

Statin Use in Relation to Intraocular Pressure, Glaucoma, and Ocular Coherence Tomography Parameters in the UK Biobank

Jihye Kim,^{1,*} Marianne T. Kennedy Neary,^{2,*} Hugues Aschard,^{1,3} Mathew M. Palakkamanil,⁴ Ron Do,⁵ Janey L. Wiggs,⁶ Anthony P. Khawaja,^{7,†} Louis R. Pasquale,^{8,†} and Jae H. Kang^{9,‡}; for the International Glaucoma Genetics Consortium (IGGC), UK Biobank Eye and Vision Consortium, and Modifiable Risk Factors for Glaucoma Collaboration

¹Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, United States

²University of Manchester & Manchester Royal Eye Hospital, Manchester, United Kingdom

³Institut Pasteur, Université de Paris, Department of Computational Biology, Paris, France

⁴Department of Ophthalmology and Visual Science, Dalhousie University, Halifax, Nova Scotia, Canada

⁵Charles Bronfman Institute for Personalized Medicine, Department of Genetics and Genomics, Icahn School of Medicine at Mount Sinai, New York, New York, United States

⁶Department of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, United States

⁷NIHR Biomedical Research Centre at Moorfields Eye Hospital & UCL Institute of Ophthalmology, London, United Kingdom

⁸Department of Ophthalmology, Icahn School of Medicine, Mount Sinai, New York, New York, United States

⁹Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States

Correspondence: Jihye Kim, Harvard T. H. Chan School of Public Health, 655 Huntington Avenue, Boston, MA 02115, USA;

jihyekim@hsph.harvard.edu

JK and MTKN contributed equally to this work as first authors.

APK, LRP and JHK contributed equally to this work as last authors.

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PURPOSE. The purpose of this study was to evaluate the relationship between statin use and glaucoma-related traits.

METHODS. In a cross-sectional study, we included 118,153 UK Biobank participants with data on statin use and corneal-compensated IOP. In addition, we included 192,283 participants (8982 cases) with data on glaucoma status. After excluding participants with neurodegenerative diseases, 41,638 participants with macular retinal nerve fiber layer thickness (mRNFL) and 41,547 participants with macular ganglion cell inner plexiform layer thickness (mGCIPL) were available for analysis. We examined associations of statin use with IOP, mRNFL, mGCIPL, and glaucoma status utilizing multivariable-adjusted regression models. We assessed whether a glaucoma polygenic risk score (PRS) modified associations. We performed Mendelian randomization (MR) experiments to investigate associations with various glaucoma-related outcomes.

RESULTS. Statin users had higher unadjusted mean IOP \pm SD than nonusers, but in a multivariable-adjusted model, IOP did not differ by statin use (difference = 0.05 mm Hg, 95% confidence interval [CI] = -0.02 to 0.13, $P = 0.17$). Similarly, statin use was not associated with prevalent glaucoma (odds ratio [OR] = 1.05, 95% CI = 0.98 to 1.13). Statin use was weakly associated with thinner mRNFL (difference = -0.15 microns, 95% CI = -0.28 to -0.01, $P = 0.03$) but not with mGCIPL thickness (difference = -0.12 microns, 95% CI = -0.29 to 0.05, $P = 0.17$). No association was modified by the glaucoma PRS ($P_{\text{interaction}} \geq 0.16$). MR experiments showed no evidence for a causal association between the cholesterol-altering effect of statins and several glaucoma traits (inverse weighted variance $P \geq 0.14$).

CONCLUSIONS. We found no evidence of a protective association between statin use and glaucoma or related traits after adjusting for key confounders.

Statins are a class of lipid-lowering drugs that lower 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity to decrease low density lipoprotein (LDL) cholesterol levels, and they are indicated for the primary prevention of cardiovascular disease.^{1,2} In the United States, approximately 39.2 million adults aged 40+ years were statin users in 2012 to 2013,¹ whereas in the

United Kingdom, the prescription prevalence for statins was 128 per 1000 person-years in 2013.³ Biologically, statins have pleiotropic effects,^{4,5} including effects on nitric oxide synthesis and thrombosis formation, and antioxidant and immunomodulatory effects. Given the widespread use of statins, there is intense interest in their impact on non-cardiovascular outcomes, including eye diseases.^{6,7}

Studies of statin use and glaucoma have yielded mixed results. A meta-analysis of observational studies published in 2016 suggested an inverse relation between statin use and glaucoma with short-term use.⁸ However, a subsequent large observational study of health professionals observed that after careful control for chronological age, the relation between statin use and incident primary open-angle glaucoma (POAG) was null,⁹ and a recent database study in Australia reported an adverse relation between long-term statin use and glaucoma.¹⁰

Given the inconsistency in prior studies, we used the UK Biobank with questionnaire data, intraocular pressure (IOP) measures, ocular coherence tomography (OCT) parameters, and genetic biomarkers to evaluate the relation between statin use and various glaucoma-related traits, to test the hypothesis that statins may protect against glaucoma. We also created a genetic instrument variable that served as a proxy for HMG-CoA activity for a Mendelian Randomization (MR) study, which reflected long term propensity for having lower LDL levels and has been strongly associated with lower risk of myocardial infarction and death from cardiovascular disease.^{11,12}

METHODS

The UK Biobank

The UK Biobank is a population-based study that has collected health-related data on >500,000 participants aged 40 to 69 years at baseline (2006–2010). We used baseline questionnaire data (<http://www.ukbiobank.ac.uk>), high throughput genotyping data, ophthalmic data, and OCT imaging data. The UK Biobank was approved by the National Information Governance Board for Health and Social Care and the National Health Service North West Multicenter Research Ethics Committee (reference number 06/MRE08/65). This research was conducted using the UK Biobank Resource under application number 36741. This research study adhered to the tenets of the Declaration of Helsinki.

