JAMA Ophthalmology | Original Investigation

Calcium Channel Blocker Use and Associated Glaucoma and Related Traits Among UK Biobank Participants

Alan Kastner, MD, MSc; Kelsey V. Stuart, MBBCh, MSc; Giovanni Montesano, MD; C. Gustavo De Moraes, MD, PhD; Jae H. Kang, ScD; Janey L. Wiggs, MD, PhD; Louis R. Pasquale, MD; Pirro Hysi, PhD; Sharon Y. L. Chua, PhD; Praveen J. Patel, MD; Paul J. Foster, PhD; Peng T. Khaw, PhD; Anthony P. Khawaja, PhD; for the UK Biobank Eye and Vision Consortium

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 among UK Biobank participants.

DESIGN, SETTING, AND PARTICIPANTS This population-based cross-sectional study included UK Biobank participants with complete data (2006-2010) for analysis of glaucoma status, intraocular pressure (IOP), and optical coherence tomography (OCT)–derived inner retinal layer thicknesses. Data analysis was conducted in January 2023.

EXPOSURE Calcium channel blocker use was assessed in a baseline touchscreen questionnaire and confirmed during an interview led by a trained nurse.

MAIN OUTCOMES AND MEASURES The primary outcome measures included glaucoma status, corneal-compensated IOP, and 2 OCT-derived inner retinal thickness parameters (macular retinal nerve fiber layer [mRNFL] and macular ganglion cell–inner plexiform layer [mGCIPL] thicknesses). We performed logistic regression and linear regression analyses to test for associations with glaucoma status and IOP and OCT-derived inner retinal thickness parameters, respectively.

RESULTS This study included 427 480 adults. Their median age was 58 (IQR, 50-63) years, and more than half (54.1%) were women. There were 33 175 CCB users (7.8%). Participants who had complete data for glaucoma status (n = 427 480), IOP (n = 97 100), and OCT-derived inner retinal layer thicknesses (n = 41 023) were eligible for respective analyses. After adjustment for key sociodemographic, medical, anthropometric, and lifestyle factors, use of CCBs (but not other antihypertensive agents) was associated with greater odds of glaucoma (odds ratio [OR], 1.39 [95% CI, 1.14 to 1.69]; $P = .001$). Calcium channel blocker use was also associated with thinner mGCIPL (−0.34 µm [95% CI, −0.54 to −0.15 µm]; $P = .001$) and mRNFL (−0.16 µm [95% CI, −0.30 to −0.02 µm]; $P = .03$) thicknesses but not IOP (−0.01 mm Hg [95% CI, −0.09 to 0.07 mm Hg]; $P = .84$).

CONCLUSIONS AND RELEVANCE In this study, an adverse association between CCB use and glaucoma was observed, with CCB users having, on average, 39% higher odds of glaucoma. Calcium channel blocker use was also associated with thinner mGCIPL and mRNFL thicknesses, providing a structural basis that supports the association with glaucoma. The lack of association of CCB use with IOP suggests that an IOP-independent mechanism of glaucomatous neurodegeneration may be involved. Although a causal relationship has not been established, CCB replacement or withdrawal may be considered should glaucoma progress despite optimal care.

Invited Commentary

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A full list of members of the UK Biobank Eye and Vision Consortium appears in Supplement 2.

Corresponding Author: Alan Kastner, MD, MSc, Clínica Oftalmológica Pasteur, Avenida Luis Pasteur 5917, Vitacura, Santiago 7640671, Chile (alankastner@gmail.com).

JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2023.3877
Published online September 7, 2023.

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

In a large exploratory study of insurance claims data in the US, CCB use was associated with incident glaucoma requiring a procedural treatment.[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 race and ethnicity and comorbidities, this result is consistent with several previous population-based studies that have demonstrated similar associations.[4-7]

Given the global prevalence of both hypertension and glaucoma[8,9] and the fact that the 2 conditions frequently coexist,[4,10] this association may have important clinical implications for millions of individuals worldwide and warrants further investigation. This association may be particularly relevant in aging and older populations, such as in the UK and US, where multimorbidity is a common occurrence.[11]

Limited experimental data suggest that CCBs may have acute ocular hypotensive activity, 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 pathophysiologic mechanisms. Additionally, the use of objective structural glaucoma-related biomarkers may mitigate misclassification bias and help validate any observed associations with glaucoma.

We aimed to examine the association of CCB use with glaucoma in a large cohort using data from the UK Biobank. We further explored associations of CCB use with IOP and 2 optical coherence tomography (OCT)–derived inner retinal thickness parameters.

Key Points

Question To what extent are systemic calcium channel blockers, a commonly prescribed medication class, associated with glaucoma and clinically relevant related traits?

Findings In this cross-sectional study of 427 480 adult UK Biobank participants, calcium channel blocker use was adversely associated with glaucoma prevalence and optical coherence tomography–derived inner retinal thicknesses but not intraocular pressure.

Meaning These findings suggest that calcium channel blockers may represent an important modifiable risk factor for glaucoma, potentially through an intraocular pressure–independent mechanism.

