

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

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PURPOSE. To investigate whether caffeine, which transiently increases intraocular pressure (IOP) is associated with the risk of primary open-angle glaucoma (POAG).

METHODS. A total of 79,120 women from 1980 to 2004 and 42,052 men from 1986 to 2004, who were 40+ years of age, did not have POAG, and reported undergoing eye examinations, were observed. Information on caffeine consumption, potential confounders, and POAG diagnoses were repeatedly updated in validated follow-up questionnaires. One thousand eleven incident POAG cases were confirmed with medical record review. Cohort-specific and pooled analyses across cohorts were conducted to calculate multivariate rate ratios (RRs).

RESULTS. Compared with daily intake of less than 150 mg, the pooled multivariate RRs were 1.05 (95% confidence interval [CI], 0.89–1.25) for consumption of 150 to 299 mg/d, 1.19 (95% CI, 0.99–1.43) for 300 to 449 mg/d, 1.13 (95% CI, 0.89–1.43) for 450 to 559 mg/d, and 1.17 (95% CI, 0.90–1.53) for 600+ mg/d (*P* for trend = 0.11). However, for consumption of five or more cups of caffeinated coffee daily, the 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 a family history of glaucoma, particularly in relation to POAG with elevated IOP (*P* for trend = 0.0009; *P* interaction = 0.04).

CONCLUSIONS. 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 result may be due to chance, but warrants further study. (*Invest Ophthalmol Vis Sci.* 2008;49:1924–1931) DOI:10.1167/iops.07-1425

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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 the development^{2–4} 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 causes 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) causes 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 causes sustained, clinically significant IOP elevation, which could in turn increase the risk of development of POAG. However, to our knowledge, no population-based studies have examined the relationship between caffeine intake and the risk of POAG. Because caffeinated drinks such as coffee, tea, and colas, are consumed worldwide, even among older persons at risk of POAG (e.g., 80% of U.S. adults older than 50 years consume caffeine daily¹⁴), it is important to investigate this relationship.

We report the results of a prospective study of 79,120 women in the Nurses' Health Study (NHS) and 42,052 men in the Health Professionals Follow-up Study (HPFS) who were followed up 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.

METHODS

The NHS began in 1976 when 121,700 U.S. registered female nurses aged 30 to 55 years replied to a mailed health questionnaire (70% response rate).¹⁵ The HPFS started in 1986 with 51,529 U.S. 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 up with biennial questionnaires on numerous lifestyle habits, including caffeine consumption and newly diagnosed illnesses such as glaucoma. Follow-up response 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, the 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; the study period was restricted to 1980 to 2004 in the NHS and 1986 to 2004 in the HPFS. Generally, a participant contributed person-time if he or she was at least 40 years of age (as glaucoma risk increases after age 40) and reported having had an eye examination during the risk period (to minimize possible detection

bias). Participants contributed person-time in approximate 2-year units from the return date of the first questionnaire until a report of glaucoma, cancer, death, loss to follow-up, or 2004, whichever occurred first.

At baseline, the following participants were excluded: (1) 23,239 women who did not respond to the 1980 semiquantitative food frequency questionnaire (FFQ) assessment, (2) 5,994 women and 1,596 men with inadequate diet information on the FFQ (considered adequate information for women was fewer than 10 of 61 items blank and 500–3500 kcal/d, whereas fewer than 70 of 131 items blank in the FFQ, with a total caloric intake range of 800–4200 kcal/d 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 suspected glaucoma, (5) 739 women and 973 men lost to follow-up immediately after baseline, and (6) 6,472 women and 3,658 men who reported no eye examination during follow-up. After these exclusions, 80,831 women and 42,557 men remained. In addition, for each 2-year period, participants who were younger than 40 years or who did not report an eye examination were also considered ineligible. After excluding those temporarily ineligible because they were younger than 40 (17,045 women and 236 men) or did not report undergoing an eye examination when first asked (19,046 women and 12,512 men), 44,740 women and 29,809 men contributed person-time in the first 2 years from the NHS (1980–1982) and the HPFS (1986–1988). At later periods, these ineligible participants were allowed to contribute person-time, if they reached 40 years of age and reported having undergone eye examinations. Hence, by 2004, 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 examination criterion was determined by selecting those who responded positively to the question of whether they had undergone an eye examination within the previous 2 years. For example, if an NHS participant answered positively only in 1994 and 1996, then she contributed person-time only from 1992 to 1994 and 1994 to 1996. Because this question was first asked in 1990 in both cohorts, eye examination eligibility was determined this way from the risk period 1988 to 1990 and onward. For the initial periods 1980 to 1988 in NHS and 1986 to 1988 in HPFS, eye examination eligibility was based on responses to the first questions (asked in 1990).