Assessment of Statin and Non-Statins Hypolipidemic Drug Use

Trained nurses collected data on prescription drugs or supplements regularly used via in-person interviews at baseline. If a participant indicated on a touchscreen display that they were taking cholesterol lowering drugs, the interviewer recorded the type of medicine used. If the participant indicated they were not using any medications, the interviewer confirmed that the statement was correct. Interviewers did not collect information about dosing or duration of medication use. The statin types used by participants included simvastatin, atorvastatin, rosuvastatin, pravastatin, and fluvastatin. We also analyzed data on use of non-statin hypolipidemic drugs, which included fibric acid agents, bile acid sequestrants, niacin-derivatives, cholesterol absorption inhibitors, omega-3 fats, and other miscellaneous antihyperlipidemic agents.

IOP and Glaucoma Status Ascertainment

In 2009 to 2013, IOP measurements in both eyes were taken using the Ocular Response Analyzer noncontact tonometer (Reichert Corp., Philadelphia, PA, USA) at 6 locations throughout the United Kingdom.¹³ Subjects with eye surgery

or an eye infection in the prior month were excluded. As a primary outcome, we analyzed corneal-compensated IOP (IOPcc), which is least influenced by measurement artifact due to corneal biomechanics,¹⁴ and excluded extreme outliers.¹⁵ Participants with a history of glaucoma laser or surgical treatment were excluded as their untreated IOP level would not be captured. For those participants on ocular hypotensive therapy, we adopted the convention of adjusting the measured IOP upward by 30%, as we have done previously.^{16,17} IOPcc measurements were available for right and left eyes on 127,798 and 127,428 participants, respectively. We used the mean of all available right and left eye values. Ultimately, 118,153 eligible participants had complete data for the assessment of the relation between statin use and IOPcc.

At baseline (2006–2010), 9198 out of 215,562 participants reported that they had glaucoma. Participants completed a touch screen questionnaire and were considered to have glaucoma if in response to the question, “Has a doctor told you that you have any of the following problems with your eyes?” they chose glaucoma from the menu. Participants were also considered to have glaucoma if they reported a history of glaucoma surgery or laser treatment on the questionnaire or if they carried an International Classification of Diseases, Ninth Revision, (ICD-9) or ICD, 10th Revision (ICD-10) code for glaucoma (ICD-9 = 365.* or ICD-10 = H40.** [excluding H40.0* and H42.*]). Ultimately, 192,283 participants (including 8982 glaucoma cases) had sufficient data for the assessment of the relationship between statin use and glaucoma.

OCT Data

Under the auspices of the UK Biobank Eye and Vision Consortium, from 2009 to 2010, there were 67,321 individuals who underwent macular spectral domain OCT (SD-OCT) imaging as part of the baseline examination.¹⁸ Loss of retinal ganglion cell (RGC) bodies and their axons are hallmarks of glaucomatous degeneration, and because approximately 50% of RGC bodies reside in the macula region, the macular retinal nerve fiber layer (mRNFL) and macular ganglion cell inner plexiform layer (mGCIPL) thicknesses in the macula are useful glaucoma-related biomarkers.^{19,20} The Topcon 3D OCT1000 Mark II was used to complete SD-OCT imaging in a dark room without pupil dilation. The 3-dimensional 6 × 6 mm² macular volume scan mode (512 A scans per B scan and 128 horizontal B scans in a raster pattern) was used for imaging. Both eyes were imaged starting with the right eye. The OCT images were stored as downloadable electronic files from a secure portal. The mRNFL and mGCIPL were segmented using version 1.6.1.1 of the Topcon Advanced Boundary Segmentation algorithm.¹⁸ All OCT images with a quality score less than 45 were removed from the data set. Furthermore, as outlined by Khawaja et al.¹⁸ using various indicator scores that identify blinks, eye motion artifacts, and segmentation failures, we removed participants in the bottom 20th percentile of data quality. The final data set consisted of 41,638 participants for mRNFL and 41,547 participants for mGCIPL after excluding participants with Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis who could have non-glaucomatous reductions in RNFL and GCIPL thicknesses. For mRNFL and mGCIPL measures intended for analyses, we used the mean of all available right and left eye values.

Genotyping Data, Glaucoma Multi-Trait Analysis of Genome Wide Association Study Polygenic Risk Score and MR Experiments

Genetic data on 488,000 participants were generated using 2 closely related genotyping platforms: the Affymetrix UK BiLEVE Axiom Array, which called genotypes at 807,411 markers on approximately 50,000 individuals,²¹ and the Affymetrix UK Biobank Axiom Array, which generated genotypes at 825,925 markers for approximately 450,00 individuals. The smaller number of available data partially reflects post-study opt outs and other technical factors. Quality controls and imputation (the determination of genotypes at loci by inference and not by direct genotyping) were performed jointly for these platforms, as previously described.¹⁵ Imputation was based on genetic architecture ascertained in the 1000 Genomes Project, UK 10K, and the Haplotype Reference Consortium reference panels. After quality control, 92,693,895 genetic markers of 487,442 participants were available.

To evaluate interactions with a polygenic risk score (PRS), we calculated a PRS for each participant using 2673 independent common single nucleotide polymorphisms (SNPs) associated at $P \leq 0.001$ for glaucoma from a multi-trait analysis of genomewide association study (GWAS; MTAG) that included the UK Biobank.²² We applied the effect estimates from the MTAG study to generate a glaucoma 2673-gene variant PRS in the UK Biobank that also predicted earlier age at glaucoma diagnosis, glaucoma progression, and need for surgical intervention in an independent Australian data set.²² We chose the glaucoma MTAG PRS because it best captures the genetic variation for POAG, which is a complex disease with optic nerve vulnerability across the spectrum of IOP. The PRS was derived using a standard weighted sum of individual SNPs (i.e. $PRS = \sum_{i=1}^{2,673} \hat{\beta}_i \times SNP_i$ where $\hat{\beta}_i$ is the estimated effect size of SNP_i on glaucoma extracted from the aforementioned GWAS).²² We normalized the glaucoma PRS with mean of 0 and standard deviation (SD) of 1 for analyses.