Methods

This cross-sectional study used data from the UK Biobank. This multisite prospective data resource includes more than half a million participants aged 37 to 73 years at recruitment (2006-2010), with extensive participant phenotyping and a wealth of genetic, proteomic, and metabolomic data (eMethods in Supplement 1).[14-16] Multiple repeat and supplementary assessments, including an eye and vision substudy (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.[18] The UK Biobank was approved by the National Health Service North West Multicentre Research Ethics Committee 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 provided electronic informed consent and were not compensated for their involvement. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Assessment of CCB Use

Calcium channel blocker 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). Antihypertensive agents were grouped according to the following classes: CCBs (dihydropyridine, phenylalkylamine, benzothiazepine, or other), diuretics (thiazide, loop, or potassium-sparing), renin-angiotensin system (RAS) inhibitors (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers), and systemic β-blockers. The full code list comprising the CCB medication class and its subtypes is provided in eTable 1 in Supplement 1. No information was recorded regarding the dosage, frequency, or time each medication was in use.

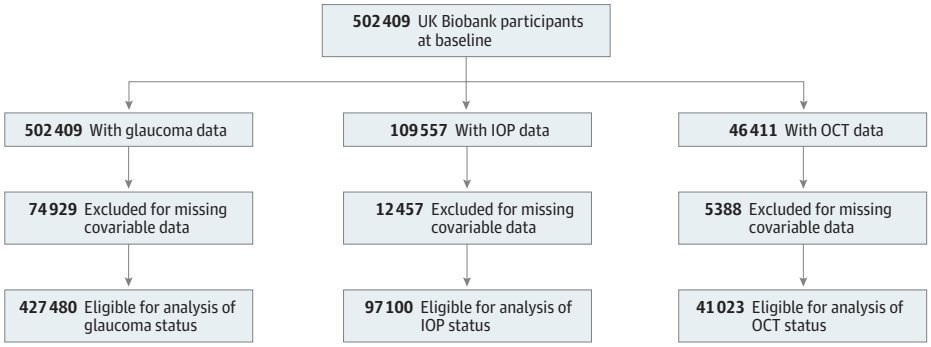
Glaucoma Case Ascertainment

Glaucoma status at the time of the baseline assessment was based on *International Classification of Diseases, Ninth Revision* (*ICD-9*) or *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) codes for eye conditions in participants' linked hospital episode statistics records (eMethods in Supplement 1). For the main analyses, we defined glaucoma cases as participants with an *ICD* code for primary open-angle glaucoma (POAG) or unspecified glaucoma before, or up to 1 year after, the initial visit. During administration of the baseline touchscreen questionnaire (2006-2010), a subset of approximately 175 000 UK Biobank participants were also given the opportunity to self-report a glaucoma diagnosis, a previous history of glaucoma surgery or laser therapy, or the use of ocular hypotensive drops. We considered individuals with a positive response to any of these questions as case participants 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 sub-

Figure. Flowchart Outlining UK Biobank Participants Eligible for This Study



Participants were excluded if they were missing data on the following covariables: age, sex, self-reported race or ethnicity, education level, Townsend Deprivation Index, systolic blood pressure, diabetes, body mass index, total cholesterol, smoking status, and alcohol consumption frequency. IOP indicates intraocular pressure; OCT, optical coherence tomography.

set of participants from 6 assessment centers.[17] This included measurement of IOP in approximately 115 000 participants and macular spectral domain OCT imaging of approximately 65 000 participants (eMethods in Supplement 1). For this analysis, glaucoma-related outcomes included corneal-compensated IOP and 2 inner retinal OCT parameters shown to be useful glaucoma-related biomarkers: macular retinal nerve fiber layer (mRNFL) and macular ganglion cell-inner plexiform layer (mGCIPL) thicknesses.[19,20]

Assessment of Covariables

To account for potential confounding bias, we considered a variety of demographic, lifestyle, and systemic health status variables in our analyses (eMethods in Supplement 1). These variables were selected a priori and included age, sex, self-reported race and ethnicity (Asian, Black, White, multiple races or ethnicities, or other race or ethnicity [specific data for the category "other" were unavailable]), education level, Townsend Deprivation Index, diabetes, body mass index, total plasma cholesterol, smoking status, and alcohol consumption frequency. Race and ethnicity data were included in the analyses, given its known influence in the risk of glaucoma.

Statistical Analysis

Baseline participant characteristics, stratified by CCB use, were described and compared using a 2-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 covariables described in the previous section (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 β-blockers) to gauge whether the observed CCB association was class specific or general 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 further adjusted for mean systolic blood pressure (SBP). Finally, we considered all associations according to 3 CCB subtypes (dihydropyridines, phenylalkylamines, and benzothiazepines).

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 or 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 race and ethnicity by testing the significance of a multiplicative interaction term added to the final multivariable regression models. To address the possibility that ocular hypotensive medication may affect IOP, we excluded all participants reporting topical glaucoma therapy use. Finally, we repeated our primary analyses with further adjustment for refractive error (mean spherical equivalent) and a glaucoma polygenic risk score,[21] as these are important estimators of glaucoma status.

