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Intraocular Pressure, Glaucoma, and Dietary Caffeine Consumption

A Gene–Diet Interaction Study from the UK Biobank

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Purpose: We examined the association of habitual caffeine intake with intraocular pressure (IOP) and glaucoma and whether genetic predisposition to higher IOP modified these associations. We also assessed whether genetic predisposition to higher coffee consumption was related to IOP.

Design: Cross-sectional study in the UK Biobank.

Participants: We included 121 374 participants (baseline ages, 39–73 years) with data on coffee and tea intake (collected 2006–2010) and corneal-compensated IOP measurements in 2009. In a subset of 77 906 participants with up to 5 web-based 24-hour-recall food frequency questionnaires (2009–2012), we evaluated total caffeine intake. We also assessed the same relationships with glaucoma (9286 cases and 189 763 controls).

Methods: We evaluated multivariable-adjusted associations with IOP using linear regression and with glaucoma using logistic regression. For both outcomes, we examined gene–diet interactions using a polygenic risk score (PRS) that combined the effects of 111 genetic variants associated with IOP. We also performed Mendelian randomization using 8 genetic variants associated with coffee intake to assess potential causal effects of coffee consumption on IOP.

Main Outcome Measures: Intraocular pressure and glaucoma.

Results: Mendelian randomization analysis did not support a causal effect of coffee drinking on IOP ($P > 0.1$). Greater caffeine intake was associated weakly with lower IOP: the highest ($\geq$232 mg/day) versus lowest ($<$87 mg/day) caffeine consumption was associated with a 0.10-mmHg lower IOP ($P_{trend} = 0.01$). However, the IOP PRS modified this association: among those in the highest IOP PRS quartile, consuming $>$ 480 mg/day versus $<$ 80 mg/day was associated with a 0.35-mmHg higher IOP ($P_{interaction} = 0.01$). The relationship between caffeine intake and glaucoma was null ($P \geq 0.1$). However, the IOP PRS also modified this relationship: compared with those in the lowest IOP PRS quartile consuming no caffeine, those in the highest IOP PRS quartile consuming $\geq$ 321 mg/day showed a 3.90-fold higher glaucoma prevalence ($P_{interaction} = 0.0003$).

Conclusions: Habitual caffeine consumption was associated weakly with lower IOP, and the association between caffeine consumption and glaucoma was null. However, among participants with the strongest genetic predisposition to elevated IOP, greater caffeine consumption was associated with higher IOP and higher glaucoma prevalence. *Ophthalmology 2021;128:866-876 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.aaojournal.org.

Caffeine consumption, such as from coffee or tea, is a common behavior throughout the world.[1] Keen interest exists in whether caffeine consumption has an intraocular pressure (IOP)-modifying effect,[2] as even modest elevations in ocular tension can increase glaucoma risk.[3] At a population level, small shifts in the distribution of ocular tension could lead to a significant change in the number of people experiencing optic nerve damage. Many studies of healthy persons,[4–13] glaucoma suspects,[14,15] or glaucoma patients[14–17] have examined the acute effects on IOP of consuming various caffeine-containing substances. Most studies observed modest acute IOP increases after ingestion over a 1- to 4-hour period, ranging from 0 to 4 mmHg. Fewer studies have examined the relationship between habitual coffee consumption and IOP or glaucoma risk. For example, habitual coffee consumption can modulate the effects of acute caffeine consumption on IOP.[4] In the Blue Mountains Eye Study, although no association was found between habitual caffeine consumption and IOP among healthy participants, among those with open-angle glaucoma, consuming 200 mg/day or more versus consuming less than 200 mg/day was associated with a

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suggestive, but nonsignificant, 2.3-mmHg higher IOP.[18] Studies of the relationship between coffee drinking and glaucoma risk have reported conflicting results,[19–22] and the association may depend on family history of glaucoma.[20,21] Thus, additional larger studies with adequate power to evaluate gene−caffeine consumption interactions are needed. In addition, Mendelian randomization (MR) methods may provide association results that inherently have much less confounding bias to resolve conflicting data on the relationship between habitual coffee or caffeine consumption and IOP.[23] Indeed, genome-wide association studies (GWASs) indicate that IOP is a polygenic trait,[24,25] and a higher IOP polygenic risk score (PRS) is associated with a higher risk of primary open-angle glaucoma (POAG).[26] Furthermore, a handful of genetic loci have been discovered that are associated with higher caffeine consumption.[27]

We used UK Biobank data, the largest available resource that allowed for a powerful evaluation of the relationship between various sources of caffeine consumption and IOP and glaucoma.[28] In addition, the large sample size also permitted an exploration of whether genetic predisposition to higher IOP modifies the relationship between coffee, tea, or caffeine consumption and IOP and glaucoma. Finally, the high throughput genotyping data available in the UK Biobank provided an opportunity to assess whether genetic loci linked to coffee consumption[27] were associated with IOP using MR (Appendix, available at www.aaojournal.org, for more explanation of IOP PRS, MR, and the gene−environmental interaction models used).

Methods

The UK Biobank

The UK Biobank is a large-scale prospective cohort study of 502 506 participants between 39 and 73 years of age at recruitment from 2006 through 2010. A wide range of phenotypic information as well as biological samples were collected from these participants.[28] The overall study protocol (http://www.ukbiobank.ac.uk/resources/) and individual test procedures (http://biobank.ctsu.ox.ac.uk/crystal/docs.cgi) are available online. At baseline, participants provided electronically signed consent and completed an extensive touchscreen questionnaire and physical measurements in 22 initial assessment centers. They also provided blood, urine, and saliva samples that were collected to generate genetic, proteomic, and metabolomic data.[29] All participants also provided consent for follow-up through linkage to their health-related records (e.g., primary care, screening programs, and disease-specific registry data), and repeated assessments have been conducted in a subset of participants to augment the baseline information. The UK Biobank was approved by the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee (reference no., 06/MRE08/65). This research was conducted using the UK Biobank Resource under application number 36741. All research adhered to the tenets of the Declaration of Helsinki.

Assessment of Dietary Caffeine Consumption

Information on habitual coffee and tea consumption was assessed in the baseline questionnaire (2006−2010). Participants were asked, "How many cups of coffee do you drink each day (including decaffeinated coffee)?" and "How many cups of tea do you drink each day (including black and green tea)?" For both questions, participants were asked to select the number of cups per day ("less than 1," "Do not know," "Prefer not to answer," or they indicated the number of cups). For our analyses, we combined all entries of 6 cups or more per day (in line with the second dietary instrument, see below) and treated the category of less than 1 cup per day as 0.5 cups per day. As a follow-up question, coffee drinkers were asked, "What type of coffee do you usually drink?" They selected from "decaffeinated coffee," "instant coffee," "ground coffee," and "other type of coffee."