We also performed an MR analysis using 5 genomewide significant gene 3-HMG-CoA variants associated with lower serum LDL levels.¹¹ Analogous to a randomized controlled trial, MR leverages the random allocation of genotypes and allows for the evaluation of associations between genetically predicted levels of a risk factor (e.g. statin use) and genetic predicted propensity for a disease outcome (e.g. glaucoma), which would assist with inferring the causal effect of the risk factor on the outcome.²³ Briefly, MR leverages genotypic differences that exist at conception. The instrumental variable comprises multiple variants that capture the lifetime exposure in a dose-response manner. We conducted the MR study in participants of European descent from the UK Biobank plus other cohorts to optimize the ability to find associations with glaucoma-related traits. More details regarding the MR experiments can be found in the Supplementary Methods.

Statistical Analysis

We compared baseline characteristics of non-statin users and statin users by using mean (SD) difference for continuous variables and differences in frequencies for categorical variables. When variables had missing values for >5% of the study population, a missing indicator was used. If $\leq 5\%$ were missing, then the median value (for continuous vari-

ables) or the largest category (for categorical variables) was used. To examine associations between statin use and IOP or OCT parameters, we used multiple linear regression models adjusted for covariates. We created five nested models to address confounding (especially confounding by indication) and detection bias by including numerous covariates, including demographic factors, conditions that are indicated for statin use (e.g. diabetes and cardiovascular disease), blood pressure, blood cholesterol level, and beta-blocker use. To evaluate the relationship between statin use and glaucoma, we conducted multiple logistic regression analyses adjusting for the same covariates.

To assess whether the glaucoma MTAG PRS modified the relation between statin use and the various outcomes, we tested the significance of adding a multiplicative (MTAG PRS*statin) interaction term in models with the main effects of statin use and the MTAG PRS; in these models, we also included the following multiplicative interaction terms to minimize confounding: total cholesterol *MTAG PRS, cardiovascular disease *MTAG PRS, triglyceride *MTAG PRS, age *MTAG PRS, age² *MTAG PRS, and non-statin hypolipidemic drug use *MTAG PRS.²⁴

We conducted additional sensitivity analyses: (1) analyses excluding those with glaucoma for analyses of IOP and of OCT parameters, and (2) analyses where the reference group were restricted to people who did not take any hypolipidemic medicines (versus those who were non-statin users).

RESULTS

The mean age (SD) of the UK Biobank population ($n = 118,153$) at baseline was 56.5 (8.1) years. The population was 82.1% Caucasian and 54.4% were women. The demographics for the specific study population for each analysis described below were similar (Supplementary Table S1).

Statin Use and IOP in the UK Biobank

For the assessment of statin use and IOP, we included 118,153 participants (Table 1). Among statin users, the majority (92.7%) reported using either simvastatin or atorvastatin. Statin users were older than non-statin users (61.4 [6.1] versus 55.9 [8.1] years), less likely to be women (38.6% vs. 56.7%), and more likely to be using beta-blockers (20.7% vs. 3.0%). Statin users had higher systolic blood pressure, higher body mass index (BMI) and were more likely to report diabetes. The average total cholesterol among statin users was lower (4.7 [0.9] mmol/L) compared to non-statin users (5.9 [1.0] mmol/L; of note, "high cholesterol" is defined as a total level >6.2 mmol/L). The crude average IOP was higher for statin users versus non-statin users (16.3 [3.9] mm Hg vs. 15.9 [3.8] mm Hg). The comparison of statin users, users of non-statin hypolipidemic drugs, and non-users of hypolipidemic medicines is provided in Supplementary Table S2.

In a basic multivariable model adjusted for age, age-squared, sex, ethnicity, deprivation, spherical equivalent, and non-statin hypolipidemic medication use, statin use was associated with lower IOP (model 1: difference in IOP = -0.13 mm Hg, $P = 2.9E-05$; Table 2). This association was slightly attenuated with additional adjustment for cigarette smoking, alcohol use, physical activity, and caffeinated beverage consumption (model 2: difference = -0.10 mm Hg, $P = 0.0027$). The association remained significant after

TABLE 1. Characteristics of 118,153 UK Biobank Participants With Intraocular Pressure Measurements According to Statin Use at Baseline (2009–2013)