All statistical analyses were performed using Stata, version 17.0 (StataCorp LLC). *P* values were 2 sided and were not adjusted for multiple comparisons. Data analysis was conducted in January 2023.

Results

Participant Characteristics

We selected a total of 427 480 participants for this study as outlined in the **Figure**. Their median age was 58 (IQR, 50-63) years; 54.1% were women and 45.9% were men. A total of 1.8% of participants self-identified as Asian, 1.6% as Black, 94.8% as White, and 1.8% as other or multiple races and ethnicities. Participants who had complete data for glaucoma status (n = 427 480), IOP (n = 97 100), and OCT-derived inner retinal layer thicknesses (n = 41 023 [40 486 and 40 583 for mGCIPL and mRNFL thickness, respectively]) were eligible for respective analyses. Of all included participants, 114 311 (26.7%) had a history of physician-diagnosed systemic hypertension and 33 175 (7.8%) were CCB users (29 508 had hypertension [89.0%] and 3667 did not [11.0%]).

Baseline participant characteristics, stratified by CCB use, are presented in **Table 1**. We observed that CCB users were more likely to be older, male, and Black and to have lower education levels, higher Townsend Deprivation Index values, hypertension, diabetes, higher SBP, higher body mass index, and lower total cholesterol than nonusers.

Table 1. Characteristics of Eligible UK Biobank Participants[a]

Characteristic	Participant group		Difference (95% CI)	*P* value
	CCB users (n = 33 175)	CCB nonusers (n = 394 305)		
Age, y, mean (SD)	61.2 (6.2)	56.1 (8.1)	5.0 (4.9 to 5.1)	<.001
Sex				
Women	13 473 (40.6)	217 860 (55.3)	−14.6 (−15.2 to −14.1)	<.001
Men	19 702 (59.4)	176 445 (44.7)	14.6 (14.1 to 15.2)	<.001
Race and ethnicity				
Asian	814 (2.5)	7058 (1.8)	0.7 (0.5 to 0.8)	<.001
Black	1211 (3.7)	5406 (1.4)	2.3 (2.1 to 2.5)	<.001
White	30 548 (92.1)	374 853 (95.1)	−3.0 (−3.3 to −2.7)	<.001
Other or multiple races or ethnicities[b]	602 (1.8)	6988 (1.8)	0.0 (−0.1 to 0.2)	.57
Education level[c]				
<O	14 975 (45.1)	131 830 (33.4)	11.7 (11.1 to 12.3)	<.001
O	6792 (20.5)	85 765 (21.8)	−1.3 (−1.7 to −0.8)	<.001
A	3064 (9.2)	45 083 (11.4)	−2.2 (−2.5 to −1.9)	<.001
Undergraduate degree or higher	8344 (25.2)	131 627 (33.4)	−8.2 (−8.7 to −7.7)	<.001
Townsend Deprivation Index, mean (SD)	−1.0 (3.2)	−1.4 (3.0)	0.4 (0.4 to 0.4)	<.001
Hypertension				
No	3667 (11.1)	309 502 (78.5)	−67.4 (−67.8 to −67.1)	<.001
Yes	29 508 (88.9)	84 803 (21.5)	67.4 (67.1 to 67.8)	<.001
Diabetes				
No	27 635 (83.3)	377 109 (95.6)	−12.3 (−12.7 to −11.9)	<.001
Yes	5540 (16.7)	17 196 (4.4)	12.3 (11.9 to 12.7)	<.001
Systolic blood pressure, mm Hg, mean (SD)	145.8 (17.1)	137.1 (18.6)	8.7 (8.5 to 8.9)	<.001
BMI, mean (SD)	29.4 (4.8)	27.2 (4.4)	2.2 (2.2 to 2.3)	<.001
Total plasma cholesterol, mmol/L, mean (SD)	5.2 (1.2)	5.7 (1.1)	−0.6 (−0.6 to −0.5)	<.001
Smoking status				
Never	15 659 (47.2)	218 226 (55.3)	−8.1 (−8.7 to −7.6)	<.001
Former	14 321 (43.2)	135 058 (34.3)	8.9 (8.3 to 9.5)	<.001
Current	3195 (9.6)	41 021 (10.4)	−0.8 (−1.1 to −0.4)	<.001
Alcohol consumption frequency				
Never or special occasions only	7591 (22.9)	73 792 (18.7)	4.2 (3.7 to 4.6)	<.001
1-3 Times/mo	3208 (9.7)	44 222 (11.2)	−1.5 (−1.9 to −1.2)	<.001
1-2 Times/wk	7730 (23.3)	102 561 (26.0)	−2.7 (−3.2 to −2.2)	<.001
3-4 Times/wk	7014 (21.1)	92 701 (23.5)	−2.4 (−2.8 to −1.9)	<.001
Daily or almost daily	7632 (23.0)	81 029 (20.6)	2.5 (2.0 to 2.9)	<.001
Statin use	17 294 (52.1)	56 983 (14.5)	37.7 (37.1 to 38.2)	<.001
Glaucoma prevalence	137 (0.4)	652 (0.2)	0.2 (0.2 to 0.3)	<.001
IOP, mm Hg, mean (SD) (n = 97 100)	16.4 (3.7)	16.0 (3.4)	0.4 (0.3 to 0.5)	<.001
mGCIPL thickness, µm, mean (SD) (n = 40 486)	74.2 (5.3)	75.3 (5.2)	−1.1 (−0.9 to 1.3)	<.001
mRNFL thickness, µm, mean (SD) (n = 40 583)	28.2 (3.8)	29.0 (3.8)	−0.8 (−0.9 to −0.6)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CCB, calcium channel blocker; IOP, intraocular pressure; mGCIPL, macular ganglion cell–inner plexiform layer; mRNFL, macular retinal nerve fiber layer.