The web-based hybrid dietary assessment instrument (Oxford WebQ), a validated food frequency questionnaire covering a 24-hour recall period, captured data on dietary patterns.[30–32] The instrument was repeated up to 5 times between 2009 and 2012. We used the WebQ data to estimate caffeine consumptions from 19 questions on caffeine-containing foods and beverages such as coffee, tea, low-calorie drinks, carbonated drinks, and chocolate products. The WebQ first asked whether the participant drank coffee yesterday. If the participant responded with "yes," then more information was requested about coffee type and the number of cups per day (i.e., half, 1, 2, 3, 4, 5, and 6 cups or more). The WebQ also asked about tea consumption and the number of cups of 5 specific tea types: black, rooibos, green, herbal, or other tea. For coffee and tea, the participant was asked an additional question: "Was it decaffeinated coffee?" and "Was your standard tea decaffeinated?" The answer categories were "no," "yes" and "varied." We categorized the tea and coffee responses as "caffeinated" for everyone answering with "no" and "varied" (assuming that most beverages in the "varied" answer would have been caffeinated). For carbonated drinks and low-calorie drinks, the number of glasses or cans the participant drank the previous day was ascertained as half, 1, 2, 3, 4, 5, and 6 or more. Chocolate intake was assessed from 7 items: chocolate bar, milk chocolate, dark chocolate, chocolate- or yogurt-covered raisins, chocolate sweets, chocolate-covered biscuits, and chocolate biscuits.

Participants reported the number of portions as quarter, half, 1, 2, 3, 4, 5, or more servings. Using the reported dietary data in the WebQ and published reports on caffeine content,[33–35] we calculated the total caffeine consumption using all the caffeine-containing foods mentioned above. Per-individual consumption of each caffeinated-containing food was averaged over all available time points. More details for deriving total caffeine intake appear in the Appendix and Tables S1 and S2 (available at www.aaojournal.org).

Intraocular Pressure and Glaucoma Status Ascertainment

For 122 143 UK Biobank participants, ophthalmic data, including IOP, were collected in 2009 at 6 assessment centers across the United Kingdom. Intraocular pressure was measured once for each eye using the Ocular Response Analyzer noncontact tonometer (Reichert Corp). Participants were excluded if they reported surgery in either eye within the previous 4 weeks or an eye infection. We used corneal-compensated IOP, which is derived from a linear combination of the inward and outward applanation tensions.[36] To handle extreme IOP values, we excluded measurements in the top and bottom 0.5 percentiles.[26] Given the impact of glaucoma treatment on IOP, we excluded participants who had a history of glaucoma laser therapy or surgery. We imputed pretreatment IOP for participants using glaucoma medication by dividing the measured IOP by 0.7.[24,26,37] Participant-level IOP values were calculated by averaging the right-eye and left-eye values for each

participant. If data were available for only 1 eye, then we used that eye's IOP value as the participant's IOP.

At baseline (2006−2010), participants with prior ophthalmic examinations completed a touchscreen questionnaire and were considered to have glaucoma if they chose the "glaucoma" response to the question, "Has a doctor told you that you have any of the following problems with your eyes?" Participants also were considered to have glaucoma if they reported a history of glaucoma surgery or laser therapy on the questionnaire or if they carried an International Classification of Diseases, Ninth Revision or Tenth Revision, code for glaucoma (Ninth Revision, 365.*; Tenth Revision, H40.** (excluding H40.01* and H42.*).

Genotyping Data, Intraocular Pressure Polygenic Risk Score, and Mendelian Randomization Experiments

Genetic data on 488,377 UK Biobank participants were generated using 2 genotyping arrays. The Affymetrix UK BiLEVE Axiom Array returned genotypes at 807 411 markers on 49 950 individuals.[38] The Affymetrix UK Biobank Axiom Array provided genotypes at 825 925 markers for the remaining 438 427 individuals. Because these platforms shared 95% of genetic markers, quality controls and imputation (the determination of genotypes at loci by inference and not by direct genotyping) were performed jointly, as described previously.[28] Specifically, imputation was based on genetic architecture ascertained in the 1000 Genomes Project, the UK 10K, and the Haplotype Reference Consortium reference panels. After quality control, 92 693 895 genetic markers of 487 442 participants were available in the data release.

For gene−diet interaction tests, we calculated the PRS for each participant using 111 independent common single nucleotide polymorphisms (SNPs) associated at the genome-wide significant level ($P \leq 5 \times 10^{-8}$) with IOP from a recent GWAS meta-analysis including the UK Biobank.[26] The PRS was derived using a standard weighted sum of individual SNP, that is, $\text{PRS} = \sum_{i=1}^{111} \widehat{\beta}_i \times \text{SNP}_i$, where $\widehat{\beta}_i$ is the estimated effect size of SNP_i on IOP level extracted from the aforementioned GWAS.[26] We normalized the IOP PRS with mean of 0 and standard deviation (SD) of 1 for analyses. For interaction analyses, all dietary exposure data were treated as continuous variables. To assess the potential causal effects of coffee drinking on IOP, we performed a 2-sample MR analysis in participants of European descent using 8 independent genome-wide significant SNPs associated with higher habitual coffee consumption.[27]

Statistical Analysis

Baseline characteristics of coffee and tea drinkers were compared across none, low (less than median consumption), and high (more than median consumption) consumers of either beverage by using mean difference and SD for continuous variables and distribution differences (i.e., counts and percentages) for categorical variables. To examine the main associations between coffee, tea, or caffeine intake and IOP, we used multiple linear regression models adjusted for covariates obtained from the baseline self-administered questionnaire. Covariates included a priori-determined IOP risk factors reported in prior studies[39]: age (years), gender, ethnicity (White, Black, and other), smoking status (never, past, and current smoker), number of cigarettes smoked among current smokers, alcohol intake (daily or almost daily, 3−4 times per week, 1−2 times per week, 1−3 times per month, special occasions only, never), physical activity (metabolic equivalent of task in hours per week), Townsend deprivation index (range, −6 to 11; a higher index score indicates more relative poverty for a given residential area), body mass index (kg/m^2), systolic blood pressure (mmHg), history of diabetes (yes or no), and total energy intake (kcal/day; for the subset with caffeine data). In the analysis for caffeine, we used quintile groups of total caffeine intake (<87 mg/day, 87−<139 mg/day, 139−<183 mg/day, 183−<232 mg/day, and ≥232 mg/day), and trends across the groups were examined by testing the association between median values of the caffeine groups.

