The Association of Calcium-Channel Blocker Use with Glaucoma and Related Traits in the United Kingdom Biobank

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Supplement 1: eMethods, eTables 1–4, eFigure 1, eReferences, STROBE checklist
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Question: To what extent are systemic calcium-channel blockers, a commonly prescribed medication class, associated with glaucoma and clinically relevant related traits among UK Biobank participants?

Findings: In this population-based, cross-sectional study of up to 427 480 adults, calcium-channel blocker use was adversely associated with glaucoma prevalence and OCT-derived inner retinal thicknesses, but not intraocular pressure.

Meaning: Calcium-channel blockers may represent an important modifiable risk factor for glaucoma, potentially through an intraocular pressure-independent mechanism.

ABSTRACT

Importance: Calcium-channel blocker (CCB) use has been associated with an increased risk of glaucoma in exploratory studies.

Objective: To examine the association of systemic CCB use with glaucoma and related traits in the United Kingdom (UK) Biobank.

Design: Cross-sectional study (2006–2010).

Setting: Population-based.

Participants: We included 427 480, 97 100, and 41 023 participants with complete data for the analyses of glaucoma status, intraocular pressure (IOP), and optical coherence tomography (OCT)-derived inner retinal layer thicknesses, respectively.

Exposure: CCB use assessed in a baseline touchscreen questionnaire and confirmed during a trained nurse-led interview.

Main Outcome Measures: Glaucoma status, corneal-compensated IOP, macular retinal nerve fiber layer (mRNFL) thickness and macular ganglion cell-inner plexiform layer (mGCIPL) thickness.

Results: Among all included participants (median age 58 years, 54.1% women, 94.8% White), 33 175 (7.8%) were CCB users. After adjustment for key sociodemographic, medical, anthropometric and lifestyle factors, the use of CCBs (but not other antihypertensives) was associated with greater odds of glaucoma (odds ratio [OR], 1.39; 95% confidence interval [CI], 1.14 to 1.69; *P*=.001). CCB use was also associated with thinner mGCIPL (-0.34 μm; 95% CI, -0.54 to -0.15: *P*=.001) and thinner mRNFL (-0.16 μm; 95% CI, -0.30 to -0.02; *P*=.03), but not IOP (-0.01 mmHg; 95% CI, -0.09 to 0.07; *P*=0.84).

Conclusion and Relevance: We identified an adverse association between CCB use and glaucoma, with CCB users, on average, having 39% higher odds of glaucoma. CCB use was also associated with a thinner mGCIPL and mRNFL, providing a structural basis that supports the association with glaucoma. The lack of an association with IOP suggests that an IOP-independent mechanism of glaucomatous neurodegeneration may be involved. Although a causal relationship has not been

64 established, CCB replacement or withdrawal may be a consideration should a glaucoma patient continue
65 to progress despite optimal care.

INTRODUCTION

Calcium-channel blockers (CCBs) are a commonly used class of medication, frequently prescribed in the management of various cardiovascular diseases, particularly hypertension. Up to 40% of patients with hypertension are prescribed a CCB and, across all medication classes, CCBs account for almost 4% of all primary care prescriptions in the United Kingdom (UK).[1,2]

CCB use has been associated with incident glaucoma requiring a procedural treatment in a large exploratory study of insurance claims data in the United States (US).[3] Although the study was limited by a lack of detailed clinical findings and was not able to account for potentially important confounding factors, including ethnicity and comorbidities, this result is consistent with several previous population-based studies which have demonstrated similar associations.[4–7]

Given the global prevalence of both hypertension and glaucoma,[8,9] and the fact that the two conditions frequently co-exist,[4,10] this association may have important clinical implications for millions of individuals worldwide and warrants further investigation. This may be particularly relevant in ageing and elderly populations, such as the UK and US, where multimorbidity is a common occurrence.[11]

Limited experimental data have suggested that CCBs may have an acute ocular hypotensive effect, especially in individuals with glaucoma.[12,13] It would therefore also be important to assess whether CCB use is associated with intraocular pressure (IOP) on a population level, as this may offer insights into potential underlying pathophysiological mechanisms. Additionally, the use of objective structural glaucoma-related biomarkers may mitigate misclassification bias and help validate any observed associations with glaucoma.

We therefore aimed to examine the association of CCB use with glaucoma in a large cohort using data from the United Kingdom (UK) Biobank data resource. We further explored associations with IOP and two optical coherence tomography (OCT)-derived inner retinal thickness parameters.

METHODS

Reporting guidelines

This study is reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (**Supplement 1**).

Study population

We used data from the UK Biobank, a multisite prospective data resource, including over half a million participants aged 37–73 years at recruitment (2006–2010), with extensive participant phenotyping and a wealth of genetic, proteomic, and metabolomic data (**eMethods** of **Supplement 1**).[14–16] Multiple repeat and supplementary assessments, including an eye and vision sub-study (2009–2010), have been conducted in participant subsets to augment the baseline data.[17] Additional outcomes are available through linkage with nationwide health records and registries. Detailed descriptions, including the study protocol and individual test procedures, are available online (https://www.ukbiobank.ac.uk).

Assessment of calcium-channel blocker use

CCB use was assessed in the baseline UK Biobank questionnaire (2006–2010). All self-reported medications were recorded and subsequently confirmed by a trained nurse in an interview conducted during the same visit. Medications were then matched to a comprehensive drug list obtained from the British National Formulary (78th edition). Antihypertensives were grouped according to the following classes: CCBs (dihydropyridine, phenylalkylamine, benzothiazepine, and other), diuretics (thiazide, loop, and potassium-sparing), renin angiotensin system (RAS) inhibitors (angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers), and systemic beta blockers. The full code list comprising the CCB medication class and its subtypes is available online (**eTable 1** of **Supplement 1**). No information was recorded regarding the dosage, frequency, or time each medication was in use.

Glaucoma case ascertainment

Glaucoma status at the time of the baseline assessment was based on International Classification of Disease (ICD) coded eye conditions in participants' linked hospital episode statistics (HES) records

(**eMethods** of **Supplement 1**). For the main analyses, we defined glaucoma cases as participants with an ICD code for POAG or unspecified glaucoma before, or up to 1 year after, the initial visit. A subset of approximately 175 000 UK Biobank participants were also given the opportunity to self-report a diagnosis of glaucoma, a previous history of glaucoma surgery or laser therapy, or the use of ocular hypotensive drops, during the baseline touchscreen questionnaire (2006–2010). We considered participants with a positive response to any of these questions as cases in our sensitivity analyses.

