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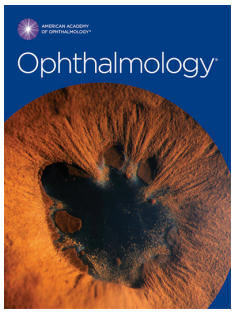

Intraocular pressure, glaucoma and dietary caffeine consumption: a gene–diet interaction study from the UK Biobank

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Intraocular pressure, glaucoma and dietary caffeine consumption: a gene–diet interaction study from the UK Biobank

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Running head: IOP, glaucoma and caffeine: genetic interactions in the UK Biobank

Abbreviations and Acronyms: IOP = Intraocular pressure; PRS = polygenic risk score; MR = Mendelian Randomization; SD = standard deviation; GWAS = genome-wide association study; POAG = primary open-angle glaucoma; UKB = UK Biobank; ORA = Ocular Response Analyzer; IOPcc = corneal-compensated IOP; SNP = single nucleotide polymorphism; MET = Metabolic Equivalent of Task; BMI = body mass index; OR = odds ratio.

Tables #3; Figures #2

This article contains additional online-only material. The following should appear online-only: Supplementary Appendix, Supplemental Tables 1, 2, 3, 4, 5, 6, 7, 8, 9, and Supplemental Figure 1.

Abstract:

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

Design: A 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 five web-based 24-hour-recall food frequency questionnaires (2009-2012) we evaluated total caffeine intake. We also assessed the same relations with any glaucoma (9,286 cases and 189,763 controls).

Method: 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), which combined the effects of 111 genetic variants associated with IOP. We also performed two-sample Mendelian Randomization (MR) using 8 genetic variants associated with coffee intake, to assess potential causal effects of coffee consumption on IOP.

Main Outcome and Measures: IOP; glaucoma.

Results: Mean IOP was 16.0 mmHg (Standard Deviation=3.8). MR analysis did not support a causal effect of coffee drinking on IOP (P>0.1). Greater caffeine intake was weakly associated with lower IOP: the highest (≥232mg/day) vs. lowest (<87mg/day) caffeine consumption was associated with a 0.10 mmHg lower IOP (P_{trend}=0.01). However, this association was significantly modified by IOP PRS: among those in the highest IOP PRS quartile, consuming >480mg/day versus <80 mg/day was associated with a 0.35 mmHg higher IOP ($P_{interaction}$=0.01). The relation between caffeine intake and glaucoma was null (P≥0.1). However, this relation was also significantly modified by IOP PRS: compared to those in the lowest IOP PRS quartile consuming no caffeine, those in the highest IOP PRS quartile consuming ≥321mg/day had a 3.90-fold higher glaucoma prevalence ($P_{interaction}$=0.0003).

Conclusions: Habitual caffeine consumption was weakly associated 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.

Introduction

Caffeine consumption, such as from coffee or tea, is a common behavior throughout the world.[1] There is keen interest 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 normal subjects,[4-13] glaucoma suspects[14, 15] or glaucoma patients[14-17] have examined the acute effects of consuming various caffeine-containing substances on IOP. Most studies observed modest acute post-ingestion IOP increases over a 1-4 hour period, ranging from nil to 4 mmHg. There have been fewer studies of the relation 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, while there was no association between habitual caffeine consumption and IOP among normal subjects, among those with open-angle glaucoma, consuming ≥ 200 mg/day versus consuming < 200 mg/day was associated with a suggestive, but non-significant 2.3 mmHg higher IOP.[18] Studies of the relation 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 relation between habitual coffee/caffeine consumption and IOP.[23] Indeed, genome-wide association studies (GWAS) indicate

that IOP is a polygenic trait, [24, 25] and a higher IOP polygenic risk score (PRS) is associated with a higher primary open-angle glaucoma (POAG) risk. [26] Furthermore, a handful of genetic loci have been discovered that are associated with higher caffeine consumption. [27]

We used UK Biobank (UKB) data, the largest available resource which allowed for a powerful evaluation of the relation between various sources of caffeine consumption and IOP/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/caffeine consumption and IOP/glaucoma. Finally the high throughput genotyping data available in the UKB provided an opportunity to assess whether genetic loci linked to coffee consumption[27] were associated with IOP using MR (see **Supplemental Appendix** for more explanation of IOP PRS, MR and the gene x environmental interaction models employed).

Methods

The UK Biobank (UKB)

The UKB is a large-scale prospective cohort study of 502,506 participants aged between 39-73 years at recruitment in 2006-2010. A wide range of phenotypic information as well as biological samples were collected on 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 electronic 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 UKB was approved by the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee (reference number 06/MRE08/65). This research has been conducted using the UKB Resource under application number 36741.