To evaluate associations of coffee, tea, and caffeine intake with glaucoma status, we carried out multiple logistic regression analyses adjusting for the same covariates used in multiple linear regression models and used similarly defined exposure categories. All IOP PRS−diet interactions also used multiple regression adjusting for the same covariates. Interaction terms were defined as the product between the IOP PRS (standardized with mean of 0 and SD of 1) and coffee intake (cups/day), tea intake (cups/day), or total caffeine intake (per 80 mg/day). We also performed 2-sample MR analysis to test causal effects of coffee drinking on IOP.[40−42] We measured the association between 8 SNPs associated with higher coffee intake[27] and coffee consumption (β_{coffee}) and IOP (β_{IOP}) in the UK Biobank data.

We conducted various secondary analyses: (1) sensitivity analyses excluding those with glaucoma for analyses of IOP, (2) sensitivity analyses using a different definition of glaucoma (a more specific definition that captured POAG, namely, H40.1 and 365.1 from hospital records), (3) a subgroup analysis for men and women to explore gender-specific effects, and (4) a stratified analysis to examine the main associations of coffee and IOP by coffee types (ground, instant, decaffeinated, and others).

Results

The sample sizes for eligible UK Biobank participants with complete data for our various analyses are presented in Figure 1. Basic demographic characteristics for the UK Biobank population overall (n = 502 506) and its various subsets used in our analyses are provided in Table S3 (available at www.aaojournal.org).

Consumption of Coffee, Tea, and Total Caffeine

One hundred twenty-one thousand three hundred seventy-four UK Biobank participants contributed to the analysis of caffeinated product consumption and measured IOP (Table 1). The mean age was 56.8 years (SD, 8.0 years), and 53.8% of the participants were women. The average IOP was 16.0 mmHg (SD, 3.8 mmHg). Most participants (76.4%) were White. Mean coffee intake was 1.9 cups/day (SD, 1.7 cups/day), and mean tea intake was 3.1 cups/day (SD, 2.1 cups/day). The association between coffee and tea consumption tended to be reciprocal. Higher coffee consumption tended to be associated with being a current smoker and with more regular alcohol consumption. Of the 121 374 participants, 77 906 also completed the Web-Q diet questionnaires, allowing for an assessment of caffeine consumption from all sources. Total mean caffeine intake ranged from 8.9 mg/day for noncoffee drinkers to 135.3 mg/day for high coffee consumers (>1 cup/day). Total mean caffeine intake ranged from 2.9 mg/day for nontea drinkers to 114.0 mg/day for high tea consumers (>3 cups/day).

Consumption of Coffee, Tea, and Total Caffeine in Relationship to Intraocular Pressure

Using data on coffee and tea consumption at baseline, with maximum adjustment for confounding factors and mutual

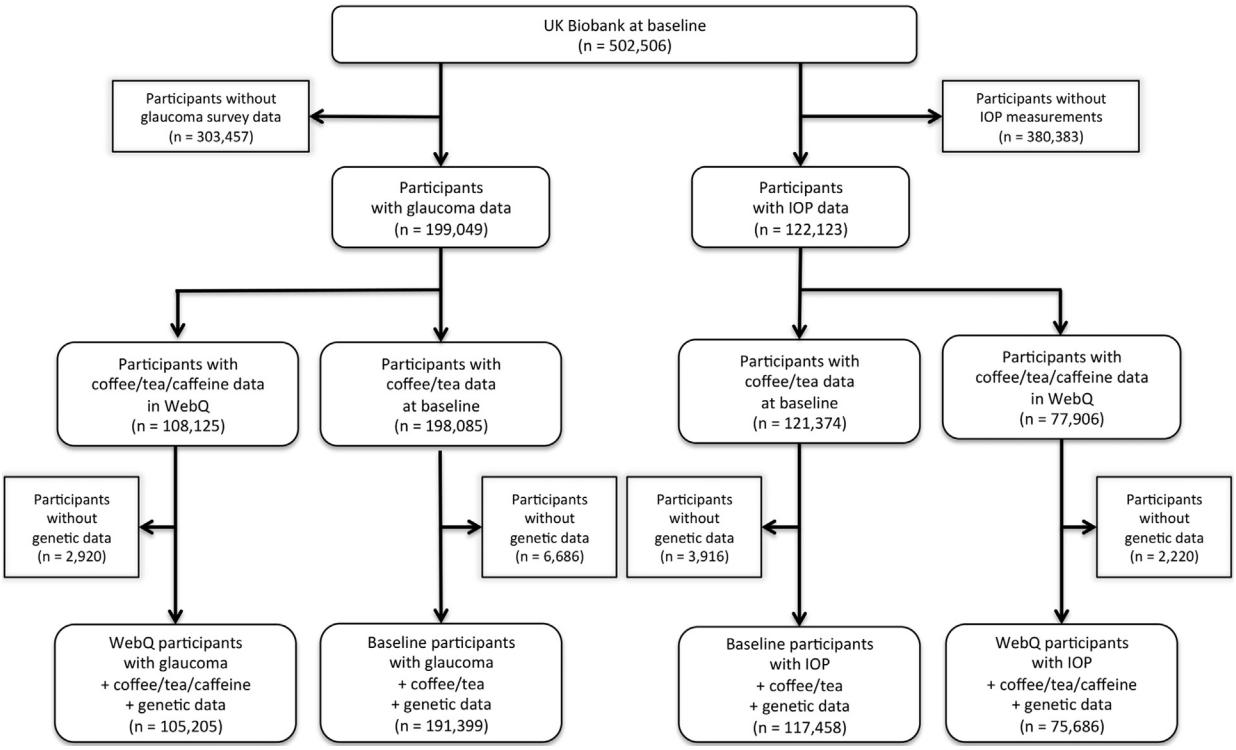

Figure 1. Flowchart outlining eligible participants for this study in the UK Biobank. This flow diagram summarizes the number of participants available for each analysis. IOP = intraocular pressure.

adjustment of caffeine sources, we observed weak inverse linear associations between coffee and tea intake and IOP (difference in IOP with each cup/day increase, −0.05 mmHg [$P < 0.001$] for each beverage; Table 2). Among participants who completed the Web-Q questionnaire, we observed no association between coffee or tea consumption and IOP, but we observed an inverse trend between caffeine consumption and IOP (difference in IOP between highest versus lowest quintile of caffeine intake, −0.10 mmHg; $P = 0.01$ for trend). For the baseline analysis, we observed similar associations for men and women (Table S4, available at www.aaojournal.org). When we evaluated intake of different coffee types, instant coffee and decaffeinated coffee use were associated weakly with lower IOP, whereas beverages with a higher caffeine content, such as ground and other types of coffee, were weakly positively associated with IOP when using the WebQ questionnaire (Table S5, available at www.aaojournal.org).