Measurement of Caffeine Consumption

In both cohorts, dietary intake data were collected repeatedly during follow-up with the use of a validated, self-administered, semiquantitative FFQ. FFQs were administered in 1980, 1984, 1986, 1990, 1994, and 1998 for the NHS and in 1986, 1990, 1994, and 1998 for the HPFS. The NHS 1980 FFQ included 61 food and beverage items; the 1984 NHS FFQ was expanded to 116 items, and similar versions of it were used from 1986 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 on 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 FFQ 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 drinks,¹⁹ 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 was employed every 2 years and has three steps. First, in each mailed questionnaire administered every 2 years to participants, we asked about whether participants received eye examinations and whether they received a diagnosis of glaucoma from an eye care provider. In the second step, we followed up on the participants who stated that they received a diagnosis of glaucoma. We sought permission to retrieve the medical records related to the glaucoma diagnosis, and then we requested the eye care providers to complete a glaucoma questionnaire to provide us information on maximum IOP, information about the status of the filtration apparatus, structural information regarding the optic nerve, history of 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 or 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 showing that angles were not occluded in either eye; (2) slit lamp biomicroscopy showing no indication in either eye of pigment dispersion syndrome, uveitis, exfoliation syndrome, trauma, or rubeosis; and (3) reproducible test results showing that 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 examination 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 two reliable tests. There was no requirement for the type of perimetry performed; however, in 95% of cases, full static threshold testing was documented and in <1% were kinetic visual fields used. For static threshold or suprathreshold testing, we considered 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 considered the field reliable unless there was notation by the examiner to the contrary.

During follow-up, 5809 women and 2529 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 suspected glaucoma (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 1680 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 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 do single assessments.²¹ All caffeine intakes at each questionnaire were adjusted for 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 POAG 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 questions regarding 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 (RRs) and their 95% confidence intervals (CIs). For multivariate analyses, we controlled for potential glaucoma risk factors by including them simultaneously in Cox proportional hazards analyses 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 (kilograms per square meter); pack years of smoking; physical activity (quartiles of activity intensity/day); cumulatively updated alcohol intake (grams/day); report of a physician examination; 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 from the 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 by 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 examinations, history of physician examinations, and diagnoses of other eye diseases—namely, cataract and age-related macular degeneration).

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

Because caffeine increases IOP, we hypothesized that higher caffeine intake may be more strongly associated with glaucoma that is

more likely to involve IOP-related optic nerve damage. Thus, we separately analyzed the risk of high-tension POAG defined as a maximum IOP of ≥ 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 nonsmokers.

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 of 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 biological parents or in any siblings. In this and in other stratified analyses described herein, we 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. The women consumed more caffeine (mean, 328 mg/d) than did the men (mean, 235 g/d), with 12.6% consuming 600+ mg of caffeine per day compared with only 7.3% of the men (Table 1). The highest consumers of caffeine were less likely to be African American, had less hypertension, and engaged in less physical activity. Among the women, those consuming the highest amounts of caffeine were less likely to have diabetes and be obese. The 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 multivariate analyses.

In all primary analyses, we did not observe heterogeneity in the results between the men and women, and thus we pooled all cohort-specific results. Age-adjusted and multivariate analysis results were similar. Compared with the reference group of <150 mg of caffeine/day, the pooled multivariate relative risk (RR, 95% confidence interval [CI]) of POAG was 1.05 (95% CI, 0.89–1.25) for 150 to 299 mg/d, 1.19 (95% CI, 0.99–1.43) for 300 to 449 mg/d, 1.13 (95% CI, 0.89–1.43) for 450 to 599 mg/d, and 1.17 (95% CI, 0.90–1.53) for 600+ mg/d (*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 caffeine/day, the pooled multivariate relative risk (RR, 95% CI) of POAG was 1.19 (95% CI, 0.97–1.47) for 600+ mg/d (*P* for linear trend = 0.06). However, caffeine intake as of the most recent FFQ was not associated with the risk of POAG (*P* for linear trend = 0.61).

In the secondary analyses, there was little evidence of bias due to possible differences in ophthalmic surveillance by caffeine intake category. Results were similar to the main multivariate analysis results after we also adjusted for the number of reported eye examinations, history of physician examinations, and history of cataracts or age-related macular degeneration (Table 2). Similarly, the results were virtually identical with the main results when we added total fluid intake in the models, indicating negligible confounding by total fluid intake (Table 2).

TABLE 1. Age and Age-Standardized Characteristics According to Cumulatively Updated Caffeine Intake

	Categories of Cumulatively Updated Caffeine Intake (mg/d)				
	0-149	150-299	300-449	450-599	600+
Percent 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, y)					
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/d)					
Women	0.2	1.0	2.2	3.2	4.7
Men	0.2	1.2	2.3	3.1	4.3
Tea (cups/d)					
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 (BMI \geq 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/d)					
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
Reported eye examinations (<i>n</i>)†					
Women	5.4	5.4	5.3	5.2	4.6
Men	4.7	4.9	4.9	4.7	4.5

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

† Participants were asked up to eight times during follow-up about eye examinations in the past 2 years.