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 or more cups 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?” and 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 five 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 or not. 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 or more). The WebQ also asked about tea consumption and the number of cups of five 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/coffee as “caffeinated” for everyone answering with “no” and “varied” (assuming that the majority of the beverages in the ‘varied’ answer option 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 seven items: chocolate bar, milk chocolate, dark chocolate, chocolate/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-

182 containing foods mentioned above. Per-individual consumption of each caffeinated-
183 containing foods were averaged over all available time points. More details for deriving
184 total caffeine intake appear in the **Supplemental Appendix** and **Supplemental Tables**
185 **1-2**.
186
187 *IOP and glaucoma status ascertainment*
188 For 122,143 UKB participants, ophthalmic data, including IOP, were collected in 2009 at
189 6 assessment centers across the UK. IOP was measured once for each eye using the
190 Ocular Response Analyzer (ORA) noncontact tonometer (Reichert Corp., Philadelphia,
191 PA). Participants were excluded if they reported either eye surgery within the previous 4
192 weeks or an eye infection. We used corneal-compensated IOP (IOPcc), which is
193 derived from a linear combination of the inward and outward applanation tensions. [36] To
194 handle extreme IOP values, we excluded measurements in the top and bottom 0.5
195 percentiles. [26] Given the impact of glaucoma treatment on IOP, we excluded participants
196 who had a history of glaucoma laser or surgery. We imputed pre-treatment IOP for
197 participants using glaucoma medication by dividing the measured IOP by 0.7. [24, 26, 37]
198 Participant-level IOP values were calculated by averaging the right- and left-eye values
199 for each participant. If data were available for only one eye, then we used that eye's IOP
200 value as the participant's IOP.
201
202 At baseline (2006-2010), participants with prior ophthalmic examinations completed a
203 touchscreen questionnaire and were considered to have glaucoma if they chose the
204 "Glaucoma" response to the question, "Has a doctor told you that you have any of the

following problems with your eyes?". Participants were also considered to have glaucoma if they reported a history of glaucoma surgery or laser on the questionnaire or if they carried an ICD9/10 code for glaucoma (ICD 9: 365.*; ICD10: H40.** (excluding H40.01* and H42.*).

Genotyping data, IOP polygenic risk score and MR experiments

Genetic data on 488,377 UKB participants was generated using two 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. Since 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 previously described.[28] Specifically, imputation was based on genetic architecture ascertained in the 1000 Genomes Project, UK 10K, and the Haplotype Reference Consortium reference panels. After quality control, 92,693,895 genetic markers of 487,442 participants were available 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 ($P \leq 5\times10^{-8}$) with IOP from a recent GWAS meta-analysis including the UKB. [26] The PRS was derived using a standard weighted sum of individual SNP, i.e., PRS $=\sum_{i=1}^{111} \hat{\beta}_i \times \mathrm{SNP}_i$ where $\hat{\beta}_i$ 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 was 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 (below median consumption), and high (above 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 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), sex, ethnicity (Caucasian, 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 a week, 1-2 times a week, 1-3 times a month, special occasions only, never), physical activity (Metabolic Equivalent of Task (MET)-hours/week), Townsend deprivation index (range: -6 to 11; a higher index score indicates more relative poverty for a given residential area), body mass index (BMI) (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, 87 - < 140, 140 - < 184, 184 - < 232, 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 0 and SD 1) and coffee intake (cup/day), tea intake (cup/day), or total caffeine intake (per 80 mg/day). We also performed two-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 UKB 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 sex-specific effects, and (4) a stratified analysis to examine the main associations of coffee and IOP by coffee types (ground, instant, and decaffeinated, and others).

Results

The sample sizes for eligible UKB subjects with complete data for our various analyses are presented in **Figure 1**. Basic demographic characteristics for the UKB population overall (n=502,506) and its various subsets used in our analyses are provided in **Supplemental Table 3**.

Consumption of coffee, tea, and total caffeine

121,374 UKB participants contributed to the analysis of caffeinated product consumption and measured IOP (**Table 1**). The mean age (SD) was 56.8 (8.0) years and 53.8% of the participants were women. The average IOP was 16.0 (SD: 3.8) mmHg. The majority of participants (76.4%) were Caucasian. Mean coffee intake was 1.9 (SD: 1.7) cups/day and mean tea intake was 3.1 (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/d for non-coffee drinkers to 135.3 mg/d for high coffee consumers (>1 cup/day). Total mean caffeine intake ranged from 2.9 mg/d for non-tea drinkers to 114.0 mg/d for high tea consumers (>3 cup/day).