Consumption of Coffee, Tea, and Total Caffeine in Relationship to Glaucoma

Next, we explored diet−glaucoma relationships among participants who completed the baseline glaucoma questionnaire, regardless of whether they had IOP measurements (9229 glaucoma patients and 188 856 control participants; Table 3). We did not observe significant associations between baseline tea or coffee intake and glaucoma. In the WebQ dataset (3850 patients and 104 275 control participants), we also observed no associations between coffee, tea, or caffeine consumption and glaucoma ($P \geq 0.05$ for all). Also, we did not find any association of coffee, tea, and caffeine intake with the more specific outcome of POAG (Table S6, available at www.aaojournal.org).

Genetic Modification of Caffeine Product Consumption and Intraocular Pressure Relationships

We next assessed whether the association of coffee, tea, and caffeine intake with IOP is modified by an IOP PRS. These analyses were restricted further to participants with genetic data (n = 117 458). As expected,[26] a higher IOP PRS was associated strongly with higher IOP ($\beta = 0.76$ mmHg per 1 SD of PRS; $P < 0.001$). We found evidence for significant effect modification of the IOP PRS on the associations between tea consumption and IOP ($P = 0.001$ for interaction), but not on the association between coffee consumption and IOP (Fig 2A, B, upper panel). Caffeine and IOP PRS interactions were observed for those who completed the WebQ questionnaire and had genetic data (n = 75 686; Fig 2C, upper panel; $P = 0.01$ for interaction). Figure 2 illustrates that among those with the highest genetic susceptibility for higher IOP, greater tea or caffeine consumption was associated with higher IOP levels, but among those with a lower IOP PRS (lowest 3 quartiles), higher tea or caffeine consumption was associated with no change in IOP or slightly lower IOP. Most notably, among those in the highest quartile of the IOP PRS, IOP increased from 16.95 mmHg for those with the lowest caffeine intake (i.e., 0 mg/day) to 17.3 mmHg for those with the highest quintile of caffeine intake (i.e., ≥480 mg/day) (Fig 2C, upper panel). In secondary analyses to address the possibility that those with glaucoma may change their caffeine consumption, we excluded people with a self-report of glaucoma; the IOP PRS and dietary interactions were not qualitatively different (IOP PRS × baseline coffee consumption, n = 114 810 participants: $P = 0.76$ for interaction; IOP PRS × baseline tea consumption, n = 114 810 participants:

Table 1. Characteristics by Coffee and Tea Consumption Status among UK Biobank Participants with Intraocular Pressure Measurements and Coffee and Tea Data at Baseline (n = 121 374)

Variable	Coffee Consumption			Tea Consumption		
	Nondrinkers, 0 Cups/Day (n = 26 967)	*Low Consumption, ≤1 Cup/Day (n = 34 726)*	*High Consumption, >1 Cup/Day (n = 59 681)*	*Nondrinkers, 0 Cups/Day (n = 17 244)*	*Low Consumption, ≤3 Cups/Day (n = 49 980)*	*High Consumption, >3 Cups/Day (n = 54 150)*
Age (yrs), mean (SD)	55.6 (8.2)	57.2 (8.0)	57.2 (7.9)	55.9 (8.2)	56.6 (8.2)	57.4 (7.8)
Gender, no. (%)						
Male	11 376 (42.2)	15 390 (44.3)	29 314 (49.1)	7546 (43.8)	23 341 (46.7)	25 193 (46.5)
Female	15 591 (57.8)	19336 (55.7)	30 367 (50.9)	9698 (56.2)	26 639 (53.3)	28 957 (53.5)
Ethnicity, no. (%)*						
White (genetically)	18 607 (69.3)	26 091 (75.5)	47 979 (80.7)	13 324 (77.6)	35 551 (71.5)	43 802 (81.2)
Black (self-report)	367 (1.4)	412 (1.2)	383 (0.6)	121 (0.7)	686 (1.4)	355 (0.7)
Other	7861 (29.3)	8076 (23.4)	11 070 (18.6)	3726 (21.7)	13 490 (27.1)	9791 (18.1)
Smoking status, no. (%)						
Never	16 308 (60.7)	20 221 (58.4)	30 919 (52.0)	9211 (53.5)	28 431 (57.1)	29 814 (55.2)
Past	8270 (30.8)	11 828 (34.2)	21 782 (36.6)	5918 (34.4)	17 111 (34.3)	18 884 (35.0)
Current	2290 (8.5)	2560 (7.4)	6766 (11.4)	2074 (12.1)	4274 (8.6)	5270 (9.8)
Alcohol drinking frequency, no. (%)						
Never or special occasions only	8928 (33.1)	6761 (19.5)	9447 (15.8)	4295 (24.9)	9689 (19.4)	11 152 (20.6)
At least once per month	18 017 (66.9)	27 948 (80.5)	50 188 (84.2)	12 940 (75.1)	40 253 (80.6)	42 960 (79.4)
Physical activity (MET hr/wk), mean (SD)	44.9 (46.5)	43.6 (42.8)	43.7 (44.0)	44.0 (46.0)	41.8 (41.7)	45.9 (45.8)
BMI (kg/m^2), mean (SD)	27.4 (4.7)	27.0 (4.5)	27.4 (4.5)	27.9 (4.9)	27.1 (4.5)	27.2 (4.4)
SBP (mmHg), mean (SD)	136.6 (18.6)	137.4 (18.5)	137.7 (18.1)	136.8 (18.3)	137.2 (18.3)	137.7 (18.4)
Diabetes (yes), no. (%)	1797 (6.7)	2002 (5.8)	3450 (5.8)	1234 (7.2)	3080 (6.2)	2935 (5.4)
Deprivation index, mean (SD)†	−0.6 (3.1)	−1.1 (3.0)	−1.3 (2.9)	−0.9 (3.1)	−1.0 (3.0)	−1.2 (2.9)
Coffee intake (cups/day), mean (SD)	0.0	0.9 (0.2)	3.3 (1.4)	3.1 (2.1)	2.1 (1.6)	1.3 (1.5)
Coffee type, no. (%)						
Noncoffee drinker	26 967 (100.0)	0 (0.0)	0 (0.0)	2856 (16.6)	7860 (15.8)	16 251 (30.2)
Decaffeinated	0 (0.0)	6354 (18.5)	11 090 (18.7)	2809 (16.4)	7267 (14.6)	7368 (13.7)
Instant	0 (0.0)	17 086 (49.7)	33 566 (56.6)	8372 (48.8)	21 894 (44.1)	20 386 (37.9)
Ground	0 (0.0)	9868 (28.7)	13 865 (23.4)	2898 (16.9)	11 791 (23.8)	9044 (16.8)
Others	0 (0.0)	1050 (3.1)	785 (1.3)	237 (1.4)	806 (1.6)	792 (1.5)
Tea intake (cups/day), mean (SD)	3.8 (2.0)	3.7 (1.8)	2.5 (2.0)	0.0	2.0 (0.9)	5.1 (0.9)
Total caffeine intake (mg/day), mean (SD)‡	8.9 (27.8)	49.1 (48.9)	135.3 (89.0)	2.9 (13.7)	49.8 (38.2)	114.1 (57.1)
Quintiles of total caffeine intake, no. (%)‡,‖						
Quintile 1	5851 (36.7)	4924 (21.8)	4807 (12.2)	3847 (34.6)	7725 (23.7)	4010 (11.7)
Quintile 2	2871 (18.0)	4479 (19.8)	4219 (10.7)	1340 (12.1)	6288 (19.3)	3941 (11.5)
Quintile 3	4409 (27.7)	6758 (29.9)	8420 (21.4)	1898 (17.1)	7468 (22.9)	10 221 (29.9)
Quintile 4	2431 (15.3)	4251 (18.8)	8901 (22.6)	1794 (16.2)	5308 (16.3)	8481 (24.8)
Quintile 5	374 (2.3)	2157 (9.6)	13 054 (33.1)	2226 (20.0)	5802 (17.8)	7557 (22.1)
Total energy intake (kcal/day), mean (SD)‡	2059.4 (809.5)	2088.4 (749.3)	2138.6 (751.2)	2069.6 (836.0)	2091.3 (739.2)	2135.5 (761.3)
IOP (mmHg), mean (SD)	15.8 (3.8)	16.1 (3.8)	16.0 (3.8)	15.9 (3.8)	16.1 (3.8)	15.9 (3.8)
IOP polygenic risk score, mean (SD)¶	0.05 (1.0)	0.02 (1.0)	−0.0002 (1.0)	0.02 (1.0)	0.03 (1.0)	0.005 (1.0)