Assessment of glaucoma-related traits

Ophthalmic assessment (2009–2010) was introduced as an additional enhancement to the initial baseline measures for a subset of participants from six assessment centers.[17] This included measurement of IOP in ~115 000 participants and macular spectral domain OCT imaging of ~65 000 participants (**eMethods** of **Supplement 1**). For this analysis, glaucoma-related outcomes included corneal-compensated IOP, as well as two inner retinal OCT parameters which have been shown to be useful glaucoma-related biomarkers – macular retinal nerve fiber layer (mRNFL) and macular ganglion cell-inner plexiform layer (mGCIPL) thickness.[18,19]

Assessment of covariables

We also considered a variety of demographic, lifestyle, and systemic health status variables in our analyses (**eMethods** of **Supplement 1**) in order to account for potential confounding bias. These were selected a priori and included: age, sex, self-reported ethnicity, education level, Townsend deprivation index, diabetes, body mass index, total cholesterol, smoking status and alcohol consumption frequency.

Statistical analyses

Baseline participant characteristics, stratified by CCB use, were described and compared using a two-sample t-test or test of proportion, where appropriate. We examined the association of CCB use with glaucoma prevalence using multivariable logistic regression, adjusted for all the covariables described above ("maximally-adjusted models"). We then performed similar analyses for any antihypertensive medication use and for the other major antihypertensive medication classes (diuretics, RAS inhibitors,

and systemic beta blockers) to gauge whether the observed CCB association represented a class-specific effect or a general effect across all antihypertensive medications. To aid direct comparability of results, associations with IOP, mGCIPL and mRNFL were assessed using multivariable linear regression models adjusted for the same covariables as used in the glaucoma analysis. To address potential confounding by indication, we assessed the effect of further adjustment for mean systolic blood pressure (SBP; mmHg). Finally, we considered all associations according to three CCB subtypes (dihydropyridines, phenylalkylamines, and benzothiazepines). All statistical analyses were performed using Stata (Version 17.0. StataCorp LLC. 2021. College Station, TX, USA). *P*-values were two sided and were not adjusted for multiple comparisons.

Sensitivity analyses

We performed sensitivity analyses using alternative case definitions, including: any ICD-coded glaucoma; ICD-coded POAG only; self-report and/or any ICD-coded glaucoma; self-report and/or ICD-10 coded POAG/unspecified glaucoma; and self-report and/or ICD-coded POAG. We additionally assessed whether the main association with glaucoma was modified by hypertension, sex, or ethnicity, by testing the significance of a multiplicative interaction term added to the final multivariable regression models. To address the possibility that the association with IOP may be influenced by ocular hypotensive medication, we excluded all participants reporting topical glaucoma therapy use. Lastly, we repeated our primary analyses with further adjustment for refractive error (mean spherical equivalent) and a glaucoma polygenic risk score,[20] as these are important predictors of glaucoma status.

Ethical considerations

The UK Biobank was approved by the NHS North West Multicentre Research Ethics Committee (06/MRE08/65) and the National Information Governance Board for Health and Social Care. This research was conducted under UK Biobank application number 36741 and conformed to the tenets of the Declaration of Helsinki. Study participants were not compensated for their involvement in the study.

RESULTS

Participant characteristics

The participant selection process is outlined in **Figure 1**. We included 427 480, 97 100, 40 486, and 40 583 participants with complete data for the analyses of glaucoma status, IOP, mGCIPL thickness, and mRNFL thickness, respectively. Median age at baseline was 58 years (interquartile range, 50–63), with a predominance of female (54.1%) and White (94.8%) participants. Of all included participants, 114 311 (26.7%) had a history of physician-diagnosed systemic hypertension and there were 33 175 (7.8%) CCB users (29 508 with hypertension [89.0%] and 3 667 without hypertension [11.0%]).

Baseline participant characteristics, stratified by CCB use, are presented in **Table 1**. CCB users were more likely to be older, men, Black, less educated, more deprived, hypertensive, diabetic, have higher SBP and BMI, and lower total cholesterol than non-users. Lower average total cholesterol levels in CCB users may be the result of a difference in statin use between groups (CCB users, 52.1%; non-users, 14.5%; $P<.001$). Participants reporting CCB use also had a higher glaucoma prevalence, higher average IOP, thinner average mGCIPL thickness, and thinner average mRNFL thickness than non-users.

Association of antihypertensive medication use with glaucoma status

In maximally-adjusted regression models, antihypertensive medication use was adversely associated with glaucoma (odds ratio [OR], 1.29; 95% confidence interval [CI], 1.10 to 1.52; $P=.002$). This association appeared to be driven by CCB use (OR, 1.39; 95% CI, 1.14 to 1.69; $P=.001$), with no association demonstrated for diuretic (35 099 users; OR, 1.03; 95% CI, 0.84 to 1.28; $P=.75$), RAS inhibitor (55 983 users; OR, 1.12; 95% CI, 0.93 to 1.34; $P=.24$), or systemic beta blocker (29 818 users; OR, 0.93; 95% CI, 0.74 to 1.18; $P=.56$) use (**Table 2**). Associations were materially unchanged when additionally adjusting for SBP and concurrent use of more than one antihypertensive medication class.

Association of CCB use with glaucoma and related traits

Results for the association of CCB use with glaucoma and related traits are presented in **Table 3**. The main association with glaucoma status (OR, 1.39; 95% CI, 1.14 to 1.69; $P=.001$) was unchanged by the

inclusion of SBP to the model. CCB use was also associated with thinner OCT-derived inner retinal parameters, with only slight attenuation of the associations after further adjustment for SBP. Those reporting the use of CCBs had thinner mGCIPL (-0.34μm; 95% CI, -0.54 to -0.15; *P*=.001) and mRNFL (-0.16μm; 95% CI, -0.30 to -0.02; *P*=.03) than non-users. In maximally-adjusted regression models, CCB use was not associated with IOP (-0.01mmHg; 95% CI -0.09 to 0.07; *P*=.84). Further adjustment for SBP, however, resulted in an association with lower IOP (-0.15mmHg; 95% CI -0.23 to -0.07; *P*<.001). The complete results of the models for glaucoma status, IOP, and OCT-derived inner retinal parameters are available online (**eTables 2 and 3** of **Supplement 1**).

Association of CCB subtypes with glaucoma and related traits

Dihydropyridines (e.g., amlodipine) were by far the most used CCB subtype (n=29 314, 88.4%), followed by benzothiazepines (e.g., diltiazem, n=3 022, 9.1%) and phenylalkylamines (e.g., verapamil, n=951, 2.9%). There were no 'other CCB' users. The associations for dihydropyridine users were consistent with the results of the main analyses (**Table 4**). Benzothiazepine users had higher odds of glaucoma (OR, 1.80; 95% CI, 1.14 to 2.86; *P*=.01) and lower IOP (-0.51mmHg; 95% CI -0.77 to -0.24; *P*<.001), but no association with mGCIPL or mRNFL thickness. There were no associations for phenylalkylamine users.

Sensitivity analyses

Sensitivity analyses using alternative glaucoma case definitions are presented in **eTable 4** of **Supplement 1**. Overall, analyses including self-report as a component of the case definition showed weaker associations than those based on ICD-codes alone. Of the various glaucoma definitions used, only the narrowest ICD-coded definition of POAG (476 cases) did not demonstrate an association with CCB use.