Consumption of coffee, tea, and total caffeine in relation to IOP

Using data on coffee and tea consumption at baseline, with maximal adjustment for confounding factors and mutual adjustment of caffeine sources, we observed weak inverse linear associations between coffee and tea intake with 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, 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 mm Hg; *P-trend* = 0.01). For the baseline analysis, we observed similar associations for men and women (**Supplemental Table 4**). When we evaluated

intake of different coffee types, instant coffee and decaffeinated coffee use were weakly associated 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 (**Supplemental Table 5)**.

Consumption of coffee, tea, and total caffeine in relation to glaucoma

Next we explored diet-glaucoma relations among participants who completed the baseline glaucoma questionnaire, regardless of whether they had IOP measures (9,229 glaucoma cases and 188,856 controls) (**Table 3**). We did not observe significant associations between baseline tea or coffee and glaucoma. In the WebQ dataset (3,850 cases and 104,275 controls), 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 with the more specific outcome of POAG (**Supplemental Table 6**).

Genetic modification of caffeine product consumption – IOP relations

We next assessed whether the association of coffee, tea and caffeine intake with IOP is modified by an IOP PRS. These analyses were further restricted to participants with genetic data (n=117,458). As expected,[26] a higher IOP PRS was strongly associated with higher IOP (β = 0.76 mmHg per 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-interaction* = 0.001) but not on the association between coffee consumption and IOP (**Figure 2A** and **2B** upper panel). Caffeine – IOP PRS interactions were observed for subjects who completed the WebQ and had genetic data

(n=75,686, **Figure 2C** - upper panel; *P-interaction* = 0.01). **Figure 2** illustrates that among those with the highest genetic susceptibility for higher IOP, greater tea or caffeine consumption were associated with higher IOP levels, but among those with a lower IOP PRS (lowest three 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 mm Hg for those in the lowest quintile of caffeine intake to 17.3 mmHg for those with the highest quintile of caffeine intake (**Figure 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 – dietary interactions were not qualitatively different (IOP PRS x baseline coffee consumption, n=114,810 subjects, p-interaction = 0.76; IOP PRS x baseline tea consumption, n=114,810 subjects, p-interaction = 0.01; IOP PRS x caffeine consumption, n=74,060 subjects, p-interaction = 0.05)

Genetic modification of diet – glaucoma relations

We next assessed whether the association of coffee, tea and caffeine intake with glaucoma is modified by IOP PRS. As anticipated,[26] there was a positive association between IOP PRS and glaucoma prevalence (Odds Ratio (OR) = 1.57 per SD of PRS, $P < 0.001$). The relation between coffee consumption and glaucoma was not modified by the IOP PRS (**Figure 2A**, lower panel *P-interaction* = 0.75). We did observe significant and positive effect modification by IOP PRS on the association between tea consumption and glaucoma ($OR_{interaction} = 1.02$, *P-interaction* = 0.01 for tea; **Figure 2B**, lower panel). Compared to tea non-drinkers with the lowest quartile of IOP PRS, those

consuming 3 to 6 cups/day and the highest quartile of IOP PRS had higher risk of glaucoma approaching 3-fold; yet, those consuming 3-6 cups/day and the lowest quartile of IOP PRS had slightly lower glaucoma risk. We also observed significant and positive effect modification of the association between caffeine consumption and glaucoma by IOP PRS using 3,767 glaucoma cases and 101,438 controls ($OR_{interaction}$ = 1.06, *P-interaction* = 0.0003; **Figure 2C** lower panels). Specifically, compared to those in the lowest category of caffeine consumption and the lowest quartile of IOP PRS, those in the highest category of caffeine and highest quartile of IOP PRS had a 3.9 OR of glaucoma (**Figure 2C**, lower panel). Also, among those in the same strata of the highest quartile of IOP PRS, the highest vs lowest caffeine consumption had a 1.3 fold higher glaucoma odds (**Figure 2C**, lower panel). In secondary analyses, the IOP PRS did not modify the associations of coffee, tea, and caffeine intakes with POAG (P-*interaction* ≥ 0.22, **Supplemental Table 7**).

Mendelian Randomization (MR) Analyses

All 8 coffee consumption SNPs [27] were also positively associated with coffee drinking in the UKB (**Supplemental Figure 1;** n = 92,699; all β > 0). Conversely, the same SNPs were variably associated with IOP (**Supplemental Figure 1;** β range: -0.5 mmHg to +0.6 mmHg) and the MR revealed no evidence of a causal relationship between coffee intake and IOP among UKB participants with European decent (all P > 0.1; **Supplemental Table 8 and Supplemental Figure 2**).