BMI = body mass index; IOP = intraocular pressure; MET = metabolic equivalent of task; SBP = systolic blood pressure; SD = standard deviation.
*For Whites, ethnicity is based on principal component analysis. For other ethnicities, it is based on self-report.[26]
†Unit was 1 unit of the Townsend deprivation index (a composite measure of deprivation based on unemployment, noncar ownership, nonhome ownership, and household overcrowding; a lower value represents higher socioeconomic status).
‡Data on total caffeine intake and total energy intake was from 77 906 participants who completed the WebQ (web-based 24-hour diet questionnaire administered up to 4 times between February 2011 and June 2012).
‖Cutoffs of caffeine (milligrams per day) quintiles among WebQ (web-based 24-hour diet questionnaire administered up to 4 times between February 2011 and June 2012) responders (n = 77 906): twentieth percentile, 86.7; fortieth percentile, 139.1; sixtieth percentile, 182.9; and eightieth percentile, 231.9.
¶The IOP polygenic risk score was normalized so that the mean was 0 and the SD was 1. Data on the IOP polygenic risk score are from the 117 458 participants with genetic data.

Table 2. Associations of Coffee, Tea, or Caffeine Intake and Intraocular Pressure

Variable	No.	Difference in Intraocular Pressure (mmHg; 95% Confidence Interval)		
		*Model 1**	*Model 2*†	*Model 3*‡
Baseline				
Coffee intake (cups/day)	121 374	−0.03 (−0.04 to −0.02)	−0.03 (−0.04 to −0.02)	−0.05 (−0.06 to −0.03)
Tea intake (cups/day)	121 374	−0.04 (−0.05 to −0.03)	−0.03 (−0.04 to −0.02)	−0.04 (−0.06 to −0.03)
WebQ§				
Coffee intake (cups/day)	77 906	0.01 (−0.03 to 0.04)	0.00 (−0.03 to 0.03)	−0.02 (−0.06 to 0.01)
Tea intake (cups/day)	77 906	−0.01 (−0.03 to 0.01)	0.00 (−0.02 to 0.02)	−0.01 (−0.03 to 0.02)
Quintiles of total caffeine intake, mg/day				
1 (0−<86.6)	15 581	Reference	Reference	Reference
2 (86.6−<139.1)	15 581	0.01 (−0.07 to 0.09)	−0.01 (−0.10 to 0.07)	−0.02 (−0.10 to 0.07)
3 (139.1−<182.9)	15 576	0.06 (−0.02 to 0.14)	0.04 (−0.05 to 0.13)	0.03 (−0.05 to 0.12)
4 (182.9−<231.9)	15 583	−0.07 (−0.16 to 0.01)	−0.10 (−0.19 to −0.01)	−0.10 (−0.19 to −0.01)
5 (≥231.9)	15 585	−0.12 (−0.21 to −0.04)	−0.09 (−0.18 to −0.004)	−0.10 (−0.19 to −0.01)
P value for trend‖		0.001	0.01	0.01

*Adjusting for age (linear age in yrs), gender (male or female), and ethnicity (genetic White, self-reported Black, all others).
†Model 1 with further adjustment for smoking status (never, past, or present), number of cigarettes (0 for never or past smokers, number of cigarettes smoked daily by current smokers), frequency of alcohol drinking (never or special occasion only, 1−3 times/mo, 1−2 times/wk, 3−4 times/wk, daily or almost daily), physical activity (metabolic equivalent of task [hr/wk]), deprivation index (linear score), BMI (kg/m^2), systolic blood pressure (mmHg), and diabetes (yes/no).
‡For coffee intake: model 2 with further adjustment for tea intake (cups/day). For tea intake: model 2 with further adjustment for coffee intake (cups/day). For total caffeine intake: model 2 with further adjustment for total energy intake (kcal/day).
§Web-based 24-hour diet questionnaire administered up to 4 times between February 2011 and June 2012.
‖Obtained from the *P* value of a continuous variable representing the median values of the quintile groups; the *P* value for trend provides a test of whether a linear association exists with increasing quintile of caffeine.