[a] Unless stated otherwise, values are presented as No. (%) of participants.

[b] Specific data for the category "other" were unavailable.

[c] Subject-based qualifications conferred in the UK as part of the General Certificate of Education. <O indicates less than ordinary level; O, ordinary level; and A, advanced level.

Lower mean total cholesterol levels among CCB users may be the result of a difference in their statin use compared with nonusers (52.1% vs 14.5%; $P < .001$). Participants reporting CCB use also had a higher prevalence of glaucoma, higher mean IOP, and thinner mean mGCIPL and mRNFL thicknesses than nonusers.

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% CI, 1.10 to 1.52]; $P = .002$). This association appeared to be affected by CCB use (OR, 1.39 [95% CI, 1.14

Table 2. Association of Antihypertensive Medication Use With Glaucoma Among UK Biobank Participants

Description	No. of participants	Model A[a]		Model B[b]	
		Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Any antihypertensive medication	88 007	1.29 (1.10 to 1.52)	.002	NA	NA
Antihypertensive medication class					
Calcium channel blocker	33 175	1.39 (1.14 to 1.69)	.001	1.39 (1.13 to 1.70)	.001
Diuretic	35 099	1.03 (0.84 to 1.28)	.75	0.96 (0.77 to 1.20)	.75
RAS inhibitor	55 983	1.12 (0.93 to 1.34)	.24	1.07 (0.88 to 1.30)	.47
Systemic β-blocker	29 818	0.93 (0.74 to 1.18)	.56	0.90 (0.71 to 1.14)	.39

Abbreviations: NA, not applicable; RAS, renin-angiotensin system.

[a] Model A was adjusted for age (in years), sex (female or male), self-reported race and ethnicity (Asian, Black, White, multiple races or ethnicities, and other race or ethnicity [specific data for the category "other" were unavailable]), education level (<O [less than ordinary level], O [ordinary level], A [advanced level], or undergraduate degree or higher), Townsend Deprivation Index (in units), diabetes (no or yes), body mass index (calculated as weight in kilograms divided by height in meters squared), total cholesterol (in millimoles per liter), smoking status (never, former, or current), and alcohol consumption frequency (never or special occasion only, 1-3 times/mo, 1-2 times/wk, 3-4 times/wk, or daily or almost daily).

[b] Model B was adjusted as for model A plus additional adjustment for systolic blood pressure (in millimeters of mercury) and simultaneous use of other antihypertensive medications.

Table 3. Association of Calcium Channel Blocker Use With Glaucoma and Related Traits Among UK Biobank Participants

Outcome	No. of participants	Model A[a]		Model B[b]	
		Effect estimate (95% CI)	*P* value	Effect estimate (95% CI)	*P* value
Glaucoma, odds ratio	427 480	1.39 (1.14 to 1.69)	.001	1.39 (1.14 to 1.69)	.001
IOP, mm Hg	97 100	−0.01 (−0.09 to 0.07)	.84	−0.15 (−0.23 to −0.07)	<.001
mGCIPL thickness, µm	40 486	−0.34 (−0.54 to −0.15)	.001	−0.31 (−0.50 to −0.11)	.001
mRNFL thickness, µm	40 583	−0.16 (−0.30 to −0.02)	.03	−0.14 (−0.29 to 0.00)	.049

Abbreviations: IOP, intraocular pressure; mGCIPL, macular ganglion cell–inner plexiform layer; mRNFL, macular retinal nerve fiber layer.

[a] Model A was adjusted for age (in years), sex (female or male), self-reported race and ethnicity (Asian, Black, White, multiple races or ethnicities, and other race or ethnicity [specific data for the category "other" were unavailable]), education level (<O [less than ordinary level], O [ordinary level], A [advanced level], or undergraduate degree or higher), Townsend Deprivation Index (in units), diabetes (no or yes), body mass index (calculated as weight in kilograms divided by height in meters squared), total cholesterol (in millimoles per liter), smoking status (never, former, or current), and alcohol consumption frequency (never or special occasion only, 1-3 times/mo, 1-2 times/wk, 3-4 times/wk, or daily or almost daily).

[b] Model B was adjusted as for model A plus additional adjustment for systolic blood pressure (in millimeters of mercury).

to 1.69]; *P* = .001), with no association demonstrated for use of diuretics (35 099 users; OR, 1.03 [95% CI, 0.84 to 1.28]; *P* = .75), RAS inhibitors (55 983 users; OR, 1.12 [95% CI, 0.93 to 1.34]; *P* = .24), or systemic β-blockers (29 818 users; OR, 0.93 [95% CI, 0.74 to 1.18]; *P* = .56) (**Table 2**). Associations were materially unchanged when additionally adjusting for SBP and concurrent use of more than 1 antihypertensive medication class.

