Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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

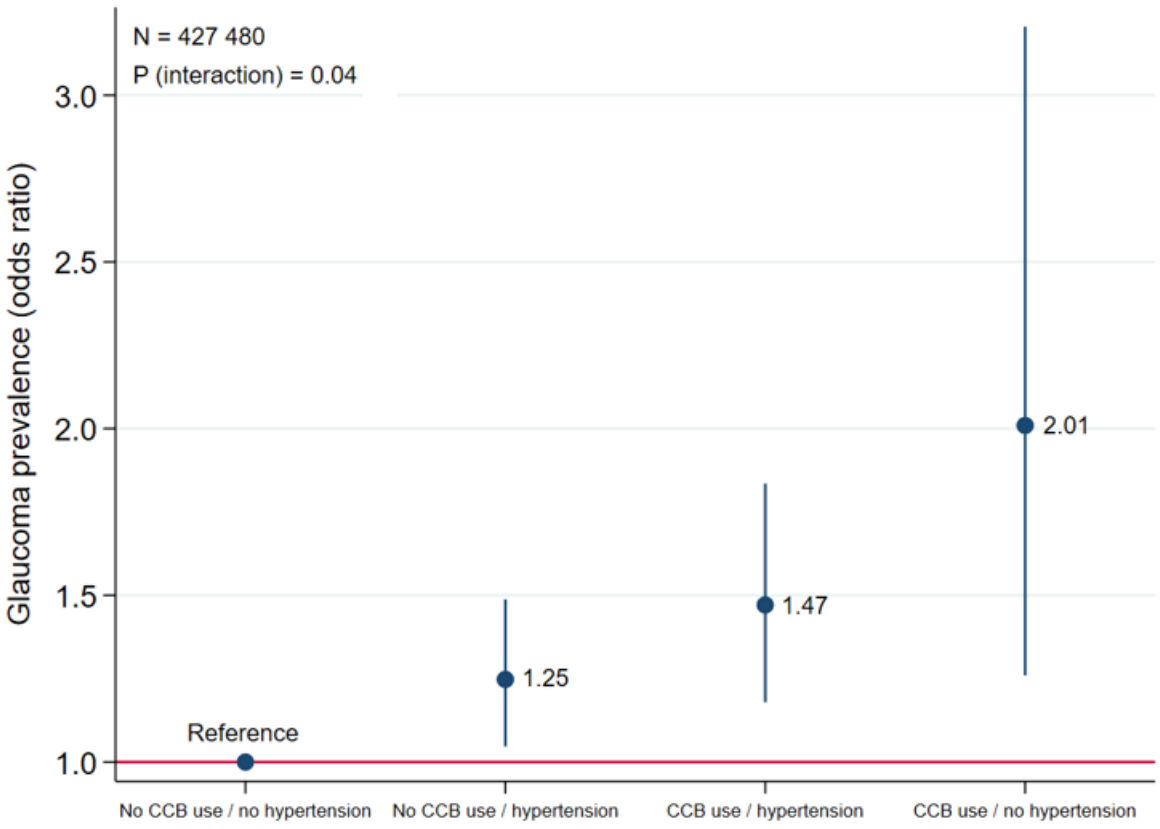
Variable	mGCIPL thickness (µm) (n = 40 486)				mRNFL thickness (µm) (n = 40 583)			
	Beta	**95% CI**	***P*-value**	**VIF**	**Beta**	**95% CI**	***P*-value**	**VIF**
CCB use	-0.34	-0.54, -0.15	.001	1.18	-0.16	-0.30, -0.02	.03	1.18
Age (per year)	-0.12	-0.12, -0.11	<.001	56.31	-0.06	-0.06, -0.05	<.001	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. 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.

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