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Caffeine Consumption and the Risk of Primary Open - Angle Glaucoma: A Prospective Cohort Study

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Abstract

Purpose—We investigated whether caffeine, which transiently increases intraocular pressure (IOP) is associated with risk of primary open-angle glaucoma (POAG).

Methods—We followed 79,120 women from 1980 and 42,052 men from 1986 to 2004 who were 40+ years old, did not have POAG, and reported receiving eye examinations. Information on caffeine consumption, potential confounders and POAG diagnoses were repeatedly updated in validated follow-up questionnaires. We confirmed 1,011 incident POAG cases with medical record review. Cohort-specific and pooled analyses across cohorts were conducted to calculate multivariable rate ratios (RR).

Results—Compared with daily intake of < 150 mg, the pooled multivariable RRs were 1.05 [95% Confidence Interval (CI), 0.89–1.25] for consuming 150–299 mg, 1.19 [95% CI, 0.99–1.43] for 300 – 449 mg/day, 1.13 [95% CI, 0.89–1.43] for 450–559 mg and 1.17 [95% CI, 0.90, 1.53] for 600+ mg+ [p for trend = 0.11]. However, for consuming 5+ cups of caffeinated coffee daily, RR was 1.61 [95% CI, 1.00, 2.59; p for trend=0.02]; tea or caffeinated cola intake were not associated with risk. Greater caffeine intake was more adversely associated with POAG among those reporting family history of glaucoma, particularly in relation to POAG with elevated IOP (p for trend = 0.0009; p-interaction=0.04).

Conclusion—Overall caffeine intake was not associated with increased risk of POAG. However, in secondary analyses, caffeine appeared to elevate risk of high-tension POAG among those with a family history of glaucoma; this may be due to chance, but warrants further study.

INTRODUCTION

Primary open-angle glaucoma (POAG) is a major cause of blindness worldwide.¹ It is characterized by progressive optic nerve deterioration ultimately leading to blindness if untreated. Little is known of its etiology; however, an important established risk factor for

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the development²⁻⁴ and progression of POAG^{5, 6} is elevated intraocular pressure (IOP). Because IOP levels may be modulated by lifestyle factors, efforts to identify activities that may lower IOP levels may be promising in developing primary prevention strategies for POAG.

Caffeine is a common exposure that influences IOP levels.⁷ With few exceptions,^{8, 9} most studies^{7, 10-13} show that caffeine ingestion from drinks such as coffee caused transient increases in IOP of approximately 2 mm Hg for a 2 hour period, whereas ingestion of similar drinks without caffeine (e.g. decaffeinated coffee) caused negligible changes in IOP.¹¹⁻¹³ Although a typical caffeinated beverage may produce modest and transient ocular hypertensive effects, it is possible that repeated exposure to caffeine throughout the day may cause sustained, clinically significant IOP elevation, which could in turn increase the risk of developing POAG. However, to our knowledge, no population-based studies have examined the relationship between caffeine intake and the risk of developing POAG. Because caffeinated drinks such as coffee, tea and cola drinks, are widely consumed worldwide, even among older persons at risk of POAG (e.g. 80% of US adults over the age of 50 consume caffeine daily¹⁴), it is thus important to investigate this relationship.

We report the results of a prospective study of 79,120 women in the Nurses' Health Study and 42,052 men in the Health Professionals Follow-up Study followed for at least 18 years, in whom comprehensive dietary histories were assessed multiple times, to examine the relation between caffeine consumption and risk of POAG.

SUBJECTS AND METHODS

The Nurses' Health Study (NHS) began in 1976 when 121,700 US registered female nurses aged 30 to 55 years replied to a mailed health questionnaire (70% response rate).¹⁵ The Health Professionals Follow-Up Study (HPFS) started in 1986 with 51,529 US male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopaths, and podiatrists) aged 40 to 75 years who responded to a similar mailed health questionnaire (33% response rate).¹⁶ Participants have been followed with biennial questionnaires on numerous lifestyle habits including caffeine consumption and newly diagnosed illnesses such as glaucoma. Follow-up rates were high (> 95% of the total possible person-time through 2004). This study was approved by the Human Research Committees of Brigham & Women's Hospital, Massachusetts Eye and Ear Infirmary and the Harvard School of Public Health. Our research adhered to the tenets of the Declaration of Helsinki.

The first dietary assessments including caffeine consumption occurred in 1980 for NHS and 1986 for HPFS and thus these are "baseline" years for this study and the study period was restricted to 1980 – 2004 in the NHS and 1986 – 2004 in the HPFS. Generally, a participant contributed person-time if they were at least aged 40 years (as glaucoma risk increases after age 40) and reported having had an eye exam in the period at risk (to minimize possible detection bias). Participants contributed person-time in approximate 2-year units from the return date of the first questionnaire until the earliest occurrence of either a report of glaucoma, cancer, death, loss to follow-up, or 2004.