Discussion

Overall, we observed that coffee, tea and caffeine consumption were weakly associated 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 positively associated with both IOP and glaucoma prevalence, but only among those with the highest genetic susceptibility to elevated IOP.

This is the largest study to evaluate the association between habitual caffeinated product consumption and IOP. Furthermore, it is also the first study to explore whether this relation was modified by genetic predisposition to higher IOP. There has been very little prior research that has examined the effect of habitual coffee consumption on IOP. [4, 18] In one Japanese study, after adjusting for multiple covariates, IOP was lower among male habitual coffee consumers versus abstainers. [43] Similarly, in our study there was a very modest inverse association between higher total caffeine intake and IOP (>231 compared to <87mg/d 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 there was a null association 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 have also been negative. [23, 44] However, our analysis suggests an IOP gene-caffeine interaction exists; specifically, for those below the 75th percentile of IOP PRS, caffeinated product consumption had 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/day was associated with 0.2 mmHg higher and the consumption of 480 mg/d versus no caffeine was associated with 0.35 mmHg higher IOP. While this latter association seems small, it is equivalent to the effect size of *TMCO1* rs10918274, the gene variant with strongest effect on both higher IOP and POAG risk.[26] Furthermore, the *TMCO1* risk variant was independently associated with conversion from ocular hypertension to POAG in the Ocular Hypertension Treatment Study.[45] In our study however, *TMCO1* (rs10918274) does not appear to be a key driver of the IOP PRS – diet interaction we report (**Supplemental Table 9**). When considering the IOP SNPs collectively, these results suggest that while 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 shows that higher caffeine intake does not increase glaucoma risk overall. However there was a similar interaction where greater caffeine intake was adversely associated with glaucoma for those in the highest 25 percentile of genetic predisposition to higher IOP, while greater caffeine intake was weakly inversely associated with glaucoma among those in the lower 75% of IOP PRS. These findings are consistent with studies that found that greater caffeine intake was more adversely associated 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 IOPcc in the UKB explained by GWAS SNPs[46] and the IOP PRS is about 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 was small while 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}) (**Supplemental Table 9**).

This study has strengths and limitations. A major study strength was the large sample size, which allowed for the study of how genetic markers associated with IOP might alter the relation between caffeine intake and IOP or glaucoma. Among limitations, dietary caffeine measures can be challenging to ascertain with questionnaires (see **Supplement note**). 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 indirectly validate the data on coffee consumption collected in the UKB; specifically, gene variants associated with higher coffee consumption in another dataset were indeed associated with higher coffee consumption in the UKB (**Supplemental Figure 1**). Also, while IOP was only measured once, the measures of IOP were relatively independent of central corneal thickness. The definition of self-reported glaucoma was not highly specific. The gene -

447 diet interactions were not externally validated but they were internally consistent, i.e.,
448 consistent interactions were seen for both IOP and glaucoma.
449
450 Regarding generalizability, caffeine sources differ from country to country, but this does
451 not necessarily hamper the internal validity of our findings. Daily consumption of
452 caffeine in the UKB (135 mg/d among habitual coffee drinkers (**Table 1**) is lower than in
453 the US (~210 mg/d) [47] and elsewhere. [48] In the UK, there is a propensity to consume
454 more instant coffee and tea, which have less caffeine than ground coffee that is more
455 commonly consumed elsewhere. Nevertheless, we also observed very weak significant
456 positive associations ground coffee consumption and IOP (**Supplemental Table 5;** IOP
457 difference=0.03 mm Hg per cup), although these results may have been underpowered
458 due to the low number of participants consuming higher quantities. Therefore, the
459 association with IOP at the upper ranges in the US diet remains unknown. In sensitivity
460 analysis for IOP, after excluding those who had glaucoma and may have been advised
461 to limit caffeine intake, we observed similar results with regards to diet-gene interaction
462 analysis.
463
464 This study suggests that a large panel of IOP genetic biomarkers could modify the
465 relation between caffeine dietary intake and risk of glaucoma. Currently there is no
466 approved genetic testing to identify which subset of patients might be predisposed to
467 higher IOP and glaucoma. More research is needed to confirm these gene-diet
468 interactions and to determine whether specific genetic markers are modifying the
469 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.