$P = 0.01$ for interaction; IOP PRS × caffeine consumption, n = 74 060 participants: $P = 0.05$ for interaction).

Genetic Modification of Diet and Glaucoma Relationships

We next assessed whether the association of coffee, tea, and caffeine intake with glaucoma is modified by IOP PRS. As anticipated,[26] a positive association was found between IOP PRS and glaucoma prevalence (odds ratio [OR], 1.57 per 1 SD of PRS; $P < 0.001$). The relationship between coffee consumption and glaucoma was not modified by the IOP PRS (Fig 2A, lower panel; $P = 0.75$ for interaction). We did observe a significant and positive effect modification by IOP PRS on the association between tea consumption and glaucoma ($OR_{interaction} = 1.02$; $P = 0.01$ for interaction for tea; Fig 2B, lower panel). Compared with tea nondrinkers with the lowest quartile of IOP PRS, those consuming 3 to 6 cups/day and the highest quartile of IOP PRS showed a higher risk of glaucoma approaching 3-fold; yet, those consuming 3 to 6 cups/day and the lowest quartile of IOP PRS showed slightly lower glaucoma risk. We also observed significant and positive effect modification of the association between caffeine consumption and glaucoma by IOP PRS using 3767 glaucoma patients and 101 438 control participants ($OR_{interaction} = 1.06$; $P = 0.0003$ for interaction; Fig 2C, lower panels). Specifically, compared with those in the lowest category of caffeine consumption and the lowest quartile of IOP PRS, those in the highest category of caffeine consumption and highest quartile of IOP PRS showed an OR of 3.9 for glaucoma (Fig 2C, lower panel). Also, among those in the same strata of the highest quartile of IOP PRS, the highest versus lowest caffeine consumption showed a 1.3-fold higher odds of having glaucoma (Fig 2C, lower panel). In secondary analyses, the IOP PRS did not modify the associations of coffee, tea, and caffeine intakes with POAG ($P \geq 0.22$ for interaction; Table S7, available at www.aaojournal.org).

Mendelian Randomization Analyses

All 8 coffee consumption SNPs[27] also were associated positively with coffee drinking in the UK Biobank database (Fig S1, available at www.aaojournal.org; n = 92 699; all $\beta > 0$). Conversely, the same SNPs were associated variably with IOP (Fig S1; β range, −0.5 to +0.6 mmHg), and the MR revealed no evidence of a causal relationship between coffee intake and IOP among UK Biobank participants of European descent (all $P > 0.1$; Table S8 and Fig S2, available at www.aaojournal.org).

Discussion

Overall, we observed that coffee, tea, and caffeine consumption were associated weakly with lower IOP, and the associations between these exposures and glaucoma were null. The caffeine associations were modified by an IOP PRS such that higher caffeine intake was associated positively with both IOP and glaucoma prevalence, but only among those with the highest genetic susceptibility to elevated IOP.

This is a large population-based study evaluating the association between habitual caffeinated product consumption and IOP. Furthermore, it also explored whether this relationship was modified by a genetic predisposition to higher IOP. Very little prior research has examined the effect of habitual coffee consumption on IOP.[4,18] In one

Table 3. Associations of Coffee, Tea, or Caffeine Intake and Glaucoma*

Variable	No.	Model 1†		Model 2‡		Model 3§	
		Odds Ratio (95% Confidence Interval)	*P Value*	*Odds Ratio (95% Confidence Interval)*	*P Value*	*Odds Ratio (95% Confidence Interval)*	*P Value*
Baseline							
Coffee intake (cups/day)	198 085	1.00 (0.99–1.02)	0.49	1.00 (0.99–1.02)	0.53	1.00 (0.98–1.01)	0.97
Tea intake (cups/day)	198 085	0.99 (0.98–1.00)	0.02	0.99 (0.98–1.00)	0.08	0.99 (0.98–1.00)	0.11
WebQ‖							
Coffee intake (cups/day)	108 125	1.04 (1.00–1.08)	0.04	1.04 (1.00–1.08)	0.08	1.04 (0.99–1.08)	0.10
Tea intake (cups/day)	108 125	0.96 (0.94–0.99)	0.01	0.97 (0.94–1.00)	0.04	0.97 (0.94–1.00)	0.05
Quintiles of total caffeine intake (mg/day)							
1 (0–< 87.0)	21 514	1.00		1.00		1.00	
2 (87.0–< 140.2)	21 736	0.99 (0.89–1.10)		0.97 (0.87–1.09)		0.97 (0.87–1.10)	
3 (140.2–< 183.8)	21 625	1.01 (0.91–1.12)		1.03 (0.92–1.15)		1.03 (0.92–1.15)	
4 (183.8–< 232.4)	21 625	0.99 (0.89–1.10)		1.03 (0.91–1.15)		1.03 (0.91–1.15)	
5 (≥ 232.4)	21 625	1.02 (0.92–1.13)		1.01 (0.90–1.14)		1.01 (0.90–1.14)	
P value for trend¶		0.70		0.60		0.59	

*Defined as a self-report of glaucoma. The number of patients with glaucoma was 9229, and the number of control participants was 188 856 in UK Biobank. Of the participants who completed the WebQ, 3850 had glaucoma and 104 275 were control participants.
†Adjusting for age (linear age in yrs), gender (male or female), and ethnicity (genetic White, self-reported Black, all others).
‡Model 1 with further adjustment for smoking status (never, past, or current), number of cigarettes (0 for never or past smokers, number of cigarettes smoked daily by current smokers), frequency of alcohol drinking (never or special occasion only, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, daily or almost daily), physical activity (metabolic equivalent of task in hours/wk), deprivation index (linear score), body mass index (kg/m^2), systolic blood pressure (mmHg), and diabetes (yes or no).
§For coffee intake: model 2 with further adjustment for tea intake (cups/day). For tea intake: model 2 with further adjustment for coffee intake (cups/day). For total caffeine intake: model 2 with further adjustment for total energy intake (kcal/day).
‖Web-based 24-hour diet questionnaire administered up to 4 times between February 2011 and June 2012.
¶Obtained from the *P* value of a continuous variable representing the median values of the quintile groups; the *P* value for trend provides a test of whether a linear association exists with increasing quintile of caffeine.