At baseline, the following participants were excluded: 1) 23,239 women who did not respond to the 1980 semiquantitative food frequency questionnaire assessment (FFQ), 2) 5,994 women and 1,596 men with inadequate diet information on the FFQ ("adequate" information for women was fewer than 10 out of 61 items blank and 500–3500 kcal/day while fewer than 70 out of 131 items blank in the FFQ, with a total caloric intake range of 800–4200 kcal/day was considered "adequate" for men), 3) 3,624 women and 1,927 men with prevalent cancers aside from nonmelanoma skin cancer (this exclusion was applied

because cancer diagnoses cause profound changes in lifestyle habits), 4) 801 women and 818 men with a prevalent diagnosis of glaucoma or glaucoma suspect, 5) 739 women and 973 men lost to follow-up immediately after baseline, and 6) 6,472 women and 3,658 men who never reported an eye exam during follow-up. After these exclusions, 80,831 women and 42,557 men remained. In addition, for each two-year period, participants who were under age 40 or who did not report an eye exam were also considered ineligible. After excluding those temporarily ineligible because they were under age 40 (17,045 women and 236 men) or did not report receiving an eye exam when first asked (see below; 19,046 women and 12,512 men), 44,740 women and 29,809 men respectively contributed person time in the first 2 years from the NHS (1980–82) and the HPFS (1986–88). At later periods, these ineligible participants were allowed to contribute person-time, if they reached 40 years of age, and reported receiving eye exams. Hence, by 2004, a total of 79,120 women and 42,052 men contributed person-time. Follow-up rates through 2004 were high (> 95% of the total possible person-time).

Eligibility for the eye exam criterion was determined by selecting those who responded positively to the question of whether an eye exam was received in the previous two years. For example, if a NHS participant answered positively only in 1994 and 1996, then she contributed person-time only during 1992–94 and 1994–96. Because this question was first asked in 1990 in both cohorts, eye exam eligibility was determined this way from the risk period 1988–1990 and onwards. For the initial periods 1980–88 in NHS and 1986–88 in HPFS, eye exam eligibility was based on responses to the first 1990 questions.

Measurement of caffeine consumption

In both cohorts, dietary intake data were collected repeatedly over follow-up with the use of a validated self-administered semiquantitative food frequency questionnaire (FFQ). FFQ's were administered in 1980, '84, '86, '90, '94 and '98 for the NHS and in 1986, '90, '94 and '98 for the HPFS. The NHS 1980 FFQ included 61 food / beverage items; the 1984 NHS FFQ was expanded to 116 items, and similar versions of it were used from 1986 on in both the NHS (126 items) and HPFS (131 items).

In the FFQ, participants were asked to report their average intake of a serving of a food or beverage over the preceding year. In the NHS, the 1980 FFQ asked about consumption of coffee with caffeine (in cups), tea with caffeine (in cups), and chocolate (in 1-ounce servings). From 1984 on in the NHS and from 1986 in the HPFS, the FFQ was expanded to include intakes of decaffeinated coffee (in cups) and separate items for caffeinated soda and caffeine-free sodas. The questionnaire provided nine response possibilities for intake frequency for each item ranging from “never or less than once per month” to “6 or more times per day”. To convert participants' average intake of one serving of a caffeinated beverage over the preceding year into average daily intakes of caffeine, we used information obtained from U.S. Department of Agriculture food-composition sources. The average caffeine contents used for these calculations were 137 mg caffeine per cup of coffee, 47 mg caffeine per cup of tea, 46 mg caffeine per can or bottle of cola beverage, and 7 mg caffeine per serving of chocolate.

Validity of food frequency questionnaire assessment of caffeine

The reproducibility and validity of the NHS and HPFS FFQs have been reported previously.^{17, 18} Validation studies revealed a high correlation between self-reported intake of caffeinated beverages (cups / day) according to the FFQ and diet records over 4 weeks: in the NHS, the correlations were 0.78 for coffee, 0.93 for tea and 0.84 for cola drinks¹⁹ and in the HPFS, the correlations were 0.93 for coffee, 0.77 for tea and 0.84 for cola drinks.²⁰

Case ascertainment

The glaucoma case ascertainment procedure is followed every two years and has three steps. First, in each mailed questionnaire administered every two years to participants, we ask about whether participants received eye exams and whether participants received a diagnosis of “glaucoma” from their eye care provider. In the second step, we follow-up on the participants who stated they received a diagnosis of glaucoma – we seek permission to retrieve their medical records related to their glaucoma diagnosis, then we request the eye care provider to complete a glaucoma questionnaire to provide us information on maximal IOP, information about the status of the filtration apparatus, structural information regarding the optic nerve, prior ophthalmic surgery, and any visual field loss or to send all relevant medical records. In the final step, we evaluated all the provided ophthalmic information from questionnaires / medical records and visual fields in a standardized manner.

All records were reviewed by a glaucoma specialist (LRP), masked to the caffeine consumption patterns of participants, to identify POAG cases according to standardized criteria. Only those appraised as either “definite” or “probable” POAG were included as cases in this analysis. For definite POAG cases, documentation of the following were required: (1) gonioscopy showed that angles were not occludable in either eye, (2) slit lamp biomicroscopy showed no indication in either eye of pigment dispersion syndrome, uveitis, exfoliation syndrome, trauma, or rubeosis, and (3) reproducible visual field (VF) defects were present and consistent with glaucoma (nasal step, nasal depression, paracentral scotoma, arcuate defects, or temporal wedge defects). For probable POAG cases, the slit lamp exam and visual fields criteria were also required, but for determining the angle of the anterior chamber, documentation of pupil dilation without subsequent adverse events was accepted in lieu of gonioscopy. For the cases included in the analysis, >70% met the criteria for “definite POAG”.