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599 **Figure legends**
600
601 **Figure 1:** Flowchart outlining eligible subjects for this study in UK Biobank. This flow
602 diagram summarizes the number of participants available for each analysis.
603
604 **Figure 2:** Interactions between IOP PRS and coffee, tea, and caffeine intake in the
605 relation to IOP and glaucoma prevalence. The upper panels summarize how the
606 IOP PRS modifies the relation between coffee consumption (A), tea consumption
607 (B) and caffeine consumption (C) and IOP. The lower panels summarize how the
608 IOP PRS modifies the relation between coffee consumption (A), tea consumption
609 (B) and caffeine consumption (C) and glaucoma risk. Each color represents
610 quartiles of IOP PRS (orange = 1^{st} quartile, green = 2^{nd} quartile, light blue = 3^{rd}
611 quartile, and magenta/purple = 4^{th} quartile). The asterisk indicates the OR is
612 significantly different from the OR=1 (p-value < 0.05). NB: Dietary data in the
613 lower panel is shown as ordinal data to depict the nature the interactions, while it
614 was analyzed as continuous variables.

Table 1. Characteristics by coffee and tea consumption status among UK Biobank participants with IOP measurements and coffee and tea data at baseline (n = 121,374)

	Coffee consumption			Tea consumption		
Variable / No.	**Non-drinkers** (0 cup/day) (n = 26,967)	**Low consumption** (≤ 1 cup/day) (n = 34,726)	**High consumption** (> 1 cup/day) (n = 59,681)	**Non-drinkers** (0 cup/day) (n = 17,244)	**Low consumption** (≤ 3 cups/day) (n = 49,980)	**High consumption** (> 3 cups/day) (n = 54,150)
Age (year), 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)
Sex, no. (%)						
Male	11,376 (42.2)	15,390 (44.3)	29,314 (49.1)	7,546 (43.8)	23,341 (46.7)	25,193 (46.5)
Female	15,591 (57.8)	19336 (55.7)	30,367 (50.9)	9,698 (56.2)	26,639 (53.3)	28,957 (53.5)
Ethnicity,[a] no. (%)						
White (Caucasian 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	7.861 (29.3)	8,076 (23.4)	11,070 (18.6)	3,726 (21.7)	13,490 (27.1)	9,791 (18.1)
Smoking status, no. (%)						
Never	16,308 (60.7)	20,221 (58.4)	30,919 (52.0)	9,211 (53.5)	28,431 (57.1)	29,814 (55.2)
Past	8,270 (30.8)	11,828 (34.2)	21,782 (36.6)	5,918 (34.4)	17,111 (34.3)	18,884 (35.0)
Current	2,290 (8.5)	2,560 (7.4)	6,766 (11.4)	2,074 (12.1)	4,274 (8.6)	5,270 (9.8)
Alcohol drinking frequency, no. (%)						
Never or special occasions only	8,928 (33.1)	6,761 (19.5)	9,447 (15.8)	4,295 (24.9)	9,689 (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. (%)	1,797 (6.7)	2,002 (5.8)	3,450 (5.8)	1,234 (7.2)	3,080 (6.2)	2,935 (5.4)
Deprivation Index[b], 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 (cup/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. (%)						
Non-coffee drinker	26,967 (100.0)	0 (0.0)	0 (0.0)	2,856 (16.6)	7,860 (15.8)	16,251 (30.2)
Decaffeinated	0 (0.0)	6,354 (18.5)	11,090 (18.7)	2,809 (16.4)	7,267 (14.6)	7,368 (13.7)
Instant	0 (0.0)	17,086 (49.7)	33,566 (56.6)	8,372 (48.8)	21,894 (44.1)	20,386 (37.9)
Ground	0 (0.0)	9,868 (28.7)	13,865 (23.4)	2,898 (16.9)	11,791 (23.8)	9,044 (16.8)
Others	0 (0.0)	1,050 (3.1)	785 (1.3)	237 (1.4)	806 (1.6)	792 (1.5)
Tea intake (cup/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[c] (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,[c,d] no. (%)						
Quintile 1	5,851 (36.7)	4,924 (21.8)	4,807 (12.2)	3,847 (34.6)	7,725 (23.7)	4,010 (11.7)
Quintile 2	2,871 (18.0)	4,479 (19.8)	4,219 (10.7)	1,340 (12.1)	6,288 (19.3)	3,941 (11.5)
Quintile 3	4,409 (27.7)	6,758 (29.9)	8,420 (21.4)	1,898 (17.1)	7,468 (22.9)	10,221 (29.9)
Quintile 4	2,431 (15.3)	4,251 (18.8)	8,901 (22.6)	1,794 (16.2)	5,308 (16.3)	8,481 (24.8)
Quintile 5	374 (2.3)	2,157 (9.6)	13,054 (33.1)	2,226 (20.0)	5,802 (17.8)	7,557 (22.1)
Total energy intake[c] (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,[e] 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)

Abbreviations: IOP = intraocular pressure; BMI = body mass index (kg/m$^{2)}$); MET-hr/wk = metabolic equivalent of task-hours per week; SBP = systolic blood pressure; SD = standard deviation; WebQ: Web-based 24-hour diet questionnaire administered up to 4 times between February 2011 and June 2012.