	Non-Statins Users (N = 97,560)	Statin Users (N = 20,593)
Age, y, mean (SD)	55.9 (8.1)	61.4 (6.1)
Female sex, n (%)	55,347 (56.7)	7832 (38.0)
Ethnicity, n (%)		
White (genetically determined Caucasian)	76,375 (78.3)	16,318 (79.2)
White (other)	11,841 (12.1)	2121 (10.3)
Black	3090 (3.2)	493 (2.4)
Asian (Indian / Pakistani / Bangladeshi)	3002 (3.1)	1013 (4.9)
Chinese	431 (0.4)	67 (0.3)
Other	2821 (2.9)	581 (2.8)
Townsend Deprivation Index, mean (SD)	−1.1 (3.0)	−0.9 (3.1)
Statin type, n (%)		
Simvastatin	–	14,602 (70.9)
Atorvastatin	–	4484 (21.8)
Rosuvastatin	–	768 (3.7)
Pravastatin	–	681 (3.3)
Fluvastatin	–	54 (0.3)
Multiple	–	4 (0.0)
Non-statin hypolipidemic medication use, n (%)	3305 (3.4)	1474 (7.2)
Serum total cholesterol (mmol/l), mean (SD)	5.9 (1.0)	4.7 (0.9)
Serum triglyceride (mmol/L), mean (SD)	1.7 (0.9)	1.9 (1.0)
Systolic blood pressure (mm Hg), mean (SD)	136.5 (18.3)	141.4 (17.5)
Systemic beta-blocker use, n (%)	2966 (3.0)	4255 (20.7)
Diabetes, n (%)	2307 (2.4)	4763 (23.1)
HbA1c (mmol/mol), mean (SD)	35.4 (5.2)	40.3 (9.7)
Cardiovascular disease, n (%)	2293 (2.4)	3515 (17.1)
Body Mass Index (kg/m²), mean (SD)	26.9 (4.4)	29.0 (4.5)
Physical activity (MET-hours/week), mean (SD)	44.7 (40.6)	40.4 (42.4.1)
Smoking status, n (%)		
Never	56,440 (57.9)	9712 (47.2)
Past	31,974 (32.8)	8731 (42.4)
Current	9146 (9.4)	2150 (10.4)
Alcohol drinking frequency, n (%)		
Never or special occasion only	19,440 (19.9)	4945 (24.0)
Ever and often	78,120 (80.1)	15,648 (76.0)
Coffee (cups per day), mean (SD)	1.9 (1.7)	1.9 (1.8)
Tea (cups per day), mean (SD)	3.1 (2.1)	3.1 (2.1)
Spherical equivalent, mean (SD)	−0.4 (2.7)	0.0 (2.6)
IOP (mm Hg), mean (SD)	15.9 (3.8)	16.3 (3.9)
Prevalent glaucoma, n (%)	1679 (1.7)	626 (3.1)
Glaucoma MTAG PRS, mean (SD)	0 (1.0)	0 (1.0)

Abbreviation: MTAG PRS = multi-trait analysis of genome wide association study polygenic risk score.

adjustment for covariates related to metabolic syndrome; namely, BMI, systolic blood pressure, diabetes, and HgA1c, as well as cardiovascular disease, which is often co-existent with serum lipid disorders (model 3: difference = −0.12 mm Hg, $P = 7.4E-04$). However, the relationship became nonsignificant and attenuated after additional adjustment for systemic beta-blocker use (model 4: difference = −0.06 mm Hg, $P = 0.10$) and remained nonsignificant in model 5 that also controlled for serum total cholesterol level and triglyceride levels (model 5: difference = 0.05 mm Hg; 95% confidence interval [CI] = −0.02 to 0.13, $P = 0.17$). Similarly, in model 5, specific statin types were not significantly associated with IOP (see Table 2). In sensitivity analysis excluding prevalent glaucoma cases, the relation between statin use and IOP remained nonsignificant (model 5: difference = 0.04 mm Hg, 95% CI = −0.04 to 0.11, $P = 0.31$; Supplementary Table S3). Results also remained unchanged in an alternative model where the reference group was restricted

to participants not on any hypolipidemic agents (versus the larger group of non-statin users); furthermore, use of non-statin hypolipidemic drugs showed no association with IOP in a fully adjusted multivariable model (difference = 0.005 mm Hg, 95% CI = −0.14 to 0.15, $P = 0.95$; Supplementary Table S4).

Statin Use and Self-Reported Glaucoma in the UK Biobank

Among 192,283 participants including 8982 cases of self-reported prevalent glaucoma, the relation between statin use and prevalent glaucoma was null in most models (model 5: OR = 1.05, 95% CI = 0.98 to 1.13; Table 3). When the reference group was restricted to participants not on any hypolipidemic treatments, the results were largely unchanged (see Supplementary Table S4). Furthermore, non-statin hypolipidemic treatment was also not associated

Table 2. Association Between Statin Use (2006–2010) and Intraocular Pressure (Measured in 2009–2013) in the UK Biobank: Multivariable-Adjusted Difference (95% CI) in IOP (mm Hg) by Statin Use

Statin Use	N (Sample Size)	Model 1 [†]		Model 2 [†]		Model 3 [†]		Model 4 [†]		Model 5 [†]	
		Difference (P Value)	(95% CI)	Difference (P Value)	(95% CI)	Difference (P Value)	(95% CI)	Difference (P Value)	(95% CI)	Difference (P Value)	(95% CI)
Nonuser	97,560	Ref		Ref		Ref		Ref		Ref	
User	20,593	-0.13 (2.9e-05)	(-0.18 to -0.07)	-0.10 (2.7e-03)	(-0.17 to -0.03)	-0.12 (7.4e-04)	(-0.19 to -0.05)	-0.06 (0.10)	(-0.13 to 0.01)	0.05 (0.17)	(-0.02 to 0.13)
<i>Simvastatin</i> [‡]	14,602	-0.11 (8.9e-04)	(-0.18 to -0.05)	-0.08 (0.03)	(-0.16 to -0.01)	-0.12 (1.9e-03)	(-0.20 to -0.05)	-0.07 (0.09)	(-0.15 to 0.01)	0.04 (0.30)	(-0.04 to 0.13)
<i>Atorvastatin</i> [‡]	4,484	-0.19 (9.6e-04)	(-0.30 to -0.08)	-0.17 (7.4e-03)	(-0.30 to -0.05)	-0.13 (0.05)	(-0.26 to -0.001)	-0.05 (0.47)	(-0.18 to 0.08)	0.07 (0.32)	(-0.06 to 0.20)
<i>Rosuvastatin</i> [‡]	768	-0.01 (0.94)	(-0.27 to 0.26)	0.01 (0.96)	(-0.28 to 0.30)	0.01 (0.96)	(-0.28 to 0.30)	0.08 (0.58)	(-0.21 to 0.37)	0.21 (0.16)	(-0.08 to 0.50)
<i>Pravastatin</i> [‡]	681	-0.05 (0.71)	(-0.33 to 0.23)	-0.14 (0.38)	(-0.46 to 0.17)	-0.13 (0.42)	(-0.44 to 0.18)	-0.06 (0.72)	(-0.37 to 0.25)	0.01 (0.93)	(-0.30 to 0.33)
<i>Fluvastatin</i> [‡]	54	-0.44 (0.39)	(-1.43 to 0.55)	-0.25 (0.66)	(-1.38 to 0.88)	-0.33 (0.56)	(-1.45 to 0.79)	-0.25 (0.66)	(-1.37 to 0.87)	-0.18 (0.75)	(-1.30 to 0.94)

Abbreviation: Ref = reference.