For all VF defects, we required that the same defect(s) be present on at least 2 reliable tests. There was no requirement for the type of perimetry performed; however, in 95% of cases, full static threshold testing was documented and only in <1% kinetic visual fields were used. For static threshold or suprathreshold testing, we consider the field reliable if the fixation loss rate was $\leq 33\%$, the false positive rate was $\leq 20\%$ and the false negative rate was $\leq 20\%$. For kinetic visual fields, we consider the field reliable unless there is notation by the examiner to the contrary.

During follow-up, 5,809 women and 2,529 men self-reported a glaucoma diagnosis. These were confirmed by eye care providers in 67% of women and 58% of men as follows: POAG with VF loss (29% women; 27% men), only elevated IOP or optic disc cupping (19% women; 20% men) and other types of glaucomas or glaucoma suspects (19% women; 11% men). The remaining 33% of self-reports in women and 42% in men could not be confirmed, as the participants themselves (6% women; 11% men), or their eye care providers (4% women; 5% men) could not be contacted, participants did not give permission to review their records (10% women; 11% men), participants indicated the initial report was in error (11% women; 14% men) or participants’ eye doctors disconfirmed the diagnosis of POAG (2% women; 1% men).

Of the 1,680 women and 695 men confirmed to have POAG with VF loss by their eye care providers, 658 women and 353 men met the criteria for “definite” or “probable” cases of and were included in the analyses.

Statistical Analysis

For the primary exposure, we calculated cumulatively updated caffeine intakes by averaging the intakes from all the available dietary assessments up to the start of each 2-year period at

risk. As glaucoma is a slowly developing chronic condition, we chose to study cumulatively averaged caffeine intakes as they best represent long-term intake and average measures have less measurement error than single assessments.²¹ All caffeine intakes at each questionnaire were total energy adjusted using the residual method.²²

Examining caffeinated beverages in addition to caffeine intake is important as results of such analyses strengthen the case for causality for caffeine if similar associations are found with caffeinated beverages that contribute to the caffeine intake. Also, individuals alter their caffeine intake predominately by altering their intake of caffeinated beverages, and thus the net effect of caffeinated beverages on the risk of primary open-angle glaucoma must be evaluated for possible public health recommendations. Thus we examined the risk of POAG in relation to categories of specific beverages: caffeinated coffee, tea, caffeinated soda and decaffeinated coffee. All intakes of specific caffeinated beverages were also cumulatively updated values. In the NHS, for soda and decaffeinated coffee, we used the data starting from 1984 when intakes of these beverages were first asked separately.

We calculated incidence rates of POAG by dividing the incident cases by person-years accrued for each caffeine or beverage intake category. We adjusted for age using 5-year categories, and calculated Mantel-Haenszel age-adjusted incidence rate ratios (RR) and their 95% confidence intervals (CIs). For multivariable analyses, we controlled for potential glaucoma risk factors by including them simultaneously in Cox proportional hazards analysis stratified by age in months and the specific 2-year period at risk.²³ We conducted tests for trend by including the midpoint values within each intake category.

Variables considered for inclusion were family history of glaucoma, African-American heritage (yes / no), body mass index (kg / m²), pack years of smoking, physical activity (quartiles of activity intensity / day), cumulatively updated alcohol intake (g / day), report of a physician exam, self reported history (yes / no) of hypertension, diabetes, cataract or age-related macular degeneration diagnoses, and total fluid intake (liters / day). Updated information on covariates was obtained from the biennial questionnaires; cumulatively updated alcohol intake and total fluid intake (based on intake of nearly 30 different types of beverages) was calculated using responses to the FFQs.

We first analyzed the data from each cohort separately and performed tests for heterogeneity of the cohort specific results to check for appropriateness of pooling the results. Then, we pooled the results using meta-analytic methods incorporating random effects.²⁴

Effect modification and secondary analyses

We performed several secondary analyses. First, we examined the influence of timing of exposure by examining caffeine intake only at baseline or at the most recent questionnaire. Second, we evaluated whether detection bias may have influenced the results, especially if caffeine consumption is related to better eye care. For this, we adjusted for other predictors of greater ophthalmic surveillance (i.e. number of eye exams, history of physician exams, diagnoses of other eye diseases, namely cataract and age-related macular degeneration).

We conducted additional analyses where we additionally adjusted for cumulatively updated total fluid intake. Because drinking a large quantity of fluids, particularly in a short period of time, generally causes IOP elevations,²⁵ we conducted this analysis to determine the association with caffeine intake, that was independent of total fluid intake.

Because caffeine increases intraocular pressure, we hypothesized that higher caffeine intake may be more strongly associated with glaucoma that is more likely to be IOP-related optic

nerve damage. Thus we separately analyzed the risk of “high-tension” POAG defined as those with maximum IOP ≥ 22 mm Hg before visual field loss (67.5% of all POAG cases).

Also, we conducted an analysis of caffeine intake only among participants who never smoked and who were past or current smokers. Caffeine metabolism is influenced by cigarette smoking; smoking induces the enzyme cytochrome P450 1A2 which is also involved in caffeine metabolism, and thereby reduces the effective dose of caffeine.²⁶ Thus we hypothesized that the effect of the same dose of caffeine may be greater among non-smokers.