Japanese study, after adjusting for multiple covariates, IOP was lower among male habitual coffee consumers versus abstainers.[43] Similarly, our study found a very modest inverse association between higher total caffeine intake and IOP (>231 mg/day compared with <87 mg/day total caffeine intake was associated with a 0.10-mmHg lower IOP), an association that is not likely to be clinically significant. Indeed, our analyses suggest that a null association exists between higher caffeinated beverage consumption and glaucoma risk. Furthermore, the MR analysis did not suggest any causal effect of coffee drinking on IOP. Interestingly, most MR analyses between caffeine consumption and a variety of health-related traits also have shown negative results.[23,44] However, our analysis suggests that an IOP gene score-caffeine consumption interaction exists. Specifically, for those below the seventy-fifth percentile of IOP PRS, caffeinated product consumption showed little association with IOP. In contrast, for those in the highest quartile of IOP PRS, the consumption of 6 cups versus 0 cups of tea per day was associated with a 0.2-mmHg higher IOP and the consumption of 480 mg/day versus no caffeine was associated with a 0.35-mmHg higher IOP. Although this latter association seems small, it is equivalent to the effect size of *TMC01* rs10918274, the gene variant with the strongest effect on both higher IOP and POAG risk.[26] Furthermore, the *TMC01* risk variant was associated independently with conversion from ocular hypertension to POAG in the Ocular Hypertension Treatment Study.[45] However, in our study, *TMC01* (rs10918274) does not seem to be a key driver of the IOP PRS–diet interaction we report (Table S9, available at www.aaojournal.org). When considering the IOP SNPs collectively, these results suggest that although caffeinated beverage consumption may not be associated with higher IOP overall, this may not be the case for those with the highest genetic propensity to higher IOP.

Our analysis also showed that higher caffeine intake does not increase glaucoma risk overall. However, a similar interaction was found in which greater caffeine intake was associated adversely with glaucoma for those in the highest twenty-fifth percentile of genetic predisposition to higher IOP, whereas greater caffeine intake was associated weakly inversely with glaucoma among those in the lower 75% of IOP PRS. These findings are consistent with studies that found that greater caffeine intake was associated more adversely with open-angle glaucoma among those reporting a family history of glaucoma.[20,21] To what extent an IOP PRS captures a family history of glaucoma is unknown. The variance of corneal-compensated IOP in the UK Biobank explained by GWAS SNPs[46] and the IOP PRS is approximately 15% and 4%, respectively.

It is interesting to speculate about the biology underlying a possible interaction between IOP PRS and dietary caffeine intake in modifying the risk of higher IOP and glaucoma. It is possible that those with high IOP PRS have a lower reserve to withstand the challenges of intermittent yet frequent acute elevations of IOP caused by caffeine consumption. Overall, the dietary impact on our outcomes

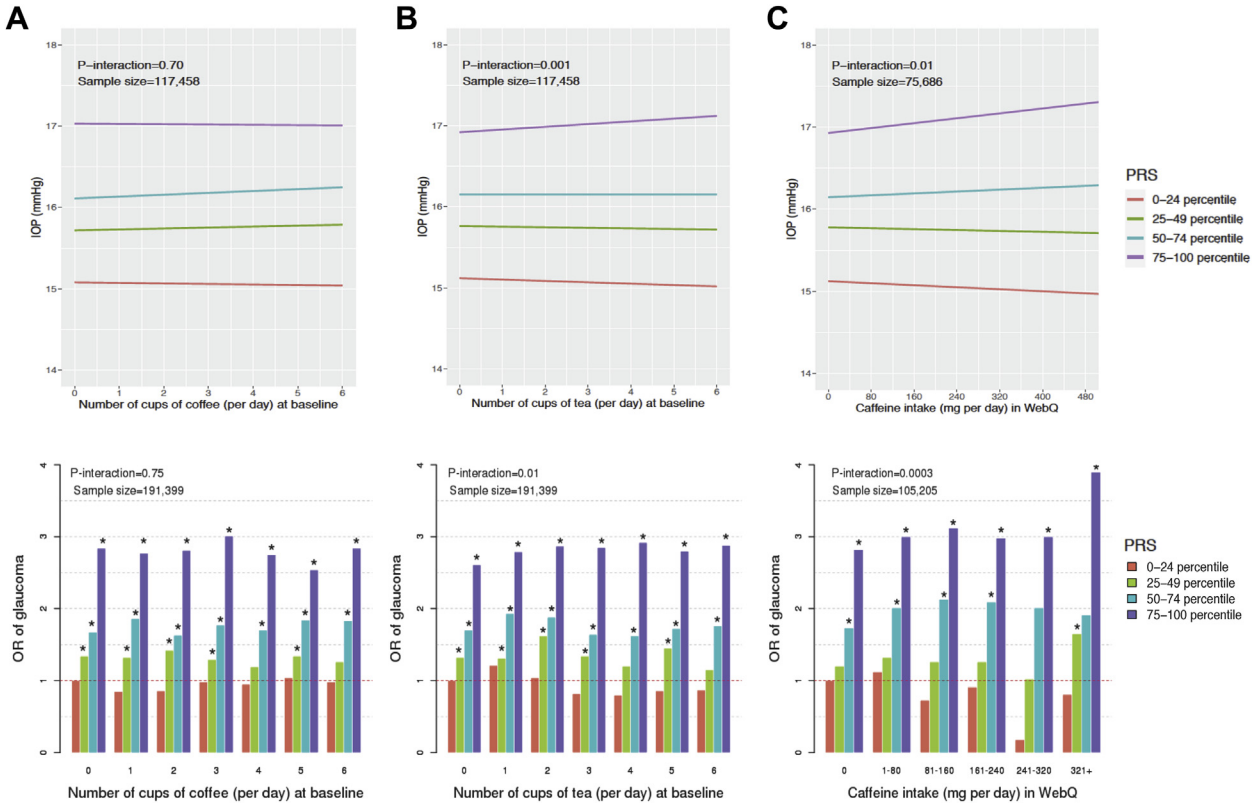

Figure 2. Graphs showing interactions between intraocular pressure (IOP) polygenic risk score (PRS) and coffee, tea, and caffeine intake in the relationship to IOP and glaucoma prevalence. The top row summarizes how the IOP PRS modifies the relationship between (**A**) coffee consumption, (**B**) tea consumption, and (**C**) caffeine consumption and IOP. The bottom row summarizes how the IOP PRS modifies the relationship between (**A**) coffee consumption, (**B**) tea consumption, and (**C**) caffeine consumption and glaucoma risk. Each color represents quartiles of IOP PRS (orange = first quartile; green = second quartile; light blue = third quartile; and purple = fourth quartile). The asterisk indicates that the odds ratio (OR) is significantly different from the OR = 1 ($P < 0.05$). Note that the dietary data in the lower panel are shown as ordinal data to depict the nature of the interactions, whereas they were analyzed as continuous variables.

was small, whereas the genetic contribution was quite robust. Whether IOP-related genes act in concert or whether specific IOP loci contribute to the gene–diet interactions we report remains to be determined. Only 9 of the 111 SNPs demonstrated a nominally positive gene–caffeine consumption interaction with respect to IOP, and none of these were significant at the Bonferroni-corrected P value cutoff (4×10^{-4}; Table S9).