[a] For Whites, ethnicity is based on Principal Component Analysis. For other ethnicities it is based on self-report (see ref 26).
[b] Unit was 1 unit of the Townsend Deprivation Index (a composite measure of deprivation based on unemployment, non-car ownership, non-home ownership, and household overcrowding; a lower value represents higher socioeconomic status)

[c] Data on total caffeine intake and total energy intake was from 77,906 participants who completed the WebQ.
[d] Cutoffs of caffeine (mg/day) quintiles among WebQ responders (n=77906): 20th percentile=86.7, 40th percentile=139.1, 60th percentile=182.9, and 80th percentile=231.9
[e] 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 was from the 117,458 participants with genetic data.

Table 2. Associations of coffee, tea, or caffeine intake and IOP (mmHg)

	No.	Model 1 *Difference in IOP (mmHg; 95% CI)*	Model 2[b] *Difference in IOP (mmHg; 95% CI)*	Model 3[c] *Difference in IOP (mmHg; 95% CI)*
Baseline				
Coffee intake (cup/day)	121,374	-0.03 (-0.04, -0.02)	-0.03 (-0.04, -0.02)	-0.05 (-0.06, -0.03)
Tea intake (cup/day)	121,374	-0.04 (-0.05, -0.03)	-0.03 (-0.04, -0.02)	-0.04 (-0.06, -0.03)
WebQ				
Coffee intake (cup/day)	77,906	0.01 (-0.03, 0.04)	0.00 (-0.03, 0.03)	-0.02 (-0.06, 0.01)
Tea intake (cup/day)	77,906	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.02)
Quintiles of total caffeine intake				
1 (0 to < 86.6 mg/d)	15,581	Reference	Reference	Reference
2 (86.6 to < 139.1 mg/d)	15,581	0.01 (-0.07, 0.09)	-0.01 (-0.10, 0.07)	-0.02 (-0.10, 0.07)
3 (139.1 to < 182.9 mg/d)	15,576	0.06 (-0.02, 0.14)	0.04 (-0.05, 0.13)	0.03 (-0.05, 0.12)
4 (182.9 to < 231.9 mg/d)	15,583	-0.07 (-0.16, 0.01)	-0.10 (-0.19, -0.01)	-0.10 (-0.19, -0.01)
5 (≥ 231.9 mg/d)	15,585	-0.12 (-0.21, -0.04)	-0.09 (-0.18, -0.004)	-0.10 (-0.19, -0.01)
P-trend[d]		0.001	0.01	0.01

Abbreviations: IOP = intraocular pressure; CI = confidence interval; WebQ = Web-based 24-hour diet questionnaire administered up to 4 times between February 2011 and June 2012.

[a] Model 1: Adjusting for age (linear age in years), sex (male/female), and ethnicity (genetic Caucasian, self-reported Black, all others)
[b] Model 2: 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 a month, 1-2 times per week, 3-4 times per week, daily or almost daily), physical activity (MET-hr/wk), deprivation index (linear score), BMI (kg/m^2), SBP (mmHg), and diabetes (yes/no)
[c] Model 3 (for coffee intake): Model 2 with further adjustment for tea intake (cup/day)
Model 3 (for tea intake): Model 2 with further adjustment for coffee intake (cup/day)
Model 3 (for total caffeine intake): Model 2 with further adjustment for total energy intake (kcal/day)
[d] P-trend was obtained from the p-value of a continuous variable representing the median values of the quintile groups; the p-trend provides a test of whether there is a linear association with increasing quintile of caffeine

Table 3. Associations of coffee, tea, or caffeine intake and glaucoma[a]

		Model 1[b]		Model 2[c]		Model 3[d]	
	No.	**OR (95% CI)**	***P-value***	**OR (95% CI)**	***P-value***	**OR (95% CI)**	***P-value***
Baseline							
Coffee intake (cup/d)	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 (cup/d)	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 (cup/d)	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 (cup/d)	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							
1 (0 to < 87.0 mg/d)	21,514	1.00		1.00		1.00	
2 (87.0 to < 140.2 mg/d)	21,736	0.99 (0.89, 1.10)		0.97 (0.87, 1.09)		0.97 (0.87, 1.10)	
3 (140.2 to < 183.8 mg/d)	21,625	1.01 (0.91, 1.12)		1.03 (0.92, 1.15)		1.03 (0.92, 1.15)	
4 (183.8 to < 232.4 mg/d)	21,625	0.99 (0.89, 1.10)		1.03 (0.91, 1.15)		1.03 (0.91, 1.15)	
5 (≥ 232.4 mg/d)	21,625	1.02 (0.92, 1.13)		1.01 (0.90, 1.14)		1.01 (0.90, 1.14)	
P-trend[e]		0.70		0.60		0.59	

Abbreviations: No. = Number; OR = odds ratio; CI = confidence interval, WebQ: Web-based 24-hour diet questionnaire administered up to 4 times between February 2011 and June 2012.