Finally, to determine whether the influence of caffeine intake differed by inherent susceptibility to POAG, we examined the associations between caffeine intake and glaucoma separately among those with and without a self-report of family history of glaucoma. The questions on family history of glaucoma were first asked to all NHS and HPFS participants in the 2000 follow-up questionnaires; self-report of family history of glaucoma was defined as a positive answer to history of glaucoma in either of the biologic parents or in any siblings. In this and in other stratified analyses described above, we have statistically tested for effect modifications by testing the significance of pooled results of interaction terms in models.

RESULTS

During 1,647,312 person-years of follow-up we identified 1011 incident cases of POAG. Women consumed more caffeine (mean = 328 mg/day) than men (mean = 235 g/day), with 12.6 % consuming 600+mg of caffeine per day compared with only 7.3% in the men (Table 1). The highest consumers of caffeine were less likely to be African American, have a history of hypertension and engage in physical activity. Among women, those consuming the highest amounts of caffeine were less likely to have diabetes and be obese. Highest consumers of caffeine were more likely to have greater lifetime exposure to cigarette smoking and drink more alcohol. All these differences were accounted for in multivariable analyses.

In all primary analyses, we did not observe heterogeneity in the results between men and women and thus we pooled all cohort-specific results. Age-adjusted and multivariable analyses were similar. Compared with the reference group of <150 mg of caffeine / day, the pooled multivariable relative risk (RR, 95% Confidence Interval (CI)) of POAG was 1.05 (95% CI, 0.89 – 1.25) for 150–299 mg / day, 1.19 (95% CI, 0.99 – 1.43) for 300–449 mg / day, 1.13 (95% CI, 0.89 – 1.43) for 450–599 mg / day and 1.17 (95% CI, 0.90 – 1.53) for 600 + mg / day (p for linear trend = 0.11) (Table 2). When we modeled caffeine as a continuous variable, there was a weak positive association (p for trend=0.06).

When we explored the influence of the timing of exposure, the association between caffeine intake at baseline was similar to the main results: compared with consuming <150 mg of caffeine / day, the pooled multivariable relative risk (RR, 95% CI) of POAG was 1.19 (95% CI, 0.97 – 1.47) for 600 + mg / day (p for linear trend = 0.06). However, caffeine intake as of the most recent FFQ was not associated with risk of developing POAG (p for linear trend = 0.61).

In secondary analyses, there was little evidence for bias due to possible differences in ophthalmic surveillance by caffeine intake categories: results were similar to the main multivariable analysis results after we additionally adjusted for number of reported eye exams, history of physician exams and history of cataracts or age-related macular degeneration (Table 2). Similarly, the results were virtually identical to the main results

when we added total fluid intake in the models, indicating negligible confounding by total fluid intake (Table 2).

When we conducted the analysis among those who never smoked, we observed a suggestive positive association between high consumption of caffeine and risk of POAG: pooled RR for 600+ mg/day versus <150 mg/day was 1.53 (95% CI, 1.00 – 2.35; p for linear trend=0.14) (Table 2). There were no associations with caffeine among past or current smokers. The p-interaction by smoking status was 0.80.

When we evaluated the association between caffeine with POAG characterized by elevated IOP at the time of diagnosis among all participants, we observed adverse associations with increasing intake of caffeine in the women but not in the men (Table 2), although the p for heterogeneity between the trends from men and women was not statistically significant (p=0.07). For example, the RR for POAG for women consuming 600 + mg / day of caffeine was 1.59 (95% CI, 1.07 – 2.36; p for linear trend = 0.007), while for men the RR was 0.72 (95% CI, 0.37 – 1.38; p for linear trend=0.78).

When we examined specific caffeinated beverages, we found that increasing intake of caffeinated coffee was adversely associated with risk of POAG (p=0.02) (Table 3). Compared with those consuming 0 cups of caffeinated coffee per day, the pooled MV RRs were only slightly elevated for 1 – 4 cups / day (range of pooled MV RR = 1.07 to 1.20) and the estimates were not statistically significant. Consumption of 5 or more cups was associated with a borderline significant 1.61 fold higher risk of POAG (95% CI, 1.00 – 2.59). The percentage of those consuming 5 or more cups among the women was 4.6% and in the men, 2.2%. The trends were similar in relation to POAG with elevated IOP. In contrast, we observed essentially null associations with intake of de-caffeinated coffee (MV RR of POAG for 2 or more cups = 0.98, 95% CI 0.76 – 1.26). We observed no material associations between intakes of other caffeinated beverages such as caffeinated soda or tea. In fact, for tea, a suggestive borderline significant inverse trend was observed with higher intake (p=0.05). Associations with caffeinated beverages and POAG with elevated IOP showed similar results as the main analyses.

Because of the possible confounding by other caffeinated beverages (e.g. those consuming 0 cups of caffeinated coffee may all be tea only drinkers and vice versa), we conducted secondary analyses where we simultaneously entered terms for caffeinated coffee and tea in the same model. Indeed, we observed some attenuation in the relative risks for both beverages; however, the general adverse associations with caffeinated coffee remained. For example, the MV RR was 1.50 (95% CI, 0.98 – 2.29) for consumption of 5 or more cups of caffeinated coffee (p linear trend = 0.05) and the MV RR was 0.91 (95% CI, 0.69 – 1.20) for consumption of 2 or more cups of tea (p linear trend = 0.10).