There was evidence that the association between CCB use and glaucoma was modified by a history of physician-diagnosed hypertension (**eFigure 1** of **Supplement 1**). In the maximally-adjusted regression model, including adjustment for baseline SBP, CCB use in those *without* hypertension (OR, 2.01; 95% CI, 1.26 to 3.21; *P*=.003) was associated with higher odds of glaucoma than CCB use in those *with*

hypertension (OR, 1.47; 95% CI, 1.18 to 1.84; *P*=.001) (OR for interaction, 0.59; 95% CI, 0.35 to 0.98; *P*=.04). There was no evidence of a differential effect by sex or ethnicity for the association with glaucoma. Results for IOP were materially unchanged when restricting analyses to participants not using ocular hypotensive agents (-0.06mmHg; 95% CI, -0.13 to 0.01; *P*=.15). Further adjustment for spherical equivalent and a glaucoma polygenic risk score resulted in a substantial sample size reduction (*n*=84 924), but a similar adverse association with glaucoma (OR, 1.59; 95% CI, 1.04 to 2.45; *P*=.03).

DISCUSSION

In this large population-based study, we found that CCB users had, on average, 39% higher odds of glaucoma than non-users, after controlling for multiple potential confounders. Consistent with this finding, we also demonstrated that mGCIPL and mRNFL (both objective structural glaucoma-related parameters) were thinner in CCB users. CCB use was not found to be associated with IOP.

An adverse association between CCB use and glaucoma has previously been demonstrated in both cross-sectional and longitudinal studies.[3–6] In a large US insurance claims study, CCBs demonstrated the strongest adverse statistical association with glaucoma of 423 different medication classes.[3] Similarly, amlodipine (a dihydropyridine CCB) was found to have the strongest statistical association with glaucoma of all 1 723 unique generic medications studied.[3] This analysis was, however, limited by a lack of data on potential confounders which may have resulted in biased results. For example, participant ethnicity was not available and the observed association may have been driven by a higher prevalence of CCB use among individuals of African descent (an important risk factor for glaucoma), in whom CCBs are standard first-line therapy.[21]

Our analyses provide further large-scale evidence supporting these previously reported associations and suggest that the adverse association between CCB use and glaucoma risk may act via IOP-independent mechanisms. While our primary analyses were based on a strict case definition which is likely to underestimate true prevalence, sensitivity analyses using less specific glaucoma definitions and conducted in up to 7 000 cases (including more than 900 CCB users) demonstrated similar associations.

To the best of our knowledge, there has been no published report of an adverse association between CCB use and glaucoma-related inner retinal parameters. A previous study of antihypertensive use from southeast Asia found no association between CCBs with average mGCIPL or peripapillary RNFL thickness.[22] While our reported effect estimates for mGCIPL and mRNFL thicknesses may seem small, on a population-level they are equivalent to the average difference seen between participants separated by 4 years in age.[23]

While limited experimental data have suggested that systemic CCBs may have an acute ocular hypotensive effect, especially in individuals with glaucoma,[12,13] this is not always a consistent finding.[24] We found no difference in average IOP between CCB users and non-users, however, this may be related to IOP assessment being limited to a single measurement, and we cannot fully exclude the possibility of a small effect on IOP. This result is consistent with a recent large meta-analysis of European population-based eye studies which also found an adverse association between CCB use and glaucoma status, but no relationship with IOP.[7] It is also important to note that our study lacked data on length, frequency, or dosage of CCB use, and whether the medication was taken on the day of IOP assessment, and our findings may therefore not fully account for the potential effect of CCBs on IOP. Although an association with lower IOP was observed after additional adjustment for baseline SBP, this may be the result of collider bias.

The implication that CCBs have a direct detrimental effect on retinal tissue is contrary to the general view of these agents being neuroprotective. In vitro studies have shown that CCBs exert protective effects on neurons undergoing apoptosis and necrosis, and these effects have also been documented in retinal ganglion cells and photoreceptors in experimental animal models.[25] This is thought to be related to the inhibition of calcium influx-mediated apoptotic pathways. Additionally, several small interventional studies have demonstrated that CCBs increase retrobulbar and optic nerve head blood flow, improve color contrast sensitivity, and may stabilize visual field loss in individuals with normal-tension glaucoma.[26–29] While the reasons for this apparent discrepancy are unclear, a simple explanation has been proposed: in vitro studies do not account for the blood pressure-lowering effects of CCBs, and the CCBs investigated in the visual field studies had no appreciable effect on blood pressure in glaucoma cases. It may be that the detrimental effects of CCBs are only manifest when coupled with the hypotensive and/or vasodilatory properties of certain CCBs, such as amlodipine.[25] This hypothesis may be supported by our interaction sensitivity analysis, in which we found that CCB use was associated with higher odds of glaucoma in those without hypertension, compared to those with hypertension, suggesting that a history of higher blood pressure may partially ameliorate the adverse association with glaucoma. While adverse associations with glaucoma were demonstrated for both dihydropyridine and

benzothiazepine users, we found no evidence for an adverse association with phenylalkylamine CCBs (which are relatively selective for the myocardium and have little effect on systemic blood pressure), although these analyses may have been limited by reduced statistical power due to a relatively small number of users. Alternatively, changes in calcium homeostasis may affect mitochondrial function which may make neurons more vulnerable to processes such as oxidative stress.[30,31]

The strengths of this study include the large sample size, allowing for the detection of small, but meaningful differences between CCB users and non-users. The wealth of participant data allowed us to adjust for multiple important confounders, which may have limited previous study designs. We were also able to account for the concurrent use of other systemic medication classes with known effects on IOP or previously reported adverse associations with glaucoma. In addition, we were able to simultaneously explore the associations of CCB use with glaucoma, IOP, and inner retinal thickness, thus providing a plausible anatomic and mechanistic basis for the observed association.

Our study is limited by glaucoma case ascertainment in the UK Biobank, which relies on a combination of self-report and linked ICD-codes. Although our primary case definition, based on ICD-codes alone, is likely to be relatively specific, it may fail to detect a significant proportion of true glaucoma cases, who may not be captured on a hospital-based database. Self-report, on the other hand, may identify more cases, but poses a risk of misclassification and/or recall bias. Another limitation is that we were not able to analyze the duration or dosage of CCB use, which may play an important role in the association with glaucoma. Together with the cross-sectional study design, this precluded us from examining for dose-response and temporal effects, further restricting our ability to make causal inferences. Although we adjusted for multiple important confounders, the observed associations might represent residual confounding by unknown or unconsidered factors. Our findings in UK Biobank participants, where almost 95% are of White ethnicity, may not be generalizable to other populations.

In keeping with other smaller population-based studies, our study adds further support to an adverse association between CCB use and glaucoma, despite no apparent relationship with IOP. This warrants further investigation to determine whether the associations are causal and to probe potential underlying biological mechanisms.