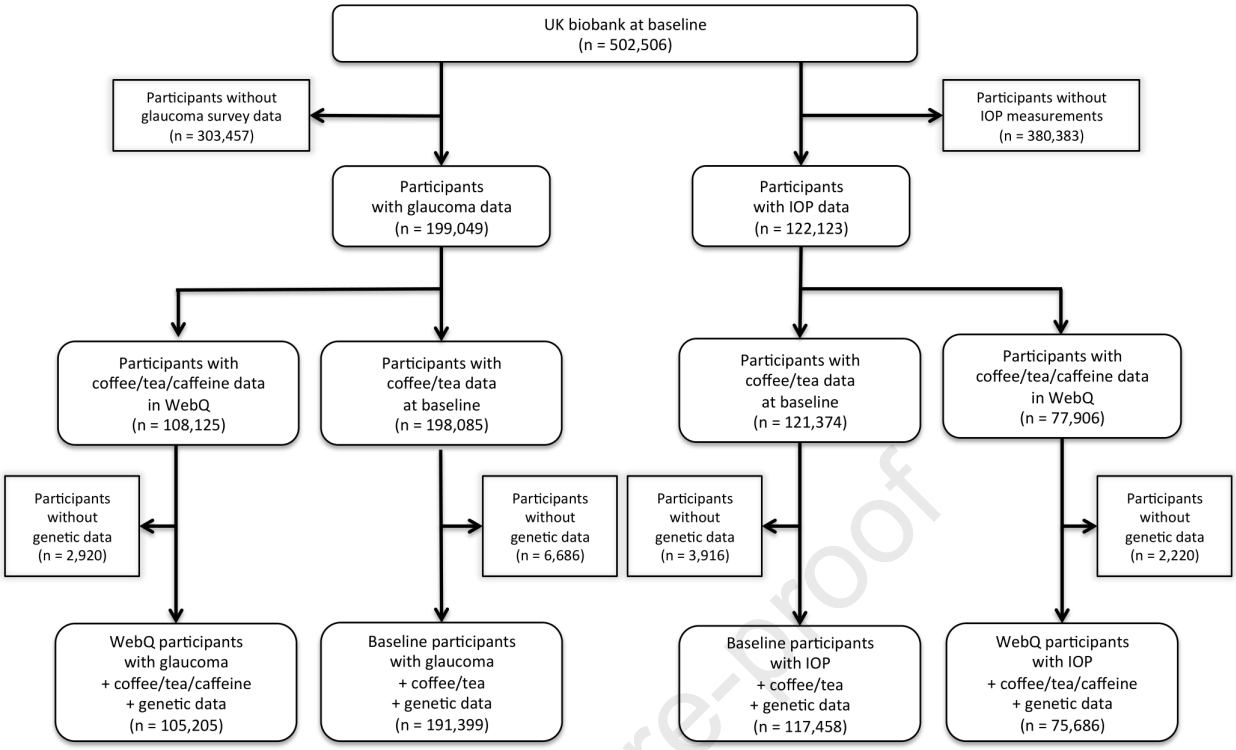
[a] Glaucoma was defined as a self-report of a glaucoma. The number of cases of glaucoma was 9,229 and the number of controls was 188,856 in UK biobank. For the participants who completed the WebQ there were 3,850 glaucoma cases and 104,275 controls.