Association of CCB Use With Glaucoma and Related Traits

Associations 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 in the model. Calcium channel blocker 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 CCB use had thinner mGCIPL (−0.34 µm [95% CI, −0.54 to −0.15 µm]; *P* = .001) and mRNFL (−0.16 µm [95% CI, −0.30 to −0.02 µm]; *P* = .03) thicknesses than nonusers. In maximally adjusted regression models, CCB use was not associated with IOP (−0.01 mm Hg [95% CI, −0.09 to 0.07 mm Hg]; *P* = .84). Further adjustment for SBP, however, resulted in an association with lower IOP (−0.15 mm Hg [95% CI, −0.23 to −0.07 mm Hg]; *P* < .001). Complete results of the models for glaucoma status, IOP, and OCT-derived inner retinal parameters are presented in eTables 2 and 3 in Supplement 1.

Association of CCB Subtypes With Glaucoma and Related Traits

Dihydropyridines (eg, amlodipine) were the most commonly used CCB subtype (29 314 [88.4%]), followed by benzothiazepines (eg, diltiazem; 3022 [9.1%]) and phenylalkylamines (eg, verapamil; 951 [2.9%]). There were no uses of other CCBs. 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 (−0.51 mm Hg [95% CI, −0.77 to −0.24]; *P* < .001) but no association with mGCIPL or mRNFL thickness. No associations were observed for phenylalkylamine users.

Sensitivity Analysis

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

Table 4. Association of CCB Subtypes With Glaucoma and Related Traits Among UK Biobank Participants

	CCB user subtype					
	Dihydropyridine (n = 29 314)		Phenylalkylamine (n = 951)		Benzothiazepine (n = 3022)	
Outcome	Effect estimate (95% CI)	*P* value	Effect estimate (95% CI)	*P* value	Effect estimate (95% CI)	*P* value
Model A[a]						
Glaucoma, odds ratio	1.33 (1.08 to 1.63)	.007	0.99 (0.32 to 3.09)	.99	1.80 (1.14 to 2.86)	.01
IOP, mm Hg	0.03 (−0.05 to 0.11)	.45	0.17 (−0.28 to 0.63)	.46	−0.51 (−0.77 to −0.24)	<.001
mGCIPL thickness, μm	−0.36 (−0.57 to −0.16)	<.001	−0.78 (−1.82 to 0.25)	.14	0.13 (−0.52 to 0.77)	.70
mRNFL thickness, μm	−0.17 (−0.32 to −0.02)	.02	0.01 (−0.75 to 0.77)	.98	−0.10 (−0.57 to 0.37)	.68
Model B[b]						
Glaucoma, odds ratio	1.33 (1.08 to 1.64)	.006	0.99 (0.32 to 3.09)	.99	1.80 (1.14 to 2.86)	.01
IOP, mm Hg	−0.12 (−0.20 to −0.04)	.005	0.11 (−0.34 to 0.56)	.62	−0.50 (−0.76 to −0.23)	<.001
mGCIPL thickness, μm	−0.32 (−0.53 to −0.12)	.002	−0.76 (−1.80 to 0.27)	.15	0.12 (−0.53 to 0.76)	.73
mRNFL thickness, μm	−0.16 (−0.30 to −0.01)	.04	0.01 (−0.74 to 0.77)	.97	−0.11 (−0.58 to 0.37)	.66

Abbreviations: CCB, calcium channel blocker; IOP, intraocular pressure; mGCIPL, macular ganglion cell–inner plexiform layer; mRNFL, macular retinal nerve fiber layer.

[a] Model A was adjusted for age (in years), sex (female or male), self-reported race and ethnicity (Asian, Black, White, multiple races or ethnicities, and other race or ethnicity [specific data for the category "other" were unavailable]), education level (<O [less than ordinary level], O [ordinary level], A [advanced level], or undergraduate degree or higher), Townsend Deprivation Index (in units), diabetes (no or yes), body mass index (calculated as weight in kilograms divided by height in meters squared), total cholesterol (in millimoles per liter), smoking status (never, former, or current), and alcohol consumption frequency (never or special occasion only, 1-3 times/mo, 1-2 times/wk, 3-4 times/wk, or daily or almost daily).

[b] Model B was adjusted as for model A plus additional adjustment for systolic blood pressure (in millimeters of mercury).

There was evidence that the association between CCB use and glaucoma was modified by a history of physician-diagnosed hypertension (eFigure in Supplement 1). In the maximally adjusted regression model, including adjustment for baseline SBP, CCB use among 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 among 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 of sex or race and ethnicity for the association with glaucoma. Results for IOP were materially unchanged when analyses were restricted to participants not using ocular hypotensive agents (−0.06 mm Hg [95% CI, −0.13 to 0.01]; *P* = .15). Further adjustment for the 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 observed that CCB users had, on average, 39% higher odds of glaucoma than nonusers after controlling for multiple potential confounders. Consistent with this finding, we also noted that mGCIPL and mRNFL (both objective structural glaucoma-related parameters) were thinner in CCB users. Calcium channel blocker use was not associated with IOP in this study.