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Table 1. Characteristics of eligible UK Biobank participants by calcium-channel blocker use

Description	CCB user (n = 33 175)	CCB non-user (n = 394 305)	Difference (95% CI)	*P*-value
Age (years), mean (SD)	61.2 (6.2)	56.1 (8.1)	5.0 (4.9, 5.1)	<.001
Sex				
Women	13 473 (40.6)	217 860 (55.3)	-14.6 (-15.2, -14.1)	<.001
Men	19 702 (59.4)	176 445 (44.7)	14.6 (14.1, 15.2)	<.001
Ethnicity				
White	30 548 (92.1)	374 853 (95.1)	-3.0 (-3.3, -2.7)	<.001
Asian	814 (2.5)	7 058 (1.8)	0.7 (0.5, 0.8)	<.001
Black	1 211 (3.7)	5 406 (1.4)	2.3 (2.1, 2.5)	<.001
Other/Mixed	602 (1.8)	6 988 (1.8)	0.0 (-0.1, 0.2)	.57
Education level				
Less than O-level	14 975 (45.1)	131 830 (33.4)	11.7 (11.1, 12.3)	<.001
O-level	6 792 (20.5)	85 765 (21.8)	-1.3 (-1.7, -0.8)	<.001
A-level	3 064 (9.2)	45 083 (11.4)	-2.2 (-2.5, -1.9)	<.001
Degree	8 344 (25.2)	131 627 (33.4)	-8.2 (-8.7, -7.7)	<.001
Townsend deprivation index, mean (SD)	-1.0 (3.2)	-1.4 (3.0)	0.4 (0.4, 0.4)	<.001
Hypertension				
No	3 667 (11.1)	309 502 (78.5)	-67.4 (-67.8, -67.1)	<.001
Yes	29 508 (88.9)	84 803 (21.5)	67.4 (67.1, 67.8)	<.001
Diabetes				
No	27 635 (83.3)	377 109 (95.6)	-12.3 (-12.7, -11.9)	<.001
Yes	5 540 (16.7)	17 196 (4.4)	12.3 (11.9, 12.7)	<.001
Systolic blood pressure (mmHg), mean (SD)	145.8 (17.1)	137.1 (18.6)	8.7 (8.5, 8.9)	<0.001
Body mass index (kg/m^2), mean (SD)	29.4 (4.8)	27.2 (4.4)	2.2 (2.2, 2.3)	<0.001
Total cholesterol (mmol/L), mean (SD)	5.2 (1.2)	5.7 (1.1)	-0.6 (-0.6, -0.5)	<0.001
Smoking status				
Never	15 659 (47.2)	218 226 (55.3)	-8.1 (-8.7, -7.6)	<.001
Former	14 321 (43.2)	135 058 (34.3)	8.9 (8.3, 9.5)	<.001
Current	3 195 (9.6)	41 021 (10.4)	-0.8 (-1.1, -0.4)	<.001
Alcohol consumption frequency				
Never or special occasions only	7 591 (22.9)	73 792 (18.7)	4.2 (3.7, 4.6)	<.001
1–3 times per month	3 208 (9.7)	44 222 (11.2)	-1.5 (-1.9, -1.2)	<.001
1–2 times per week	7 730 (23.3)	102 561 (26.0)	-2.7 (-3.2, -2.2)	<.001
3–4 times per week	7 014 (21.1)	92 701 (23.5)	-2.4 (-2.8, -1.9)	<.001
Daily or almost daily	7 632 (23.0)	81 029 (20.6)	2.5 (2.0, 2.9)	<.001
Statin use	17 294 (52.1)	56 983 (14.5)	37.7 (37.1, 38,2)	<.001
Glaucoma prevalence	137 (0.4)	652 (0.2)	0.2 (0.2, 0.3)	<.001
Intraocular pressure (mmHg), mean (SD)[1]	16.4 (3.7)	16.0 (3.4)	0.4 (0.3, 0.5)	<.001
mGCIPL thickness (μm), mean (SD)[2]	74.2 (5.3)	75.3 (5.2)	-1.1 (-0.9, 1.3)	<.001
mRNFL thickness (μm), mean (SD)[3]	28.2 (3.8)	29.0 (3.8)	-0.8 (-0.9, -0.6)	<.001

[1] N = 97 100; [2] N = 40 486; [3] N = 40 583.
Figures represent counts (n) and percentages (%), unless otherwise stated.
CCB, calcium-channel blocker; CI, confidence interval; mGCIPL, macular ganglion cell-inner plexiform layer; mRNFL, macular retinal nerve fiber layer; SD, standard deviation.

Table 2. Association of antihypertensive medication use with glaucoma in the UK Biobank

Description	Model A[1]			Model B[2]		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Any antihypertensive medication	**1.29**	**1.10, 1.52**	**.002**	N/A	N/A	N/A
Antihypertensive medication class						
Calcium-channel blockers	**1.39**	**1.14, 1.69**	**.001**	**1.39**	**1.13, 1.70**	**.001**
Diuretics	1.03	0.84, 1.28	0.75	0.96	0.77, 1.20	.75
Renin angiotensin system inhibitors	1.12	0.93, 1.34	0.24	1.07	0.88, 1.30	.47
Systemic beta blockers	0.93	0.74, 1.18	0.56	0.90	0.71, 1.14	.39

[1] Model A adjusted for: age (years), sex (women, men), self-reported ethnicity (White, Asian, Black, Other/Mixed), education level (less than O-level, O-level, A-level, degree), Townsend deprivation index (units), diabetes (no, yes), body mass index (kg/m^2), total cholesterol (mmol/L), smoking status (never, former, current), and alcohol consumption frequency (never or special occasion only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily or almost daily).
[2] Model B adjusted for: as for Model A, plus additional adjustment for systolic blood pressure (mmHg), and simultaneous use of other antihypertensive medications.
CI, confidence interval; N/A, not applicable.

Table 3. Association of calcium-channel blocker use with glaucoma and related traits in the UK Biobank

Outcome (unit)	Sample size	Model A[1]			Model B[2]		
		Effect estimate	95% CI	*P*-value	Effect estimate	95% CI	*P*-value
Glaucoma (odds ratio)	427 480	1.39	1.14, 1.69	.001	1.39	1.14, 1.69	.001
Intraocular pressure (mmHg)	97 100	-0.01	-0.09, 0.07	.84	-0.15	-0.23, -0.07	<.001
mGCIPL thickness (μm)	40 486	-0.34	-0.54, -0.15	.001	-0.31	-0.50, -0.11	.001
mRNFL thickness (μm)	40 583	-0.16	-0.30, -0.02	.03	-0.14	-0.29, 0.00	.049

[1] Model A adjusted for: age (years), sex (women, men), self-reported ethnicity (White, Asian, Black, Other/Mixed), education level (less than O-level, O-level, A-level, degree), Townsend deprivation index (units), diabetes (no, yes), body mass index (kg/m^2), total cholesterol (mmol/L), smoking status (never, former, current), and alcohol consumption frequency (never or special occasion only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily or almost daily).
[2] Model B adjusted for: as for Model A, plus additional adjustment for systolic blood pressure (mmHg).
CI, confidence interval; mGCIPL, macular ganglion cell-inner plexiform layer; mRNFL, macular retinal nerve fiber layer.