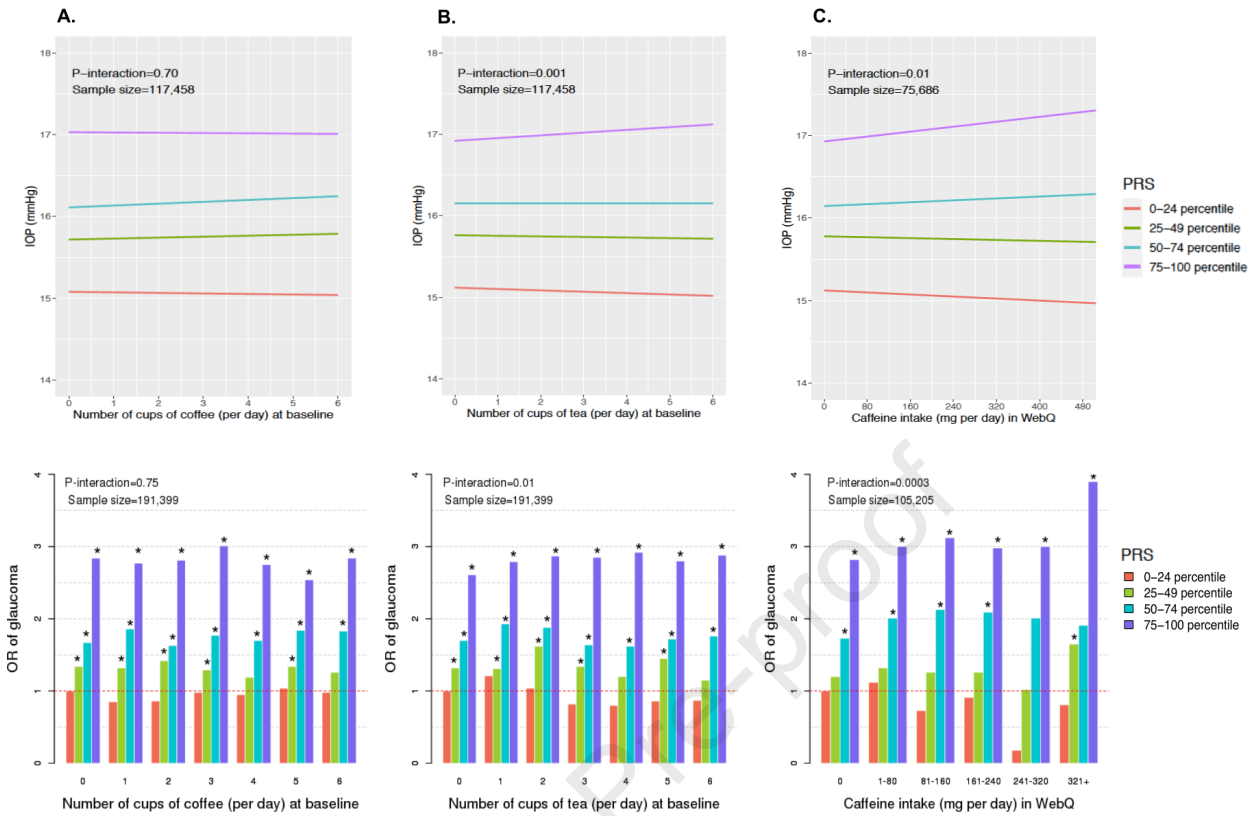
[b] Model 1: Adjusting for age (linear age in years), sex (male/female), and ethnicity (genetic Caucasian, self-reported Black, all others)

[c] Model 2: 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 a month, 1-2 times per week, 3-4 times per week, daily or almost daily), physical activity (MET-hr/wk), deprivation index (linear score), BMI (kg/m^2), SBP (mmHg), and diabetes (yes/no)

[d] Model 3 (for coffee intake): Model 2 with further adjustment for tea intake (cup/day)
Model 3 (for tea intake): Model 2 with further adjustment for coffee intake (cup/day)
Model 3 (for total caffeine intake): Model 2 with further adjustment for total energy intake (kcal/day)

[e] P-trend was obtained from the p-value of a continuous variable representing the median values of the quintile groups; the p-trend provides a test of whether there is a linear association with increasing quintile of caffeine.





Precis

For UK biobank participants, we found minimal relations between habitual caffeine consumption, intraocular pressure and glaucoma risk; however, adverse associations were observed among those who were genetically susceptible to high intraocular pressure.

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TITLE OF ARTICLE: Intraocular pressure, glaucoma and dietary caffeine consumption: a gene–diet interaction study from the UK Biobank

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Louis R. Pasquale	×	×	×	×

OTHER CONTRIBUTIONS: All authors contributed to all aspects of work. Some specific contributions include: Dr. Kim performed all analyses. Dr. Kang organized biweekly zoom conferences to discuss the data. She also performed a data check to assess the validity of the outcomes with Dr. Kim. Dr. Lentjes developed a script to derive caffeine intake from the dietary questionnaires. Drs.

Kang and Lentjes provided input on the dietary exposures in relation to the outcomes given their expertise in nutritional epidemiology. Dr. Khawaja developed a script to derive IOP PRS for study participants. Dr. Pasquale obtained funding for the project. Drs. Aschard and Pasquale provided input on the GxE aspects of the project. Drs. Do, Khawaja and Wiggs provided critical input regarding the genetics aspects of the work.