When we examined the possibility of effect modification by self-reported family history of any type of glaucoma, we found that caffeine was associated with risk of POAG more strongly in those with positive family history (Table 4). For example, the p for linear trend among those with a positive family history was borderline significant (p=0.06); in addition, for highest consumption of caffeine, the pooled MV RR for POAG was 1.50 (95% CI, 0.66 – 3.43) among those with a positive family history which contrasts with the corresponding MV RR of 1.14 (95% CI, 0.81 – 1.61) among those with no family history. This contrast was particularly striking in relation to POAG with elevated IOP and the p for interaction with family history was borderline significant (p=0.04). The linear trend was statistically significant (p=0.0009) among those with a positive family history. The RR were elevated starting from 300 mg / day as the RR was 2.01 (95% CI, 1.08 – 3.74) for 600+ mg / day among those with a positive family history. This estimate contrasts to the RR of 0.94 (95%

CI, 0.59 – 1.49) for those with 600+ mg / day among those who did not report family history of glaucoma.

DISCUSSION

In this large, prospective study, overall caffeine consumption was not associated with risk of developing primary open-angle glaucoma (POAG). In one secondary analysis, we found that greater caffeine intake was associated with increased risks of primary open-angle glaucoma characterized by elevated intraocular pressure among those with a self-reported family history of glaucoma. However, because this was the first epidemiologic investigation of the relationship between caffeine intake and glaucoma in a population-based study, these secondary results must be interpreted cautiously and confirmed in future studies.

Although the association with overall intake of caffeine was null, our results support the possibility that caffeine may have adverse effects for those with inherent susceptibility to glaucoma. For example, for those with self-reported family history of glaucoma, the risk of POAG with elevated IOP diagnosis was higher starting from 300 mg / day and gradually increased linearly with increasing dose, which contrasts with essentially null relationship among those without family history. Although this finding may be due to chance, this may have a biologic basis and thus warrants further study. In studies that compared the IOP levels with respect to caffeine intake in patients with ocular hypertension, open-angle glaucoma and healthy volunteers, it was found that those with glaucoma had a significant greater elevation in IOP (~ 3 mmHg) with acute caffeine ingestion.^{7, 27} Also, in another study among healthy West Africans,¹⁰ who may be predisposed to glaucoma,^{28, 29} a transient IOP elevation of 4 mm Hg occurred with only 30–50 mg of caffeine, a relatively small caffeine dose. Further study is needed on how caffeine consumption may interact with genetic factors that influence IOP level³⁰ or factors that may modulate susceptibility to injury in the optic nerve.

The mechanism by which caffeine may influence IOP and thereby alter the risk of glaucoma is not clear, particularly because of caffeine's varied pharmacological effects on cellular processes. For adverse effects, there is evidence that caffeine could elevate IOP by increasing aqueous humor formation.³¹ Caffeine inhibits phosphodiesterase, which would result in maintaining high intracellular levels of cAMP of the ciliary body and possibly greater production of aqueous humor.³² In animals exposed to caffeine, ultrastructural changes in the non-pigmented ciliary epithelium were observed which may increase aqueous transport.³³ In addition, acute caffeine increases blood pressure before causing elevations in IOP;^{10, 12} increased blood pressure would increase the hydrostatic pressure for aqueous formation from plasma in the ciliary process capillary network.³⁴ The effect of caffeine in the aqueous outflow is not clear^{31, 35, 36}; one investigator hypothesized that caffeine may reduce outflow by decreasing the tone of smooth muscles via adenosine receptor blockade, leading to closure of trabecular pores in the aqueous outflow path.¹⁰ Caffeine has been shown to decrease blood flow to both the macula³⁷ and the optic nerve head and choroid-retina,³⁸ which may make the optic nerve more susceptible to elevated IOP.³⁹ In our data, this was more apparent among women – higher caffeine intake showed a dose response trend with increasing risk of POAG with elevated IOP at diagnosis (although difference between the genders for this was of borderline significance). Also, in our data, there was some support for a possible threshold effect and acute dosage effect with average consumption of five or more cups of caffeinated coffee per day over several years, which is consistent with mechanistic studies that show that high levels of caffeine, in doses found in about 1–3 cups of caffeinated coffee, causes transient elevations around 1 – 3 mmHg^{7, 11–13, 40} that lasts for about 2 hours.

We observed a suggestive inverse association with consumption of an average of 1 cup of tea consumption with the risk of developing POAG. Although this may be due to chance, recent studies have shown that flavonoids, rich in tea, lower IOP⁴¹ and protect retinal ganglion cells from damage^{42, 43}, thus flavonoid intake may be a fruitful area of future glaucoma research.

The strength of this study is the prospective design of the study where intakes of caffeine were assessed before disease occurrence, making recall bias, as would occur in case-control studies, highly unlikely. This was a large study with over 1000 incident cases, and 79,120 women and 42,052 men followed for at least 18 years, with high follow-up rates. Other strengths of our study include repeated dietary and lifestyle risk factor assessment over the follow-up; the multiple dietary assessments allowed us to examine timing effects of the relation between caffeine intake and POAG in various ways (i.e., baseline intake, recent intake, cumulative intake). In using detailed questions on extensively validated food frequency questionnaires, we were able to incorporate the caffeine intake from various sources and examine the association with various caffeinated drinks. Finally, we were able to control for numerous POAG risk factors, and they were updated biennially to take into account any changes over time.