* Corneal compensated IOP (mm Hg).

[†] Model 1: Adjusted for age, age², sex, ethnicity (White, Black, Asian, and other), deprivation, and spherical equivalent, and non-statin hypolipidemic medication use.

Model 2: Adjusted for covariates in model 1 + smoking status, number of cigarettes (only among current smokers), alcohol, physical activity + missing indicator, and coffee and tea intake.

Model 3: Adjusted for covariates in model 2 + body mass index, systolic blood pressure, diabetes, cardiovascular disease, and HbA1c + missing indicator.

Model 4: Adjusted for covariates in model 3 + baseline systemic beta-blocker use.

Model 5: Adjusted for covariates in model 4 + total cholesterol level + missing indicator and triglyceride level + missing indicator.

[‡] People on multiple statins ($n = 4$) were excluded in analyses to evaluate statin type.

TABLE 3. Association Between Statin Use (2006–2010) and Prevalent Glaucoma in the UK Biobank (2006–2010): Multivariable-Adjusted Odds Ratio (95% CI)

Statin Use	Total N (N Case)	Self-reported Prevalent Glaucoma N = 192,283 (8982 [Cases] and 183,301 [Non-Cases])				
		Model 1* OR (95% CI)	Model 2* OR (95% CI)	Model 3* OR (95% CI)	Model 4* OR (95% CI)	Model 5* OR (95% CI)
Nonuser	157,332 (6613)	Ref	Ref	Ref	Ref	Ref
User	34,951 (2369)	1.09 (1.04 to 1.15)	1.07 (1.01 to 1.14)	1.02 (0.96 to 1.09)	1.03 (0.97 to 1.10)	1.05 (0.98 to 1.13)
Simvastatin†	24,465 (1635)	1.09 (1.03 to 1.15)	1.08 (1.01 to 1.15)	1.03 (0.96 to 1.10)	1.04 (0.97 to 1.12)	1.06 (0.98 to 1.14)
Atorvastatin†	7887 (555)	1.11 (1.01 to 1.21)	1.05 (0.95 to 1.17)	0.99 (0.88 to 1.10)	1.00 (0.90 to 1.12)	1.02 (0.91 to 1.15)
Rosuvastatin†	1364 (93)	1.09 (0.88 to 1.36)	1.20 (0.95 to 1.52)	1.14 (0.90 to 1.44)	1.15 (0.91 to 1.46)	1.17 (0.92 to 1.49)
Pravastatin†	1133 (83)	1.14 (0.91 to 1.44)	1.04 (0.79 to 1.37)	0.99 (0.75 to 1.31)	1.01 (0.76 to 1.33)	1.02 (0.77 to 1.34)
Fluvastatin†	96 (3)	0.40 (0.13 to 1.28)	0.54 (0.17 to 1.74)	0.52 (0.16 to 1.67)	0.53 (0.16 to 1.71)	0.53 (0.17 to 1.72)

Abbreviation: ref = reference.

* Model 1: Adjusted for age, age², sex, ethnicity (White, Black, Asian, and other), deprivation, and spherical equivalent, and non-statin hypolipidemic medication use.

Model 2: Adjusted for covariates in model 1 + smoking status, number of cigarettes (only among current smokers), alcohol, physical activity + missing indicator, and coffee and tea intake.

Model 3: Adjusted for covariates in model 2 + body mass index, systolic blood pressure, diabetes, cardiovascular disease, and HbA1c + missing indicator.

Model 4: Adjusted for covariates in model 3 + baseline systemic beta-blocker use.

Model 5: Adjusted for covariates in model 4 + serum total cholesterol + missing indicator and serum triglyceride + missing indicator.

† People on multiple statins ($n = 6$) were excluded in analyses to evaluate statin type.

with prevalent glaucoma in a fully adjusted multivariable model (OR = 1.04, 95% CI = 0.92 to 1.18; see Supplementary Table S4).

Statin Use and Glaucoma-Related OCT Parameters in the UK Biobank

The average mRNFL and mGCIPL thicknesses were 28.9 (3.8) microns and 75.2 (5.2) microns, respectively (see Supplementary Table S1). In the basic multivariable model adjusted for age, age-squared, sex, ethnicity, deprivation, spherical equivalent, and non-statin hypolipidemic treatments, statin use was associated with thinner mRNFL (model 1: difference = -0.32 microns, $P = 8.6E-10$) and mGCIPL (difference = -0.36 microns, $P = 1.3E-07$; Table 4). In model 5, the results for mRNFL were attenuated and only borderline significant (model 5: difference = -0.14 microns, 95% CI = -0.28 to -0.01 , $P = 0.03$). For mGCIPL, in model 5, results were attenuated, and nonsignificant (model 5: difference = -0.12 microns, 95% CI = -0.29 to 0.05 , $P = 0.17$). These results were nearly identical after excluding prevalent glaucoma cases (see Supplementary Table S3). In models where the reference group was restricted to participants who did not take any hypolipidemic treatments, the results were very similar (see Supplementary Table S4).