This study has strengths and limitations. A major study strength is the large sample size, which allowed for the study of how genetic markers associated with IOP may alter the relationship between caffeine intake and IOP or glaucoma. Among the limitations, dietary caffeine measures can be challenging to ascertain with questionnaires (see Supplement Appendix). For example, variation in the caffeine content of coffee depends on the amount of water, type of coffee bean, and preparation method. Nonetheless, the dietary measures were validated, and the MR analysis helped to validate indirectly the data on coffee consumption collected in the UK Biobank; specifically, gene variants associated with higher coffee consumption in another dataset indeed were associated with higher coffee consumption in the UK Biobank (Fig S1). Also, although IOP was measured only once, the measures of IOP were relatively independent of central corneal thickness. The definition of self-reported glaucoma was not highly specific. The gene–diet interactions were not validated externally, but they were internally consistent, that is, consistent interactions were seen for both IOP and glaucoma.

Regarding generalizability, caffeine sources differ from country to country, but this does not necessarily hamper the internal validity of our findings. Daily consumption of caffeine among UK Biobank participants (135 mg/day among habitual coffee drinkers [Table 1]) is lower than in the United States (approximately 210 mg/day)[47] and elsewhere.[48] In the United Kingdom, a propensity exists to consume more instant coffee and tea, which have less caffeine than ground coffee, which is consumed more commonly elsewhere. Nevertheless, we also observed very weak significantly positive associations between ground coffee consumption and IOP (Table S5; IOP difference, 0.03 mmHg per cup), although these results may have been underpowered because of the low number of participants consuming higher quantities. Therefore, the association with IOP at the upper ranges in the United States diet remains unknown. In sensitivity

analyses for IOP, after excluding those who had glaucoma and may have been advised to limit caffeine intake, we observed similar results with regard to diet−gene interaction analysis.

This study suggests that a large panel of IOP genetic biomarkers could modify the relationship between caffeine dietary intake and risk of glaucoma. Currently, no approved genetic testing exists to identify which subset of patients may be predisposed to higher IOP and glaucoma. More research is needed to confirm these gene−diet interactions and to determine whether specific genetic markers are modifying the propensity to higher IOP and glaucoma or whether it is a nonspecific critical number of any IOP markers that modify disease risk. If confirmed, our data suggest that approaches to precision nutrition that incorporate genomic data[49] may be needed to make recommendations regarding caffeine consumption and glaucoma risk.

Footnotes and Disclosures

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No animal subjects were included in this study.

Author Contributions:

Conception and design: Kim, Aschard, Kang, Lentjes, Do, Wiggs, Khawaja, Pasquale

Analysis and interpretation: Kim, Aschard, Kang, Lentjes, Do, Wiggs, Khawaja, Pasquale

Data collection: Kim, Aschard, Kang, Lentjes, Do, Wiggs, Khawaja, Pasquale

Obtained funding: Do, Wiggs, Khawaja; Study was performed as part of the authors' regular employment duties. No additional funding was provided.

Overall responsibility: Kim, Aschard, Kang, Lentjes, Do, Wiggs, Khawaja, Pasquale

Abbreviations and Acronyms:
GWAS = genome-wide association study; **IOP** = intraocular pressure; **MR** = Mendelian randomization; **OR** = odds ratio; **POAG** = primary open-angle glaucoma; **PRS** = polygenic risk score; **SD** = standard deviation; **SNP** = single nucleotide polymorphism.

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Caffeine, Coffee, Genetic risk, Glaucoma, Intraocular pressure, Polygenic risk score, Tea.

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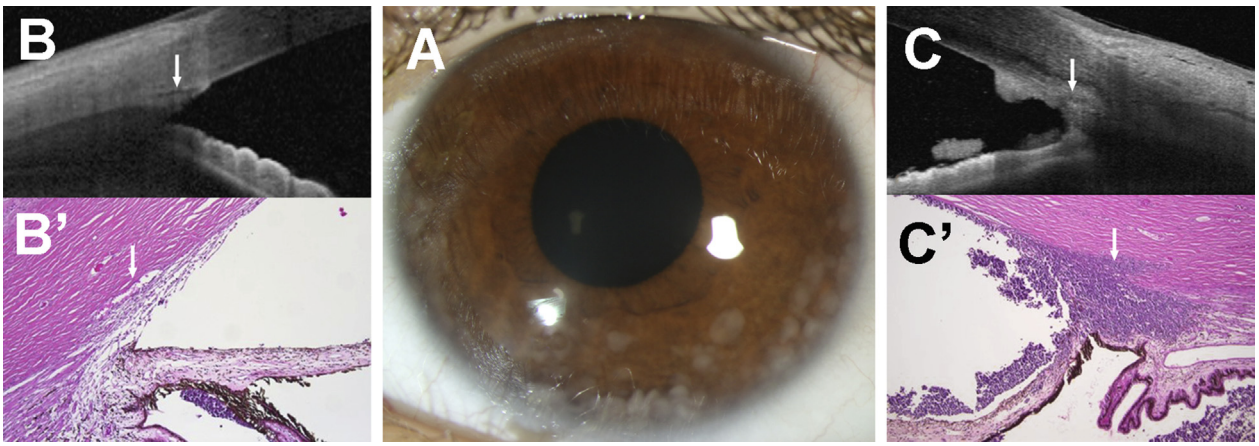
Pictures & Perspectives



OCT Imaging of Schlemm's Canal Invasion in a Retinoblastoma Patient

A 3-year-old boy with unilateral retinoblastoma Group D was seen after 3 cycles of systemic chemotherapy given elsewhere. Slit-lamp examination revealed anterior-chamber seeding (Fig **A**). Anterior-segment OCT distinguished tumor-free (Fig **B**) from invaded (Fig **C**) Schlemm's canal (*arrows*), which was confirmed after enucleation on histopathology (Figs **B**'and **C**'). Adjuvant chemotherapy to prevent metastasis is planned. This ongoing case illustrates that OCT can accurately delineate retinoblastoma extent in the anterior segment in vivo (Magnified version of Fig **A**-**C** is available online at www.aaojournal.org).

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