Table 4. Association of calcium-channel blocker subtypes with glaucoma and related traits in the UK Biobank

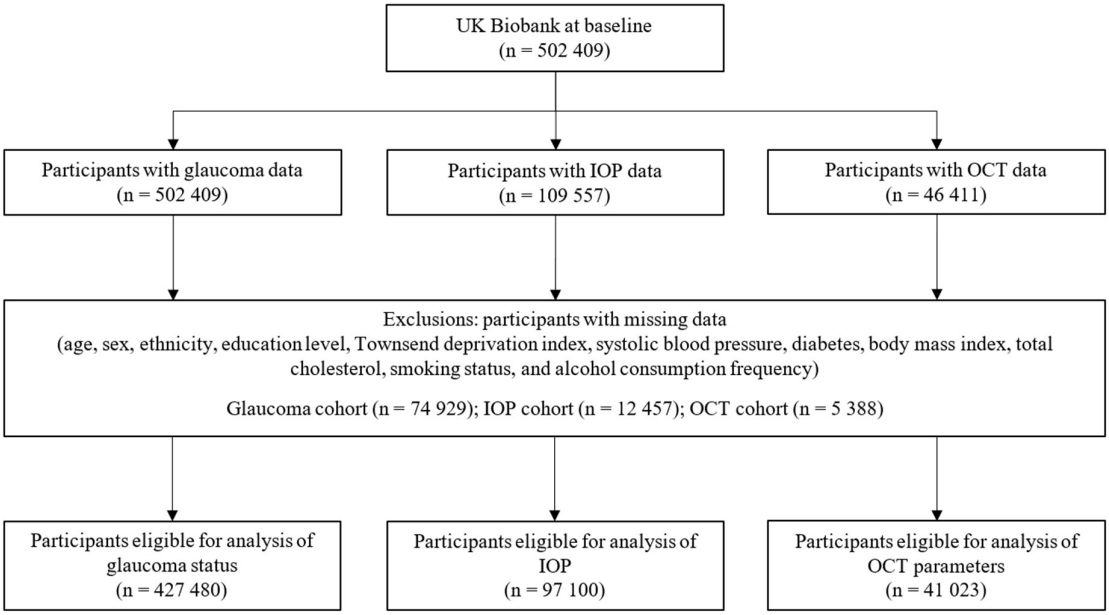
Outcome (unit)	Dihydropyridine CCBs (29 314 users)			Phenylalkylamine CCBs (951 users)			Benzothiazepine CCBs (3 022 users)		
	Effect estimate	95% CI	*P*-value	Effect estimate	95% CI	*P*-value	Effect estimate	95% CI	*P*-value
Model A[1]									
Glaucoma (odds ratio)	1.33	1.08, 1.63	.007	0.99	0.32, 3.09	.99	1.80	1.14, 2.86	.01
IOP (mmHg)	0.03	-0.05, 0.11	.45	0.17	-0.28, 0.63	.46	-0.51	-0.77, -0.24	<.001
mGCIPL thickness (µm)	-0.36	-0.57, -0.16	<.001	-0.78	-1.82, 0.25	.14	0.13	-0.52, 0.77	.70
mRNFL thickness (µm)	-0.17	-0.32, -0.02	.02	0.01	-0.75, 0.77	.98	-0.10	-0.57, 0.37	.68
Model B[2]									
Glaucoma (odds ratio)	1.33	1.08, 1.64	.006	0.99	0.32, 3.09	.99	1.80	1.14, 2.86	.01
IOP (mmHg)	-0.12	-0.20, -0.04	.005	0.11	-0.34, 0.56	.62	-0.50	-0.76, -0.23	<.001
mGCIPL thickness (µm)	-0.32	-0.53, -0.12	.002	-0.76	-1.80, 0.27	.15	0.12	-0.53, 0.76	.73
mRNFL thickness (µm)	-0.16	-0.30, -0.01	.04	0.01	-0.74, 0.77	.97	-0.11	-0.58, 0.37	.66

[1] Model A adjusted for: age (years), sex (women, men), self-reported ethnicity (White, Asian, Black, Other/Mixed), education level (less than O-level, O-level, A-level, degree), Townsend deprivation index (units), diabetes (no, yes), body mass index (kg/m^2), total cholesterol (mmol/L), smoking status (never, former, current), and alcohol consumption frequency (never or special occasion only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily or almost daily).
[2] Model B adjusted for: as for Model A, plus additional adjustment for systolic blood pressure (mmHg).
CCB, calcium-channel blocker; CI, confidence interval; IOP, intraocular pressure; mGCIPL, macular ganglion cell-inner plexiform layer; mRNFL, macular retinal nerve fiber layer.

FIGURE LEGENDS

Figure 1. Flowchart outlining eligible participants for this study in the UK Biobank

IOP, intraocular pressure; OCT, optical coherence tomography.


UK Biobank at baseline
(n = 502 409)
Participants with glaucoma data
(n = 502 409)
Participants with IOP data
(n = 109 557)
Participants with OCT data
(n = 46 411)
Exclusions: participants with missing data
(age, sex, ethnicity, education level, Townsend deprivation index, systolic blood pressure, diabetes, body mass index, total cholesterol, smoking status, and alcohol consumption frequency)
Glaucoma cohort (n = 74 929); IOP cohort (n = 12 457); OCT cohort (n = 5 388)
Participants eligible for analysis of glaucoma status
(n = 427 480)
Participants eligible for analysis of IOP
(n = 97 100)
Participants eligible for analysis of OCT parameters
(n = 41 023)

The Association of Calcium-Channel Blocker Use with Glaucoma and Related Traits in the United Kingdom Biobank

SUPPLEMENT 1

eMethods

Study population

UK Biobank participants were recruited through National Health Service (NHS) registers and invited to attend one of 22 assessment centers across the United Kingdom (UK) where extensive phenotypic information and biological samples were collected.[1,2] After providing electronic informed consent, participants completed an in-depth touchscreen questionnaire – detailing sociodemographic information, life-course exposures, and medical history – and an array of physical and cognitive measurements. Blood, urine and saliva specimens were also collected and used to generate a wealth of genetic, proteomic and metabolomic data.[3]

Glaucoma case ascertainment

Glaucoma status at the time of the baseline assessment was determined through interrogation of participants' linked hospital episode statistics (HES) records and retrieval of relevant International Classification of Disease (ICD) coded eye conditions. Specifically, ICD 9th (ICD-9) and 10th (ICD-10) revision codes, as well as the date of first occurrence, were retrieved for the following conditions: glaucoma (ICD-10 H40), open-angle glaucoma (ICD-9 365.1), POAG (ICD-10 H40.1), glaucoma suspect (ICD-10 H40.0), primary angle closure glaucoma (ICD-10 H40.2 and ICD-9 365.2), glaucoma secondary to other conditions (ICD-10 H40.3 to H40.6 and ICD-9 365.3 to 365.6), other glaucoma (ICD-10 H40.8 and ICD-9 365.8), and unspecified glaucoma (ICD-10 H40.9 and ICD-9 365.9). We excluded participants if they had a diagnosis at 30 years of age or younger, as the pathophysiological mechanisms underlying juvenile glaucoma may differ substantially from those of adult-onset disease.