Genetic Modification of Statin Use – Glaucoma-Related Outcomes

To determine whether the relation between statin use and glaucoma-related outcomes may differ by genetic propensity for glaucoma, we evaluated whether the MTAG PRS * statin interaction term was significant when added to model 5. The glaucoma MTAG PRS did not significantly modify the relation among statin use and IOP, prevalent glaucoma, mRNFL thickness, or mGCIPL thickness ($P_{\text{interaction}} \geq 0.16$; Table 5). Furthermore, the glaucoma MTAG PRS did not significantly modify the relation between non-statin hypolipidemic medicine use and the glaucoma-related outcomes ($P_{\text{interaction}} \geq 0.24$; Supplementary Table S5).

Mendelian Randomization Analyses

MR analyses showed no evidence of a causal link between HMG-CoA reductase activity and any of POAG, VCDR, IOP, mRNFL, or mGCIPL (Supplementary Table S6 and Supplementary Fig. S1). Only the analysis using the POAG data set showed significant unbalanced horizontal pleiotropy as well as global heterogeneity (Cochran's Q $P = 0.05$, $I^2 = 57.2$).

DISCUSSION

In this large study in the UK Biobank, based on the main analyses as well as the MR analysis, we did not observe any beneficial associations of statin use in relation to glaucoma prevalence or glaucoma-related traits (IOP, mRNFL, or mGCIPL); furthermore, the null associations were not modified by genetic predisposition to glaucoma.

For IOP, our nested models revealed that the relation between statin use and IOP was subject to considerable confounding, but ultimately, in a fully adjusted model, the relationship was null ($n = 118,153$). Similarly, we did not observe that non-statin hypolipidemic treatment was associated with IOP. Whereas one Singaporean study ($n = 10,033$) observed that statin use was associated with higher IOP,²⁵ our null findings are consistent with other studies that have observed null associations.^{8,26} For example, a Canadian pharmaceutical database study ($n = 8548$) showed no difference in adjunct topical IOP-lowering medication use between statin users and nonusers.²⁷ In our study, one of the strongest confounders for this association was systemic beta-blocker use. This was consistent with results from another British study of 7093 participants showing that the relation between statin use and IOP was no longer significant after controlling for systemic beta-blocker use.²⁸ Another confounder was total cholesterol; indeed, a recent meta-analysis suggested that total cholesterol is a risk factor for higher IOP.²⁹ A strength of our study was the adjustment for systemic beta-blocker use, total cholesterol levels, and other conditions that may be indications for statin use.

The relation between statin use and glaucoma has also been intensely studied and has yielded very mixed results

TABLE 4. Association Between Statin Use (2009–2010) and Macular Retinal Nerve Fiber Layer (mRNFL) and Macular Ganglion Cell Plexiform Layer (mGCPL) Thicknesses in the Macula Region (2009–2010) Among UK Biobank Participants