Some limitations of our study must be considered. We acknowledge that because of the requirement of visual field loss, our protocol may have resulted in a greater percent of cases with moderate to severe disease than would have been detected in a direct standardized ophthalmologic survey. Also, both the NHS and HPFS are over 90% Caucasian. Thus our results may not be widely generalizable to populations with higher percentages of minorities, particularly those of African or Caribbean heritage who are at greater risk of POAG. Our participants are not a random sample of US men and women, so not all findings are directly generalizable to the entire population; however, it seems unlikely that the biological relations among the subjects in this cohort will differ greatly for the general population. In previous analyses of these cohorts, we have observed associations between caffeine and several chronic diseases^{16, 44, 45} that are very similar to those found in broadly-based US populations. Another limitation of epidemiologic studies is that of residual confounding; there may be other factors associated with high coffee consumption that we were not able to account for. We also lacked IOP data in all our participants to evaluate the association between caffeine and IOP.

In addition, we could not administer repeated eye exams in these large cohorts, and instead relied on questionnaire and medical record information for disease confirmation. Because of the insidious nature of glaucoma, our method of case ascertainment may have led to low sensitivity; however, methodologically, it is established that incidence rate *ratios* can still be validly estimated even with case definitions of low sensitivity, provided that the case definition is highly specific and the ascertainment method is not related to exposure.⁴⁶ In our study, the case definition is highly specific given the requirement of reproducible visual field defects and the case ascertainment is unlikely to be related to caffeine in that we required eye exams at each follow-up cycle. Furthermore, for construct validity of our case ascertainment method, we observed associations with established risk factors such as African ancestry (rate ratio = 4.08 (95% CI, 2.42–6.86)), and a positive family history of glaucoma (rate ratio = 4.06 (95% CI, 3.33–4.96)).

In summary, in this first prospective population-based investigation of the relationship between caffeine and risk of developing primary open-angle glaucoma, we found that overall caffeine consumption was not associated with increased risk of primary open angle glaucoma. The effect modification by family history on the association with caffeine deserves further study.

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Table 1
Age and age standardized characteristics according to cumulatively updated caffeine intake

		Categories of Cumulatively Updated Caffeine Intake (mg/day)				
		0–149	150–299	300–449	450–599	600+
% of total person-time	Women	23.3	26.4	26.0	11.7	12.6
	Men	46.0	22.6	15.9	8.2	7.3
Age (mean, yr)	Women	58.5	59.1	57.6	57.8	54.6
	Men	60.9	61.3	60.4	59.5	58.1
Caffeinated coffee (cups / day)	Women	0.2	1.0	2.2	3.2	4.7
	Men	0.2	1.2	2.3	3.1	4.3
Tea (cups / day)	Women	0.5	1.0	0.8	0.9	0.7
	Men	0.3	0.7	0.5	0.5	0.5
African Americans (%)	Women	2.2	1.4	0.9	0.6	0.5
	Men	1.0	0.7	0.3	0.2	0.2
Obesity (Body mass index ≥ 30 kg/m ² , %)	Women	22.6	22.2	19.7	20.8	18.6
	Men	7.9	9.9	10.5	11.2	11.3
Hypertension (%)	Women	36.8	35.8	32.2	30.4	26.6
	Men	47.1	48.3	47.7	47.4	46.7
Diabetes (%)	Women	6.4	5.9	4.8	4.4	4.0
	Men	10.2	10.2	10.6	10.6	10.6
Highest quartile of physical activity (%)	Women	25.8	25.3	24.6	23.8	21.5
	Men	27.0	25.7	24.9	22.9	20.3
30+ pack years of smoking (%)	Women	9.3	12.3	17.6	25.3	38.5
	Men	12.0	16.4	20.3	24.5	33.3
Alcohol intake (mean, g/day)	Women	4.3	5.9	7.2	6.8	6.5
	Men	9.0	12.2	13.7	12.6	11.2
Family history of glaucoma (%)	Women	13.9	14.0	13.5	12.8	12.5
	Men	11.3	12.3	11.6	11.1	10.6
Number of reported eye exams [‡]	Women	5.4	5.4	5.3	5.2	4.6

		Categories of Cumulatively Updated Caffeine Intake (mg/day)				
		0-149	150-299	300-449	450-599	600+
	Men	4.7	4.9	4.9	4.7	4.5

* Age-standardized characteristics over the entire follow-up period, using 5-year intervals of age

† Participants were asked up to 8 times during follow-up about eye exams in the past 2 years

Table 2

Relative risk of incident primary open-angle glaucoma across quintiles of caffeine intake