Assessment of glaucoma-related outcome measures

IOP was measured in approximately 115 000 participants using an Ocular Response Analyzer (ORA; Reichert Corp., Philadelphia, PA, USA).[4] The ORA is a noncontact tonometer that measures the force required to flatten the cornea using a jet of air. Two measures of intraocular pressure are derived from its readings, a Goldman-correlated IOP (IOPg) and a corneal-compensated IOP (IOPcc). We used IOPcc for our analyses because this measure is thought to provide the most accurate assessment of true physiological IOP and to be least affected by corneal artifact.[5] To handle extreme values of IOP that may be artifacts, we excluded the top and bottom 0.5% of IOP measurements. We also excluded participants with a history of glaucoma surgery or laser therapy, visually-significant ocular trauma, corneal graft surgery or refractive laser surgery, as these participants are likely to have IOP that has been altered from physiological levels. For patients using ocular hypotensive medication, we imputed pre-treatment IOP by dividing by 0.7, based on the mean IOP reduction achieved by medication.[6] We calculated participant-level IOP as the mean of right and left eye values, if data were available for both eyes, or as either the right or left eye value, if data were available for only one eye.

Spectral-domain OCT imaging of both eyes was performed in approximately 65 000 participants using a Topcon 3D OCT-1000 Mark II system (Topcon Corp., Tokyo, Japan) in a dark room without pupil dilation using the 3-dimensional 6x6mm^2 macular volume scan mode (512 A-scans per B-scan; 128 horizontal B-scans in a raster pattern).[4] Version 1.6.1.1 of the Topcon Advanced Boundary Segmentation (TABS) algorithm was used to delineate the inner and outer retinal surfaces.[7] Quality control to exclude images of poor quality has been described in detail previously.[8] We excluded scans with an image quality score (signal strength) less than 45. Additionally, several segmentation indicators were calculated that also identified poor scan quality or segmentation failures; we excluded the poorest 20% of images for each of these indicators. The detailed methods used to derive these indicators are explained elsewhere.[9] We used average mGCIPL and mRNFL thickness parameters derived from the macula-6 grid, as these measures have been shown to be useful glaucoma-related biomarkers.[10,11] Participant-level mGCIPL and mRNFL thicknesses (in micrometers, μm) were calculated as the mean of right and left eye values for each participant with high quality images available for both eyes. If data were available only for one eye, we considered that value for the participant.

Assessment of covariables

All UK Biobank covariables used in this analysis were selected a priori and were ascertained at the time of the baseline assessment and on the same day as the ophthalmic assessment. These comprised: age , sex (women, men), self-reported ethnicity (White, Asian, Black, Other/Mixed), education level (less than O-level, O-level [intermediate high school qualification], A-level [advanced high school qualification], degree [university qualification]), Townsend deprivation index (a measure of material deprivation based on an individual's residential postcode; a higher index score indicates greater relative poverty), diabetes (no, yes), body mass index

(kg/m^2; calculated as weight/height^2), total cholesterol (mmol/L), smoking status (never, former, current), and alcohol consumption frequency (never or special occasion only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily or almost daily).

eTable 1. Full calcium-channel blocker code list used to identify medication users in this UK Biobank study

Sub-category	Code	Description
Dihydropyridine calcium-channel blockers	1140860426	atenolol+nifedipine 50mg/20mg m/r capsule
	1140860358	tenif capsule
	1140861090	adalat 5mg capsule
	1140881702	adalat 10mg capsule
	1140923572	adipine mr 10 m/r tablet
	1140879802	amlodipine
	1141200400	amlostin 5mg tablet
	1140861110	angiopine 5mg capsule
	1140860356	beta-adalat capsule
	1141187094	cabren 2.5mg m/r tablet
	1140916930	calanif 5mg capsule
	1141173766	calchan mr 10mg m/r tablet
	1140861106	calcilat 10mg capsule
	1140861176	cardene 20mg capsule
	1140927934	cardilate mr 10mg m/r tablet
	1141199858	cardioplen xl 5mg m/r tablet
	1140861120	coracten sr 10mg m/r capsule
	1141166752	coroday mr 20mg m/r tablet
	1141188836	felendil xl 5mg m/r tablet
	1140888646	felodipine
	1141165470	felodipine+ramipril
	1141188576	felogen xl 5mg m/r tablet
	1141188152	felotens xl 5mg m/r tablet
	1141145870	fortipine la40 m/r tablet
	1141152600	genalat retard 10mg m/r tablet
	1140861190	isradipine
	1141188920	keloc sr 5mg m/r tablet
	1141187962	kentipine mr 10mg m/r tablet
	1140861276	lacidipine
	1141153026	lercanidipine
	1140861282	motens 2mg tablet
	1141200782	neofel xl 5mg m/r tablet
	1140879810	nicardipine
	1140861088	nifedipine
	1141157140	nifedipress mr 10 m/r tablet
	1141150538	nifedotard 20mr m/r tablet
	1140911088	nifelease 20mg m/r tablet
	1140861114	nifensar xl 20mg m/r tablet
	1141169730	nifopress retard 20mg m/r tablet
	1140872568	nimodipine
	1140926966	nimodrel mr 10 m/r tablet
	1140872472	nimotop 30mg tablet
	1140928226	nisoldipine
	1141162546	nivaten retard 10mg m/r tablet
	1140868036	parmid 10mg tablet
	1141201814	parmid xl 5mg m/r tablet
	1140928212	plendil 2.5mg m/r tablet
	1140861194	prescal 2.5mg tablet
	1141150500	slofedipine 20mg m/r tablet
	1140928234	syscor mr 10mg m/r tablet
	1140927940	tensipine mr 10 m/r tablet
	1140926188	unipine xl 30mg m/r tablet
	1141190548	valni 20 retard 20mg m/r tablet
	1140851790	vasad 5mg capsule
	1141190160	vascalpha 5mg m/r tablet
	1141153032	zanidip 10mg tablet