Statin Use	N (Sample Size)	Model 1*			Model 2*			Model 3*			Model 4*			Model 5*		
		Ref	Difference (P Value)	(95% CI)	Ref	Difference (P Value)	(95% CI)	Ref	Difference (P Value)	(95% CI)	Ref	Difference (P Value)	(95% CI)	Ref	Difference (P Value)	(95% CI)
mRNFL (Microns) (N = 41,638)																
Nonuser	34,665	Ref			Ref			Ref			Ref			Ref		
User	6973	-0.32 (8.6e-10)	(-0.42 to -0.22)	(-0.30 (1.8e-07))	(-0.41 to -0.19)	(-0.14 (0.02))	(-0.26 to -0.02)	(-0.13 (0.03))	(-0.26 to -0.01)	(-0.14 (0.03))	(-0.26 to -0.01)	(-0.13 (0.03))	(-0.26 to -0.01)	(-0.14 (0.03))	(-0.28 to -0.01)	(-0.14 (0.03))
<i>Simvastatin</i> †	5109	-0.32 (2.9e-08)	(-0.44 to -0.21)	(-0.30 (5.6e-06))	(-0.42 to -0.17)	(-0.14 (0.04))	(-0.27 to -0.01)	(-0.13 (0.05))	(-0.27 to -0.01)	(-0.11 (0.13))	(-0.27 to -0.01)	(-0.11 (0.13))	(-0.27 to -0.01)	(-0.11 (0.13))	(-0.26 to 0.03)	(-0.11 (0.13))
<i>Atorvastatin</i> †	1368	-0.31 (3.4e-03)	(-0.51 to -0.10)	(-0.29 (0.01))	(-0.52 to -0.06)	(-0.10 (0.39))	(-0.34 to 0.13)	(-0.09 (0.45))	(-0.34 to 0.13)	(-0.05 (0.68))	(-0.33 to 0.14)	(-0.09 (0.68))	(-0.33 to 0.14)	(-0.05 (0.68))	(-0.29 to 0.19)	(-0.05 (0.68))
<i>Rosuvastatin</i> †	255	-0.21 (0.38)	(-0.67 to 0.25)	(-0.31 (0.24))	(-0.81 to 0.20)	(-0.13 (0.60))	(-0.64 to 0.37)	(-0.13 (0.63))	(-0.64 to 0.37)	(-0.10 (0.71))	(-0.63 to 0.38)	(-0.13 (0.71))	(-0.63 to 0.38)	(-0.10 (0.71))	(-0.61 to 0.41)	(-0.10 (0.71))
<i>Pravastatin</i> †	222	-0.38 (0.13)	(-0.88 to 0.11)	(-0.50 (0.07))	(-1.05 to 0.05)	(-0.36 (0.21))	(-0.91 to 0.20)	(-0.34 (0.22))	(-0.91 to 0.20)	(-0.30 (0.29))	(-0.90 to 0.21)	(-0.34 (0.29))	(-0.90 to 0.21)	(-0.30 (0.29))	(-0.85 to 0.25)	(-0.30 (0.29))
<i>Fluvastatin</i> †	18	-0.47 (0.59)	(-2.20 to 1.25)	(-0.55 (0.58))	(-2.50 to 1.40)	(-0.38 (0.71))	(-2.33 to 1.58)	(-0.36 (0.71))	(-2.33 to 1.58)	(-0.31 (0.76))	(-2.32 to 1.59)	(-0.36 (0.76))	(-2.32 to 1.59)	(-0.31 (0.76))	(-2.26 to 1.64)	(-0.31 (0.76))
mGCPL (Microns) (N = 41,547)																
Nonuser	34,592	Ref			Ref			Ref			Ref			Ref		
User	6955	-0.36 (1.3e-07)	(-0.50 to -0.23)	(-0.35 (3.3e-06))	(-0.50 to -0.21)	(-0.21 (8.5e-03))	(-0.37 to -0.05)	(-0.22 (8.9e-03))	(-0.37 to -0.05)	(-0.12 (0.17))	(-0.38 to -0.05)	(-0.22 (0.17))	(-0.38 to -0.05)	(-0.12 (0.17))	(-0.29 to 0.05)	(-0.12 (0.17))
<i>Simvastatin</i> †	5101	-0.36 (2.4e-06)	(-0.51 to -0.21)	(-0.35 (4.4e-05))	(-0.52 to -0.18)	(-0.21 (0.02))	(-0.39 to -0.04)	(-0.21 (0.02))	(-0.39 to -0.04)	(-0.11 (0.23))	(-0.39 to -0.04)	(-0.21 (0.23))	(-0.39 to -0.04)	(-0.11 (0.23))	(-0.30 to 0.07)	(-0.11 (0.23))
<i>Atorvastatin</i> †	1356	-0.29 (0.03)	(-0.56 to -0.02)	(-0.25 (0.10))	(-0.55 to 0.04)	(-0.09 (0.55))	(-0.40 to 0.22)	(-0.10 (0.55))	(-0.40 to 0.22)	(0.01 (0.96))	(-0.41 to 0.22)	(-0.10 (0.96))	(-0.41 to 0.22)	(0.01 (0.96))	(-0.31 to 0.32)	(0.01 (0.96))
<i>Rosuvastatin</i> †	258	-0.13 (0.66)	(-0.74 to 0.47)	(-0.16 (0.64))	(-0.82 to 0.50)	(-0.02 (0.96))	(-0.68 to 0.65)	(-0.02 (0.96))	(-0.68 to 0.65)	(0.10 (0.77))	(-0.69 to 0.65)	(-0.02 (0.77))	(-0.69 to 0.65)	(0.10 (0.77))	(-0.57 to 0.77)	(0.10 (0.77))
<i>Pravastatin</i> †	220	-0.97 (3.6e-03)	(-1.63 to -0.32)	(-1.22 (1.1e-03))	(-1.95 to -0.49)	(-1.09 (3.4e-03))	(-1.82 to -0.36)	(-1.09 (3.4e-03))	(-1.82 to -0.36)	(-1.04 (0.01))	(-1.82 to -0.36)	(-1.09 (3.4e-03))	(-1.82 to -0.36)	(-1.04 (0.01))	(-1.77 to -0.30)	(-1.04 (0.01))
<i>Fluvastatin</i> †	18	-1.54 (0.19)	(-3.81 to 0.74)	(-2.32 (0.08))	(-4.89 to 0.25)	(-2.19 (0.09))	(-4.76 to 0.38)	(-2.20 (0.09))	(-4.76 to 0.38)	(-2.14 (0.10))	(-4.77 to 0.37)	(-2.20 (0.10))	(-4.77 to 0.37)	(-2.14 (0.10))	(-4.71 to 0.43)	(-2.14 (0.10))

Abbreviations: mGCPL = macular ganglion cell inner plexiform layer; mRNFL = macular retinal nerve fiber layer thickness; ref = reference.

* Model 1: Adjusted for age, sex, ethnicity (White, Black, Asian, and other), deprivation, and spherical equivalent, and non-statin hypolipidemic medication use.

Model 2: Adjusted for covariates in model 1 + smoking status, number of cigarettes (only among current smokers), alcohol, physical activity + missing indicator, and coffee and tea intake.

Model 3: Adjusted for covariates in model 2 + body mass index, systolic blood pressure, diabetes, cardiovascular disease, and HbA1c + missing indicator.

Model 4: Adjusted for covariates in model 3 + baseline systemic beta-blocker use.

Model 5: Adjusted for covariates in model 4 + serum total cholesterol + missing indicator and serum triglyceride + missing indicator.

† People on multiple statins (n = 1 for mRNFL and n = 2 for mGCPL) were excluded in analyses to evaluate statin type.

TABLE 5. Multivariable-Adjusted Interactions Between Statin Use and the Glaucoma MTAG PRS on Four Glaucoma-Related Outcomes in the UK Biobank*

	IOP (mm Hg) (N = 118,153) Beta _{int} (P _{int})	Prevalent Glaucoma (N = 192,283) OR _{int} (P _{int})	mRNFL (Microns) (N = 41,638) Beta _{int} (P _{int})	mGCIPL (microns) (N = 41,547) Beta _{int} (P _{int})
MTAG PRS* Statin use (PRS* statin use)	0.05 (0.16)	0.99 (0.72)	0.04 (0.51)	-0.09 (0.27)

Abbreviations: PRS = polygenic risk score, int = interaction; OR = odds ratio; mGCIPL = macular ganglion cell inner plexiform layer; mRNFL = macular retinal nerve fiber layer thickness; MTAG = multi-trait association of genomewide association studies.

