a prospective long-term cohort with extensive covariate data. This allowed us to have a large sample of over 409 562 participants and adjust for a wide range of potential confounders, enhancing the validity of our findings. Additionally, to address the potential issue of collinearity among lipid fractions, we calculated Pearson correlation coefficients and conducted individual Cox proportional hazard models for each lipid component. Furthermore, to minimise the impact of confounding factors, we performed a polygenic risk score analysis to support the reliability of our results.

However, our study has some potential limitations. First, serum samples were collected from non-fasting individuals at a single time point during the UK Biobank baseline assessment visit, which might not accurately capture individuals' typical lipid levels. Second, hospital record linkage in the UK Biobank primarily focuses on inpatient episodes and procedures. Consequently, the use of ICD codes to identify incident glaucoma may not fully detect all cases. Although we supplemented these records with self-reported diagnoses from follow-up assessments, the coverage of these self-reports is incomplete. The reliance on self-reported data, including statin use, introduces potential recall and misclassification biases, which could affect the accuracy of the associations reported. Third, the findings may not directly apply to other ethnic groups, as the UK Biobank population predominantly consists of individuals of European ancestry. Although this may limit the generalisability of the results to other ethnicities, it does not have an impact on the internal validity of the study. Importantly, the results for LDL-C, TC, and TG should be interpreted with caution. The associations between these lipid levels and glaucoma risk showed non-significant results in polygenic risk score analyses and discrepancies in the crude models of our sensitivity analysis. These observations may be due to the complex interplay among lipid parameters, necessitating further investigation in future studies to confirm these findings and elucidate their implications fully.

In conclusion, this large long-term cohort study demonstrated that for participants aged 55 years and older, elevated HDL-C is associated with an increased risk of glaucoma, which was supported by genetic risk analysis. Cox regression also found that elevated LDL-C, TC, and TG levels were associated with a lower risk of glaucoma. The associations between serum lipids and glaucoma differed based on sex. Given that most contradictory studies were cross-sectional, the causal relationship between blood lipids and glaucoma deserves further exploration, and it is recommended that age- and sex-specific effects be taken into account when assessing the relationship between lipids and glaucoma. HDL cholesterol has been regarded as the 'good cholesterol' for seven decades. However, this study demonstrates that high levels of HDL cholesterol are not consistently associated with a favourable prognostic outcome. Further studies are needed to investigate the mechanisms behind these associations.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the UK Biobank Study has received ethical approval from the National Information Governance Board for Health and Social Care and the NHS North West Multicentre Research Ethics Committee (REC reference: 16/NW/0274). All participants in the study provided informed consent through electronic signature during the baseline assessment. This present study was conducted under application number 87083 of the UK Biobank resource. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data are available in a public, open access repository. This present study was conducted under application number 87083 of the UK Biobank resource. Data can be accessed through applications on UK Biobank website (https://www.ukbiobank.ac.uk/).

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