Phenylalkylamine calcium-channel blockers	1140866546	berkatens 40mg tablet
	1140866554	cordilox 40mg tablet
	1141169096	ethimil mr 240 m/r tablet
	1140866484	geangin 40mg tablet
	1140866460	half securon sr 120mg m/r tablet
	1141187056	ranvera mr 240mg m/r tablet
	1140866466	securon 40mg tablet
	1141153316	tarka 2mg/180mg m/r capsule
	1141153328	trandolapril + verapamil hydrochloride
	1140881692	univer 120mg m/r capsule
	1141187774	vera-til sr 120mg m/r tablet
	1140888510	verapamil
	1141150926	verapress mr 240 m/r tablet
	1141169710	vertab sr 240 m/r tablet
	1141184390	zolvera 40mg/5ml oral solution
Benzothiazepine calcium-channel blockers	1140861138	adizem-60 m/r tablet
	1140926780	adizem-xl plus m/r capsule
	1140861136	angiozem 60mg m/r tablet
	1140917428	angitil sr 90 m/r capsule
	1141175224	bi-carzem sr 60mg m/r capsule
	1140861130	britiazim 60mg m/r tablet
	1141153454	calazem 60mg m/r tablet
	1140851730	calcicard 60mg tablet
	1141157136	dilcardia sr 60mg m/r capsule
	1140879806	diltiazem
	1140926778	diltiazem hcl+hydrochlorothiazide 150mg/12.5mg m/r capsule
	1140861166	dilzem sr 60mg long acting m/r capsule
	1141185444	disogram sr 60mg m/r capsule
	1141180238	horizem sr 90mg m/r capsule
	1140923618	kentiazem 60mg m/r capsule
	1141156656	optil 60mg m/r tablet
	1140911698	slozem 120mg m/r capsule
	1140861128	tildiem 60mg m/r tablet
	1141151474	viazem xl 120mg m/r capsule
	1141174684	zemret 180 xl m/r capsule
	1141167832	zemtard 120 xl m/r capsule
	1141171804	zildil sr 60mg m/r capsule
Other calcium-channel blockers	1141153394	mibefradil
	1141153400	posicor 50mg tablet

eTable 2. Full regression models for the association of calcium-channel blocker use with glaucoma and intraocular pressure in the UK Biobank

Variable	Glaucoma (%) (n = 427 480)				IOP (mmHg) (n = 97 100)			
	OR	95% CI	*P*-value	VIF	Beta	95% CI	*P*-value	VIF
CCB use	1.39	1.14, 1.69	.001	1.16	-0.01	-0.09, 0.07	.84	1.19
Age (per year)	1.12	1.10, 1.13	<.001	33.95	0.07	0.06, 0.07	<.001	57.92
Male sex	1.15	0.98, 1.33	.08	2.03	0.56	0.52, 0.61	<.001	2.06
Ethnicity								
White	Reference				Reference			
Asian	1.63	1.07, 2.49	.02	1.05	0.08	-0.04, 0.20	.18	1.12
Black	2.49	1.67, 3.71	<.001	1.06	0.93	0.81, 1.06	<.001	1.13
Other/Mixed	1.78	1.12, 2.83	.01	1.04	-0.01	-0.14, 0.13	.94	1.07
Education level								
Less than O-level	Reference				Reference			
O-level	1.16	0.96, 1.39	.13	1.63	0.15	0.09, 0.21	<.001	1.70
A-level	1.08	0.83, 1.39	.58	1.33	0.14	0.06, 0.21	<.001	1.41
Degree	1.02	0.85, 1.23	.81	1.98	0.14	0.08, 0.19	<.001	2.29
TDI (per unit)	1.04	1.01, 1.06	.002	1.34	0.00	-0.01, 0.00	.37	1.26
Diabetes	1.67	1.34, 2.10	<.001	1.19	0.24	0.15, 0.34	<.001	1.20
BMI (per kg/m^2)	1.01	0.99, 1.02	.35	28.91	0.02	0.02, 0.03	<.001	41.48
Total cholesterol (per mmol/L)	0.95	0.89, 1.01	.13	24.40	0.15	0.13, 0.17	<.001	29.12
Smoking status								
Never	Reference				Reference			
Former	0.97	0.83, 1.13	.70	1.75	-0.10	-0.15, -0.06	<.001	1.75
Current	0.97	0.75, 1.26	.82	1.24	-0.41	-0.48, -0.33	<.001	1.24
Alcohol consumption frequency								
Never or special occasions only	Reference				Reference			
1–3 times per month	0.81	0.63, 1.05	.12	1.58	0.01	-0.07, 0.09	.76	1.59
1–2 times per week	0.77	0.63, 0.95	.01	2.40	0.12	0.05, 0.19	<.001	2.36
3–4 times per week	0.79	0.63, 0.98	.03	2.38	0.27	0.20, 0.34	<.001	2.32
Daily or almost daily	0.74	0.59, 0.93	.009	2.34	0.43	0.36, 0.51	<.001	2.31

Final multivariable regression models adjusted for age (years), sex (women, men), self-reported ethnicity (White, Asian, Black, Other/Mixed), education level (less than O-level, O-level, A-level, degree), Townsend deprivation index (units), diabetes (no, yes), body mass index (kg/m^2), total cholesterol (mmol/L), smoking status (never, former, current), and alcohol consumption frequency (never or special occasion only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily or almost daily).
BMI, body mass index; CCB, calcium-channel blocker; CI, confidence interval; IOP, intraocular pressure; OR, odds ratio; SBP, systolic blood pressure; TDI, Townsend deprivation index; VIF, variance inflation factor.

eTable 3. Full regression models for the association of calcium-channel blocker use with OCT-derived inner retinal parameters in the UK Biobank