		CATEGORIES OF CUMULATIVELY UPDATED CAFFEINE INTAKE (mg/day)						<i>p-trend</i>
		0–149	150–299	300–449	450–599	600+		
<i>Primary analyses</i>								
	Women	Cases	152	194	175	78	59	
		Person-time	281,392	319,800	314,613	141,243	151,913	
		AA RR [*]	1.00 (ref)	1.07 (0.87, 1.32)	1.12 (0.90, 1.40)	1.10 (0.83, 1.45)	1.12 (0.82, 1.53)	
		MV RR [†]	1.00 (ref)	1.11 (0.89, 1.37)	1.19 (0.95, 1.49)	1.17 (0.88, 1.55)	1.23 (0.89, 1.68)	
Cumulatively updated intake	Men	Cases	168	80	61	25	19	
		Person-time	201,572	98,992	69,675	35,953	32,158	
		AA RR	1.00 (ref)	0.95 (0.73, 1.25)	1.08 (0.81, 1.45)	0.91 (0.60, 1.38)	0.86 (0.54, 1.38)	
		MV RR	1.00 (ref)	0.97 (0.73, 1.28)	1.20 (0.88, 1.64)	1.03 (0.66, 1.60)	1.05 (0.63, 1.73)	
	Pooled [‡]	MV RR	1.00 (ref)	1.05 (0.89, 1.25)	1.19 (0.99, 1.43)	1.13 (0.89, 1.43)	1.17 (0.90, 1.53)	
<i>Secondary analyses</i>								
	Pooled	MV RR	1.00 (ref)	1.06 (0.89, 1.25)	1.18 (0.98, 1.42)	1.11 (0.87, 1.40)	1.14 (0.87, 1.49)	
	Pooled	MV RR	1.00 (ref)	1.04 (0.88, 1.24)	1.18 (0.98, 1.43)	1.10 (0.86, 1.42)	1.14 (0.86, 1.52)	
	Women	MV RR	1.00 (ref)	1.08 (0.80, 1.44)	1.16 (0.84, 1.60)	0.99 (0.63, 1.57)	1.65 (1.02, 2.66)	
	Men	MV RR	1.00 (ref)	0.90 (0.56, 1.46)	1.29 (0.60, 2.80)	1.29 (0.60, 2.80)	1.14 (0.44, 2.99)	
Among never smokers [§]	Pooled	MV RR	1.00 (ref)	1.02 (0.80, 1.32)	1.12 (0.84, 1.48)	1.06 (0.72, 1.57)	1.53 (1.00, 2.35)	
	Women	MV RR	1.00 (ref)	1.18 (0.85, 1.64)	1.21 (0.87, 1.68)	1.22 (0.83, 1.78)	0.96 (0.62, 1.48)	
	Men	MV RR	1.00 (ref)	0.88 (0.58, 1.33)	1.23 (0.80, 1.88)	0.78 (0.41, 1.49)	1.10 (0.58, 2.07)	
	Pooled	MV RR	1.00 (ref)	1.05 (0.79, 1.39)	1.22 (0.94, 1.58)	1.06 (0.71, 1.58)	1.00 (0.70, 1.43)	
Among past and current smokers [§]	Women	MV RR	1.00 (ref)	1.49 (1.12, 1.98)	1.59 (1.18, 2.13)	1.61 (1.13, 2.31)	1.59 (1.07, 2.36)	
	Men	MV RR	1.00 (ref)	0.94 (0.68, 1.30)	1.06 (0.73, 1.54)	1.13 (0.69, 1.85)	0.72 (0.37, 1.38)	
	Pooled	MV RR	1.00 (ref)	1.19 (0.76, 1.87)	1.32 (0.89, 1.95)	1.41 (1.00, 1.98)	1.12 (0.51, 2.42)	
<i>Type of POAG</i>								
POAG with IOP ≥ 22 mm Hg (case n=428 women, n=256 men)								

* AA RR = Age adjusted relative risk; adjusted for age in seven 5-year categories

[†] MV RR = Multivariable relative risk adjusted for age (years), family history of glaucoma, African-American heritage, hypertension, diabetes, BMI (<22, 22–23, 24–25, 26–27, 28–29, 30+ kg/m² categories), smoking (0, 1–9, 10–19, 20–29, 30+ pack years), physical activity (quartiles of Met-hours/week), cumulatively updated alcohol intake (0, <5, 5–14, 15–29, 30+ g/day) and total caloric intake (quintiles of calories/day)

[‡] Cohort-specific results pooled using random effects; all tests for heterogeneity were not significant

[§] Additionally adjusted for number of eye exams, history of physician exams, history of cataract and history of age-related macular degeneration

^{||} p-interaction by smoking status was 0.80

Table 3

Multivariable Relative Risk (95% Confidence Interval) of Incident Primary Open-Angle Glaucoma Across Categories of Caffeinated Beverages*