* Model for IOP: Adjusted for age, age², sex, ethnicity (White, Black, Asian, and other), deprivation, spherical equivalent, smoking status, number of cigarettes (only among current smokers), alcohol, physical activity + missing indicator, coffee and tea intake, body mass index, systolic blood pressure, diabetes, cardiovascular disease (CVD), HbA1C + missing indicator, systemic beta-blocker use, serum total cholesterol (TC), serum triglycerides (TG) + missing indicator + non-statin hypolipidemic drug use + TC*MTAG PRS + CVD*MTAG PRS + TG*MTAG PRS + age*MTAG PRS + age²*MTAG PRS + non-statin hypolipidemic drug use*MTAG PRS.

Model for prevalent glaucoma: Adjusted for age, age², sex, ethnicity (White, Black, Asian, and other), deprivation, spherical equivalent + missing indicator, smoking status, number of cigarettes (only among current smokers), alcohol, physical activity + missing indicator, coffee and tea intake, body mass index, systolic blood pressure, diabetes, cardiovascular disease (CVD), HbA1C, systemic beta-blocker use, serum total cholesterol (TC), serum triglycerides (TG) + non-statin hypolipidemic drug use + TC*MTAG PRS + CVD*MTAG PRS + TG*MTAG PRS + age*MTAG PRS + age²*MTAG PRS + non-statin hypolipidemic drug use*MTAG PRS.

Model for RNFL and GCIPL: Adjusted for age, age², sex, ethnicity (White, Black, Asian, and other), deprivation, spherical equivalent, smoking status, number of cigarettes (only among current smokers), alcohol, physical activity + missing indicator, coffee and tea intake, body mass index, systolic blood pressure, diabetes, cardiovascular disease (CVD), HbA1C + missing indicator, systemic beta-blocker use, serum total cholesterol (TC), serum triglycerides (TG) + missing indicator + non-statin hypolipidemic drug use + TC*MTAG PRS + CVD*MTAG PRS + TG*MTAG PRS + age*MTAG PRS + age²*MTAG PRS + non-statin hypolipidemic drug use*MTAG PRS.

ranging from inverse,^{8,30–33} to null,^{9,34–36} to adverse.^{10,37} Different ways of ascertaining statin use, dissimilar definitions of glaucoma, varied study methodologies, and uneven follow-up periods may have played a role in the inconsistent results. Furthermore, it is difficult to address residual confounding and to disentangle the effects of statins from the underlying indications for statin use, such as dyslipidemia, cardiovascular disease, and diabetes. No observational study on this subject is ideal, and our analysis lacked information on dosage or duration of statin use and was a cross-sectional study that assessed glaucoma by self-report. However, our cross-sectional study results were consistent with a meta-analysis that observed that use of statins overall was not associated with glaucoma incidence.⁸ In addition, our study had a large sample size, was able to control for multiple indications for statins including total serum cholesterol, evaluated multiple glaucoma outcomes, and the main analyses were augmented with an MR study.²³

Our study was among the first to assess the relation between statin use and inner retinal structure.³⁸ Because early glaucoma can affect the structures in the macula region,³⁹ OCT scanning of the macula region can be useful in diagnosing glaucoma^{19,20}; indeed, a previous UK Biobank study reported that higher IOP was associated with a thinner mGCIPL (but there was no relation with mRNFL thickness).¹⁸ However, we observed no beneficial associations between statin use and macular OCT structural parameters (mRNFL and mGCIPL). An initial significant adverse association between statin use and thinner measures was attenuated after adjustment for BMI, systolic blood pressure, diabetes, and cardiovascular disease (although for mRNFL, the adverse association remained nominally significant). The findings with OCT structural parameters collectively support the notion that statin use is not associated with glaucoma.

We also assessed whether a glaucoma MTAG PRS might interact with statin use to influence various glaucoma-related outcomes, but we did not observe any significant interactions. It is important to note that this same MTAG PRS was a powerful tool that predicted earlier age at glau-

coma diagnosis, glaucoma disease progression, and the need for glaucoma surgery.²² Furthermore, in MR analyses, we used a genetic instrument to approximate HMG-CoA activity, an instrument that predicted cardiovascular disease^{11,40} and cancer.⁴¹ With MR analyses, we were able to preclude strong associations between statin use with various glaucoma outcomes, further supporting the lack of a strong association of statin use on glaucoma.

Our study had several limitations. Although we had data on the type of statin use as well as data on non-statin hypolipidemic medicines, we did not have data on past statin use, which would have biased results toward the null. We also lacked data on dosage or duration of statin use, although the MR analyses provided some complementary data representing dose-response relations and lifetime exposures. This was a cross-sectional study that evaluated IOP, prevalent glaucoma, and OCT measures obtained at a single timepoint; furthermore, we were unable to assess statin use in relation to peripapillary RNFL thickness measures as this data was unavailable in the UK Biobank. The definition of glaucoma was not highly specific and mainly relied on participant reporting, so our results may have been susceptible to various biases related to misclassification of the outcome. Finally, because <8% of our study population was non-White, our findings may not be generalizable to people of color.

This study had several strengths. This was a large study with multiple glaucoma traits, covariates, and genotype information. Statin users had lower serum total cholesterol than nonusers, providing a measure of construct validity for the main exposure of interest. We also generated a genetic instrument that mimicked variation in HMG-CoA reductase activity and served as a surrogate of life-time statin use. This was also the first study to assess whether a glaucoma MTAG PRS might modify the relationship between statin use and glaucoma outcomes.

Overall, our study provides support for the possibility that statin use is not favorably associated with glaucoma-related outcomes and that statin use may not be an effective primary glaucoma prevention strategy.

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