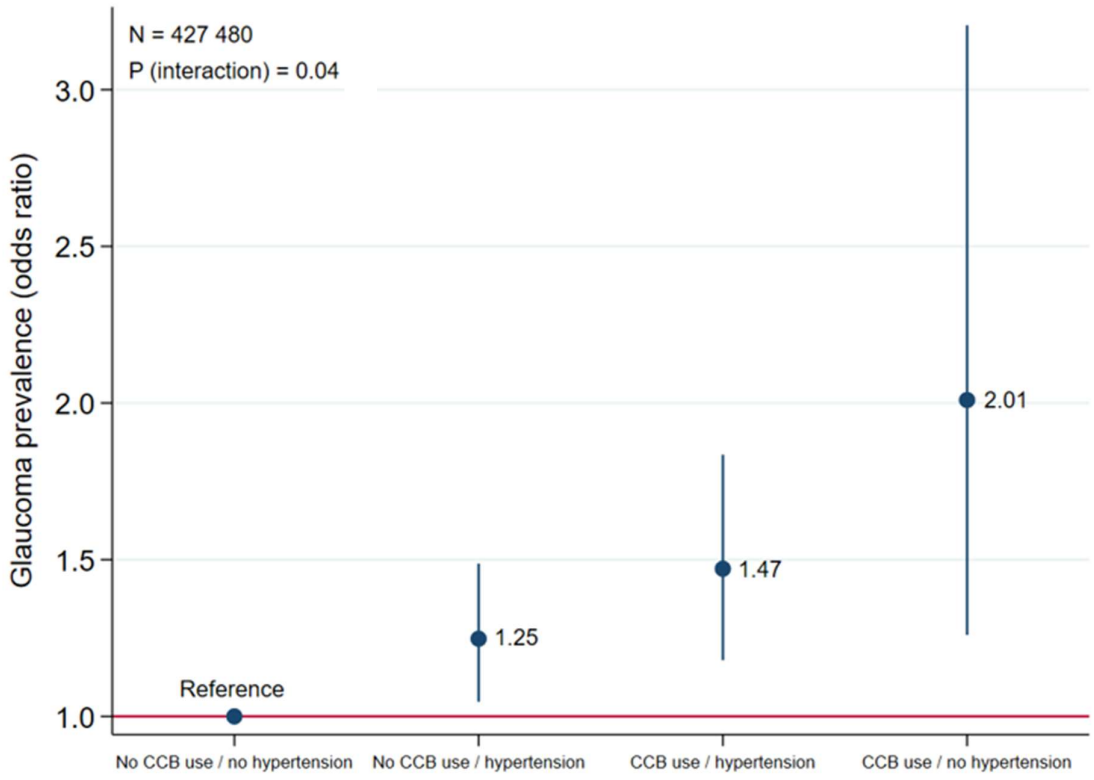
Variable	mGCIPL thickness (µm) (n = 40 486)				mRNFL thickness (µm) (n = 40 583)			
	Beta	**95% CI**	***P*-value**	**VIF**	**Beta**	**95% CI**	***P*-value**	**VIF**
CCB use	-0.34	-0.54, -0.15	.001	1.18	-0.16	-0.30, -0.02	.03	1.18
Age (per year)	-0.12	-0.12, -0.11	<.001	56.31	-0.06	-0.06, -0.05	<.001	56.31
Male sex	-0.10	-0.20, 0.01	.07	2.09	-0.60	-0.68, -0.52	<.001	2.09
Ethnicity								
White	Reference				Reference			
Asian	-1.20	-1.52, -0.89	<.001	1.09	-1.03	-1.26, -0.80	<.001	1.09
Black	-0.25	-0.56, 0.06	.11	1.12	-1.65	-1.88, -1.43	<.001	1.12
Other/Mixed	0.29	-0.03, 0.60	.07	1.07	-0.42	-0.65, -0.19	<.001	1.07
Education level								
Less than O-level	Reference				Reference			
O-level	-0.07	-0.21, 0.07	.32	1.72	0.25	0.14, 0.35	<.001	1.72
A-level	-0.15	-0.32, 0.03	.10	1.43	0.52	0.39, 0.65	<.001	1.43
Degree	-0.21	-0.34, -0.08	.001	2.31	0.59	0.50, 0.69	<.001	2.30
TDI (per unit)	-0.04	-0.06, -0.02	<.001	1.26	-0.02	-0.03, -0.01	.004	1.26
Diabetes	-0.24	-0.48, 0.00	.05	1.17	-0.38	-0.55, -0.20	<.001	1.17
BMI (per kg/m^2)	-0.03	-0.04, -0.02	<.001	42.38	-0.03	-0.04, -0.02	<.001	42.42
Total cholesterol (per mmol/L)	0.11	0.06, 0.15	<.001	29.76	-0.01	-0.04, 0.03	.68	29.74
Smoking status								
Never	Reference				Reference			
Former	0.09	-0.02, 0.20	.11	1.76	-0.04	-0.12, 0.04	.33	1.76
Current	0.26	0.09, 0.44	.003	1.24	-0.16	-0.29, -0.03	.02	1.24
Alcohol consumption frequency								
Never or special occasions only	Reference				Reference			
1–3 times per month	0.01	-0.18, 0.20	.92	1.62	0.08	-0.06, 0.22	.25	1.61
1–2 times per week	-0.04	-0.19, 0.12	.63	2.42	0.06	-0.05, 0.18	.29	2.43
3–4 times per week	-0.24	-0.40, -0.07	.004	2.39	-0.04	-0.16, 0.08	.48	2.39
Daily or almost daily	-0.56	-0.73, -0.40	<.001	2.38	-0.12	-0.25, 0.00	.049	2.38

Final multivariable regression models adjusted for age (years), sex (women, men), self-reported ethnicity (White, Asian, Black, Other/Mixed), education level (less than O-level, O-level, A-level, degree), Townsend deprivation index (units), diabetes (no, yes), body mass index (kg/m^2), total cholesterol (mmol/L), smoking status (never, former, current), and alcohol consumption frequency (never or special occasion only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily or almost daily).
BMI, body mass index; CCB, calcium-channel blocker; CI, confidence interval; mGCIPL, macular ganglion cell-inner plexiform layer; mRNFL, macular retinal nerve fiber layer; OCT, optical coherence tomography; OR, odds ratio; SBP, systolic blood pressure; TDI, Townsend deprivation index.

eTable 4. Sensitivity analyses: association of calcium-channel blocker use with glaucoma status in the UK Biobank

Glaucoma case definition	Cases / controls	Model A[1]			Model B[2]		
		Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Any ICD-coded glaucoma	1 142 / 426 338	1.30	1.10, 1.54	.002	1.30	1.10, 1.53	.003
ICD-coded POAG	416 / 427 064	1.26	0.95, 1.66	.10	1.24	0.94, 1.63	.13
Self-report and/or any ICD-coded glaucoma	6 956 / 144 291	1.11	1.03, 1.20	.005	1.11	1.03, 1.19	.009
Self-report and/or ICD-coded POAG/unspecified glaucoma	6 897 / 144 350	1.12	1.04, 1.20	.004	1.11	1.03, 1.20	.007
Self-report and/or ICD-coded POAG	6 833 / 144 414	1.12	1.04, 1.21	.004	1.11	1.03, 1.20	.007

[1] Model A adjusted for: age (years), sex (women, men), self-reported ethnicity (White, Asian, Black, Other/Mixed), education level (less than O-level, O-level, A-level, degree), Townsend deprivation index (units), diabetes (no, yes), body mass index (kg/m^2), total cholesterol (mmol/L), smoking status (never, former, current), and alcohol consumption frequency (never or special occasion only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily or almost daily).
[2] Model B adjusted for: as for Model A, plus additional adjustment for systolic blood pressure (mmHg).
CI, confidence interval; ICD, International Classification of Disease; POAG, primary open-angle glaucoma.



eFigure 1. Interaction of calcium-channel blocker use and hypertension for the association with glaucoma in the UK Biobank

Based on a multivariable logistic regression model including a multiplicative interaction term between calcium-channel blocker use and a history of physician-diagnosed hypertension, and adjusted for: age (years), sex (women, men), self-reported ethnicity (White, Asian, Black, Other/Mixed), education level (less than O-level, O-level, A-level, degree), Townsend deprivation index (units), diabetes (no, yes), body mass index (kg/m^2), total cholesterol (mmol/L), smoking status (never, former, current), alcohol consumption frequency (never or special occasion only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily or almost daily), and systolic blood pressure (mmHg).
CCB, calcium-channel blocker.

eReferences

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STROBE reporting guidelines checklist

	Item	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15