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 largest adverse statistical association with glaucoma of 423 different medication classes.[3] Similarly, amlodipine (a dihydropyridine CCB) had the largest statistical association with glaucoma of all 1723 unique generic medications studied.[3] However, that analysis was limited by a lack of data on potential confounders, which may have resulted in biased findings. For example, participant race and ethnicity was not available and the observed association may have been affected by a higher prevalence of CCB use among individuals of African ancestry (an important risk factor for glaucoma), for whom CCBs are standard first-line therapy.[22]

Our analyses provide further large-scale evidence supporting those previously reported associations and suggest that the adverse association between CCB use and glaucoma risk may act via IOP-independent mechanisms. Although our primary analyses were based on a strict case definition that is likely to underestimate true prevalence, sensitivity analyses using less specific glaucoma definitions and conducted among up to 7000 case patients (including >900 CCB users) demonstrated similar associations.

To 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 in Southeast Asia found no association between CCB use and mean mGCIPL or peripapillary retinal nerve fiber layer thickness.[23] Our reported effect estimates for mGCIPL and mRNFL thicknesses may seem small; yet on a population level, they are equivalent to the average difference seen between participants separated by 4 years in age.[24]

Limited experimental data suggest that systemic CCBs may have acute ocular hypotensive activity, especially in individuals with glaucoma.[12,13] However, this is not always a consistent finding.[25] We observed no difference in mean IOP between CCB users and nonusers. However, this may be because the IOP assessment was limited to a single measurement, and we cannot fully exclude the possibility of a small association between CCB use and IOP. This result is consistent with a recent large meta-analysis of European population-based eye studies that also found an adverse association between CCB use and glaucoma

status but none with IOP.[7] It is also important to note that our study lacked data on the length, frequency, or dosage of CCB use and whether the medication was taken on the day of IOP assessment; our findings may therefore not fully account for the potential consequences 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 are directly detrimental to retinal tissue is contrary to the general view of these agents being neuroprotective. In vitro studies have shown that CCBs exert protection on neurons undergoing apoptosis and necrosis, which has also been documented in retinal ganglion cells and photoreceptors in experimental animal models.[26] 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.[27-30] Although 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 ability of CCBs, and the CCBs investigated in the visual field studies did not appreciably affect blood pressure in glaucoma cases. It may be that the detrimental consequences of CCBs only manifest when coupled with the hypotensive and/or vasodilatory properties of certain CCBs, such as amlodipine.[26] The results of our interaction sensitivity analysis provide support for this hypothesis. We observed that CCB use was associated with higher odds of glaucoma in individuals without hypertension compared with participants with hypertension, suggesting that a history of higher blood pressure may partially ameliorate the adverse association with glaucoma. Although adverse associations with glaucoma were demonstrated for both dihydropyridine and benzothiazepine users, we observed no evidence of an adverse association with phenylalkylamine CCBs (which are relatively selective for the myocardium and have little effect on systemic blood pressure); however, 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.[31,32]

Strengths and Limitations

This study has several strengths. The first is its large sample size, which allowed for the detection of small but meaningful differences between CCB users and nonusers. 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 known to affect 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 was 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 substantial proportion of true case patients with glaucoma who may not be captured in a hospital-based database. In contrast, self-report may identify more case patients 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 its 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. Finally, the majority of UK Biobank participants (almost 95%) are White, so our findings may not be generalizable to other populations.

Conclusions

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

ARTICLE INFORMATION

Accepted for Publication: July 10, 2023.

Published Online: September 7, 2023. doi:10.1001/jamaophthalmol.2023.3877

Author Affiliations: National Institute for Health and Care Research Biomedical Research Centre, Moorfields Eye Hospital National Health Service Foundation Trust and University College London Institute of Ophthalmology, London, United Kingdom (Kastner, Stuart, Montesano, Chua, Patel, Foster, Khaw, Khawaja); Clínica Oftalmológica Pasteur, Santiago, Chile (Kastner); Division of Optometry and Vision Science, City University of London, London, United Kingdom (Montesano); Department of Ophthalmology, Edward S. Harkness Eye Institute, Columbia University Irving Medical Center, New York, New York (De Moraes); Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Kang); Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, Massachusetts (Wiggs); Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, New York (Pasquale); Department of Ophthalmology, King's College London, St Thomas' Hospital, London, United Kingdom (Hysi); Department of Twin Research and Genetic Epidemiology, King's College London, St Thomas' Hospital, London, United Kingdom (Hysi).

Author Contributions: Drs Kastner and Stuart had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Kastner and Stuart also serve as co–first authors.