<i>Caffeinated coffee (cups/day)</i>		0	<1 cup / day	1 cup / day	2 cups / day	3-4 cups / day	≥5 cups / day	<i>p-trend</i>
Women: POAG cases (n)		77	147	149	155	108	22	
Men: POAG cases (n)		80	107	59	66	31	10	
Pooled, All POAG		1.00 (ref)	1.07 (0.87, 1.32)	1.07 (0.86, 1.34)	1.17 (0.94, 1.46)	1.20 (0.93, 1.54)	1.61 (1.00, 2.59)	0.02
Pooled, POAG with IOP≥22 mmHg		1.00 (ref)	0.89 (0.69, 1.15)	1.03 (0.75, 1.42)	1.08 (0.83, 1.40)	1.16 (0.86, 1.56)	1.60 (1.00, 2.55)	0.02
<i>De-caffeinated coffee (cups/day)[†]</i>		0	<1 cup / day	1 cup / day	≥2 cups / day	<i>p-trend</i>		
Women: POAG cases (n)		131	145	68	148			
Men: POAG cases (n)		91	184	26	2			
Pooled, All POAG		1.00 (ref)	1.09 (0.92, 1.30)	1.07 (0.86, 1.34)	0.98 (0.76, 1.26)	0.88		
Pooled, POAG with IOP≥22 mmHg		1.00 (ref)	1.14 (0.85, 1.53)	0.96 (0.68, 1.36)	0.88 (0.64, 1.19)	0.23		
<i>Tea (cups/day)</i>		0	<1 cup / day	1 cup / day	≥2 cups / day	<i>p-trend</i>		
Women: POAG cases (n)		96	409	91	62			
Men: POAG cases (n)		97	208	24	20			
Pooled, All POAG		1.00 (ref)	1.01 (0.85, 1.20)	0.76 (0.58, 0.99)	0.88 (0.67, 1.16)	0.05		
Pooled, POAG with IOP≥22 mmHg		1.00 (ref)	0.99 (0.81, 1.22)	0.67 (0.37, 1.23)	0.94 (0.59, 1.51)	0.40		
<i>Caffeinated soda (serving[‡]/week)[†]</i>		<1 month	1-3 / month	1-4 / week	5+ / week	<i>p-trend</i>		
Women: POAG cases (n)		155	72	215	50			
Men: POAG cases (n)		83	38	141	41			
Pooled, All POAG		1.00 (ref)	1.09 (0.86, 1.38)	1.00 (0.84, 1.19)	1.19 (0.83, 1.71)	0.52		
Pooled, POAG with IOP≥22 mmHg		1.00 (ref)	1.16 (0.67, 1.99)	1.02 (0.78, 1.34)	1.31 (0.89, 1.92)	0.27		

* Participants with incomplete on the specific beverage have been excluded

[†] In women, information on intake of caffeinated or decaffeinated coffee was first asked separately in 1984; thus the follow-up is from 1984-2004

[‡] 1 serving for caffeinated soda is 1 "glass, bottle or can"

Table 4

Effect Modification of the Association between Caffeine intake and Incident Primary Open-Angle Glaucoma by Self-Reported Family History of Glaucoma (Multivariable Relative Risks, 95% Confidence Interval and p for interaction)*

EFFECT MODIFICATION	CATEGORIES OF CUMULATIVELY UPDATED CAFFEINE INTAKE (mg/day)						p-trend	p-interaction
	0-149	150-299	300-449	450-599	600+			
All POAG								
Women								
No Family History	1.00 (ref)	1.19 (0.90, 1.57)	1.09 (0.81, 1.46)	1.08 (0.75, 1.56)	1.12 (0.73, 1.71)	0.75		
Positive Family History	1.00 (ref)	0.81 (0.54, 1.22)	1.26 (0.84, 1.88)	1.24 (0.74, 2.08)	1.12 (0.63, 1.99)	0.19		0.58
Men								
No Family History	1.00 (ref)	0.78 (0.53, 1.12)	1.00 (0.68, 1.48)	1.06 (0.61, 1.83)	1.18 (0.65, 2.15)	0.67		
Positive Family History	1.00 (ref)	1.17 (0.63, 2.18)	2.53 (1.25, 5.16)	0.88 (0.27, 2.94)	1.81 (0.52, 6.25)	0.12		0.54
Pooled								
No Family History	1.00 (ref)	0.98 (0.64, 1.49)	1.06 (0.84, 1.34)	1.07 (0.79, 1.45)	1.14 (0.81, 1.61)	0.61		
Positive Family History	1.00 (ref)	0.90 (0.64, 1.27)	1.67 (0.85, 3.30)	1.18 (0.73, 1.89)	1.22 (0.72, 2.05)	0.06		0.43
POAG with IOP≥22 mmHg								
Women								
No Family History	1.00 (ref)	1.48 (1.02, 2.13)	1.35 (0.92, 1.98)	1.37 (0.87, 2.18)	1.04 (0.59, 1.83)	0.64		
Positive Family History	1.00 (ref)	1.27 (0.74, 2.17)	1.87 (1.10, 3.16)	1.94 (1.01, 3.71)	2.10 (1.06, 4.16)	0.006		0.15
Men								
No Family History	1.00 (ref)	0.71 (0.45, 1.11)	0.75 (0.45, 1.24)	1.04 (0.55, 1.96)	0.75 (0.33, 1.71)	0.39		
Positive Family History	1.00 (ref)	1.26 (0.61, 2.57)	3.58 (1.59, 8.06)	1.28 (0.37, 4.45)	1.66 (0.38, 7.15)	0.06		0.11
Pooled								
No Family History	1.00 (ref)	1.03 (0.50, 2.12)	1.03 (0.57, 1.84)	1.25 (0.86, 1.81)	0.94 (0.59, 1.50)	0.91		
Positive Family History	1.00 (ref)	1.26 (0.82, 1.94)	2.40 (1.29, 4.47)	1.77 (1.00, 3.15)	2.01 (1.08, 3.74)	0.0009		0.04

* This analysis was restricted to participants with complete information on family history of glaucoma in the 2000 follow-up questionnaires and who are Caucasians (>95% of the study population). "Family history" was defined as history of any glaucoma in either biological parent or any siblings