Concept and design: Kastner, Stuart, De Moraes, Foster, Khaw, Khawaja.
Acquisition, analysis, or interpretation of data: Kastner, Stuart, Montesano, De Moraes, Kang, Wiggs, Pasquale, Hysi, Chua, Patel, Foster, Khawaja.
Drafting of the manuscript: Kastner, Stuart, Montesano, Khawaja.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Kastner, Stuart, Montesano, De Moraes, Kang, Hysi.
Obtained funding: Foster, Khaw, Khawaja.
Administrative, technical, or material support: Chua, Foster, Khaw.
Supervision: De Moraes, Pasquale, Foster, Khawaja.

Conflict of Interest Disclosures: Dr Wiggs reported receiving consulting fees from Aerpio, Allergan, Editas, Maze, and Regenxbio outside the

submitted work. Dr Pasquale receiving consulting fees from Eyenovia, Twenty, Skye Biosciences, and Character Biosciences outside the submitted work. Dr Foster reported receiving consulting fees from Alphasights, GLG, Google Health, Guidepoint, PwC, and Santen outside the submitted work. Dr Khaw reported receiving consulting fees from Aerie, Alcon, Allergan, Novartis, Pfizer, and Sanofi-Aventis outside the submitted work. Dr Khawaja reported receiving consulting or lecture fees from AbbVie, Aerie, Allergan, Google Health, Heidelberg Novartis, Reichert, Santen, and Thea outside the submitted work. No other disclosures were reported.

Funding/Support: Dr Stuart was supported by a University College London UCL Overseas Research Scholarship, Fight for Sight (grant 1956A), and the Desmond Foundation. Dr Kang was supported by the US National Institutes of Health (NIH). Dr Wiggs was supported by the NIH (grants EY032559, EY027129, EY014104, EY022305, EY020928, and EY031820), Research to Prevent Blindness, and the ARVO Foundation (David Epstein Award). Dr Pasquale was supported by the Glaucoma Foundation, Research to Prevent Blindness, and the NIH (grants EY015473 and EY032559). Dr Foster was supported by Alcon, Fight for Sight (grant 1956A), and the Desmond Foundation. Dr Khaw was supported by the Helen Hamlyn Trust, the Ilse and Michael Katz Foundation, and a personal donation from John Nolan to Moorfields Eye Charity. Dr Khawaja was supported by UK Research and Innovation (Future Leaders Fellowship MR/T040912/1), a Moorfields Eye Charity Career Development Fellowship, and a Lister Institute of Preventative Medicine Fellowship. Drs Foster, Khaw, and Khawaja received financial support from the UK Department of Health through an award made by the National Institute for Health and Care Research to Moorfields Eye Hospital National Health Service Foundation Trust and UCL Institute of Ophthalmology for a Biomedical Research Centre for Ophthalmology.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: A full list of members of the UK Biobank Eye and Vision Consortium appears in Supplement 2.

Meeting Presentation: Preliminary results of this research were presented at the annual meeting of the Association for Research in Vision and Ophthalmology; May 3-7, 2020; Baltimore, Maryland.

Data Sharing Statement: See Supplement 3.

REFERENCES

1. Shemin DG, Dworkin LD. Calcium channel blockers. In: Wilcox CS, ed. *Therapy in Nephrology and Hypertension*. 3rd ed. W. B. Saunders; 2008:610-619. doi:10.1016/B978-141605484-9.50055-1

2. Audi S, Burrage DR, Lonsdale DO, et al. The 'top 100' drugs and classes in England: an updated 'starter formulary' for trainee prescribers. *Br J Clin Pharmacol*. 2018;84(11):2562-2571. doi:10.1111/bcp.13709

3. Zheng W, Dryja TP, Wei Z, et al. Systemic medication associations with presumed advanced or uncontrolled primary open-angle glaucoma. *Ophthalmology*. 2018;125(7):984-993. doi:10.1016/j.ophtha.2018.01.007

4. Langman MJS, Lancashire RJ, Cheng KK, Stewart PM. Systemic hypertension and glaucoma: mechanisms in common and co-occurrence. *Br J Ophthalmol*. 2005;89(8):960-963. doi:10.1136/bjo.2004.053397

5. Müskens RPHM, de Voogd S, Wolfs RCW, et al. Systemic antihypertensive medication and incident open-angle glaucoma. *Ophthalmology*. 2007;114(12):2221-2226. doi:10.1016/j.ophtha.2007.03.047

6. Asefa NG, Neustaeter A, Jansonius NM, Snieder H. Autonomic dysfunction and blood pressure in glaucoma patients: the Lifelines Cohort Study. *Invest Ophthalmol Vis Sci*. 2020;61(11):25. doi:10.1167/iovs.61.11.25

7. Vergroesen JE, Schuster AK, Stuart KV, et al; European Eye Epidemiology Consortium. Association of systemic medication use with glaucoma and intraocular pressure. *Ophthalmology*. Published online May 6, 2023.

8. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121(11):2081-2090. doi:10.1016/j.ophtha.2014.05.013

9. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. 2020;16(4):223-237. doi:10.1038/s41581-019-0244-2

10. Tham YC, Cheng CY. Associations between chronic systemic diseases and primary open angle glaucoma: an epidemiological perspective. *Clin Exp Ophthalmol*. 2017;45(1):24-32. doi:10.1111/ceo.12763

11. Salive ME. Multimorbidity in older adults. *Epidemiol Rev*. 2013;35:75-83. doi:10.1093/epirev/mxs009

12. Schnell D. Effect response of intraocular pressure in normal subjects and glaucoma patients to single and repeated doses of the coronary drug Adalat. In: Lochner W, Braasch W, Kroneberg G, eds. *Proceedings of the 2nd International Adalat Symposium: New Therapy of Ischemic Heart Disease*. Springer; 1975:290-302.

13. Monica ML, Hesse RJ, Messerli FH. The effect of a calcium-channel blocking agent on intraocular pressure. *Am J Ophthalmol*. 1983;96(6):814. doi:10.1016/S0002-9394(14)71934-8

14. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779. doi:10.1371/journal.pmed.1001779

15. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562(7726):203-209. doi:10.1038/s41586-018-0579-z

16. Elliott P, Peakman TC; UK Biobank. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. *Int J Epidemiol*. 2008;37(2):234-244. doi:10.1093/ije/dym276

17. Chua SYL, Thomas D, Allen N, et al; UK Biobank Eye & Vision Consortium. Cohort profile: design and methods in the eye and vision consortium of UK Biobank. *BMJ Open*. 2019;9(2):e025077. doi:10.1136/bmjopen-2018-025077

18. Biobank UK. UK Biobank study. Accessed January 10, 2023. https://biobank.ndph.ox.ac.uk/showcase/

19. Kim KE, Park KH. Macular imaging by optical coherence tomography in the diagnosis and management of glaucoma. *Br J Ophthalmol*. 2018;102(6):718-724. doi:10.1136/bjophthalmol-2017-310869

20. Oddone F, Lucenteforte E, Michelessi M, et al. Macular versus retinal nerve fiber layer parameters for diagnosing manifest glaucoma: a systematic review of diagnostic accuracy studies. *Ophthalmology*. 2016;123(5):939-949. doi:10.1016/j.ophtha.2015.12.041

21. Craig JE, Han X, Qassim A, et al; NEIGHBORHOOD Consortium; UK Biobank Eye and Vision Consortium. Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression. *Nat Genet*. 2020;52(2):160-166. doi:10.1038/s41588-019-0556-y

22. Brewster LM, Seedat YK. Why do hypertensive patients of African ancestry respond better to calcium blockers and diuretics than to ACE inhibitors and β-adrenergic blockers? a systematic review. *BMC Med*. 2013;11:141. doi:10.1186/1741-7015-11-141

23. Chong RS, Chee ML, Tham YC, et al. Association of antihypertensive medication with retinal nerve fiber layer and ganglion cell–inner plexiform layer thickness. *Ophthalmology*. 2021;128(3):393-400. doi:10.1016/j.ophtha.2020.07.051

24. Khawaja AP, Chua S, Hysi PG, et al; UK Biobank Eye and Vision Consortium. Comparison of associations with different macular inner retinal thickness parameters in a large cohort: the UK Biobank. *Ophthalmology*. 2020;127(1):62-71. doi:10.1016/j.ophtha.2019.08.015

25. Kelly SP, Walley TJ. Effect of the calcium antagonist nifedipine on intraocular pressure in normal subjects. *Br J Ophthalmol*. 1988;72(3):216-218. doi:10.1136/bjo.72.3.216

26. Araie M, Mayama C. Use of calcium channel blockers for glaucoma. *Prog Retin Eye Res*. 2011;30(1):54-71. doi:10.1016/j.preteyeres.2010.09.002

27. Yamamoto T, Niwa Y, Kawakami H, Kitazawa Y. The effect of nilvadipine, a calcium-channel blocker, on the hemodynamics of retrobulbar vessels in normal-tension glaucoma. *J Glaucoma*. 1998;7(5):301-305. doi:10.1097/00061198-199810000-00002

28. Tomita G, Niwa Y, Shinohara H, Hayashi N, Yamamoto T, Kitazawa Y. Changes in optic nerve head blood flow and retrobular hemodynamics following calcium-channel blocker treatment of normal-tension glaucoma. *Int Ophthalmol*. 1999;23(1):3-10. doi:10.1023/A:1006423919238

29. Luksch A, Rainer G, Koyuncu D, et al. Effect of nimodipine on ocular blood flow and colour contrast sensitivity in patients with normal tension glaucoma. *Br J Ophthalmol*. 2005;89(1):21-25. doi:10.1136/bjo.2003.037671

30. Koseki N, Araie M, Tomidokoro A, et al. A placebo-controlled 3-year study of a calcium blocker on visual field and ocular circulation in glaucoma with low-normal pressure. *Ophthalmology*. 2008;115(11):2049-2057. doi:10.1016/j.ophtha.2008.05.015

31. McElnea EM, Quill B, Docherty NG, et al. Oxidative stress, mitochondrial dysfunction and calcium overload in human lamina cribrosa cells from glaucoma donors. *Mol Vis*. 2011;17:1182-1191.

32. Wojda U, Salinska E, Kuznicki J. Calcium ions in neuronal degeneration. *IUBMB Life*. 2008;60(9):575-590. doi:10.1002/iub.91