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/d versus <150 mg/d 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 in the men and women was not statistically significant (*P* = 0.07). For example, the RR for POAG for the women consuming 600+ mg/d of caffeine was 1.59 (95% CI, 1.07-2.36; *P* for linear trend = 0.007), whereas for the 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 no caffeinated coffee, the risk of POAG for those consuming one to four cups per day was only slightly elevated (range of pooled MV RR was from 1.07 to 1.20), and

the estimates themselves were not statistically significant. Consumption of five 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 five or more cups among the women was 4.6% and among 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 decaffeinated coffee (MV RR of POAG for two 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 results similar to those in the main analyses.

Because of the possible confounding by other caffeinated beverages (e.g., those consuming no cups of caffeinated coffee may all be tea-only drinkers and vice versa), we conducted secondary analyses in which 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%

TABLE 2. Relative Risk of Incident POAG Glaucoma across Quintiles of Caffeine Intake

	Categories of Cumulatively Updated Caffeine Intake (mg/d)					P-trend
	0-149	150-299	300-449	450-599	600+	
Primary analyses						
Cumulatively updated intake						
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)	0.12
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)	0.54
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)	0.11
Secondary analyses (MV RR)						
Additional control for predictors of greater ophthalmic surveillance, pooled§						
Additional control for cumulatively updated total fluid intake, pooled	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)	0.18
Among never smokers						
Women	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)	0.14
Men	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)	0.68
Pooled	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)	0.14
Among past and current smokers						
Women	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)	0.87
Men	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)	0.82
Pooled	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)	0.80
Type of POAG						
POAG with IOP ≥ 22 mm Hg¶						
Women	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)	0.007
Men	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)	0.78
Pooled	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)	0.39

* Age-adjusted relative risk; adjusted for age in seven 5-year categories.

† Multivariate 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/d), and total caloric intake (quintiles of calories/d).

‡ 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.

¶ Case *n* = 428 women, *n* = 256 men.

CI, 0.98-2.29) for consumption of five or more cups of caffeinated coffee per day (*P* linear trend = 0.05) and 0.91 (95% CI, 0.69-1.20) for consumption of two 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 a positive family history (Table 4). 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 RRs were elevated starting from 300 mg/d and the RR was 2.01 (95% CI, 1.08-3.74) for 600+ mg/d, 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/d, among those who did not report a 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 POAG 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 a self-reported family history of glaucoma, the risk of POAG with elevated IOP diagnosis was higher starting from 300 mg/d 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, it may have a biological basis and thus warrants further study. In studies that compared the IOP levels with respect to caffeine intake in patients with ocular hypertension, those with open-angle glaucoma, and healthy volunteers, it was found that those with glaucoma had a significant greater elevation in IOP (~3 mm Hg) with acute

TABLE 3. Multivariate RR (95% CI) of Incident POAG across Categories of Caffeinated Beverages*

Caffeinated coffee (cups/d)	0	<1 cup/d	1 cup/d	2 cups/d	3-4 cups/d	≥5 cups/d	<i>P</i> -trend
Women: POAG cases (<i>n</i>)	77	147	149	155	108	22	
Men: POAG cases (<i>n</i>)	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 mm Hg	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
De-caffeinated coffee (cups/d)†	0	<1 cup/d	1 cup/d	≥2 cups/d	<i>P</i> -trend		
Women: POAG cases (<i>n</i>)	131	145	68	148			
Men: POAG cases (<i>n</i>)	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 mm Hg	1.00 (ref)	1.14 (0.85-1.53)	0.96 (0.68-1.36)	0.88 (0.64-1.19)	0.23		
Tea (cups/d)	0	<1 cup/d	1 cup/d	≥2 cups/d	<i>P</i> -trend		
Women: POAG cases (<i>n</i>)	96	409	91	62			
Men: POAG cases (<i>n</i>)	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 mm Hg	1.00 (ref)	0.99 (0.81-1.22)	0.67 (0.37-1.23)	0.94 (0.59-1.51)	0.40		
Caffeinated soda (serving‡/week)†	<1 mo	1-3/mo	1-4/wk	5+/wk	<i>P</i> -trend		
Women: POAG cases (<i>n</i>)	155	72	215	50			
Men: POAG cases (<i>n</i>)	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 mm Hg	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 data on the specific beverage have been excluded.

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

‡ One serving of caffeinated soda is one glass, bottle, or can.

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 to 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 pharmacologic 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

TABLE 4. Effect Modification of the Association between Caffeine Intake and Incident POAG by Self-Reported Family History of Glaucoma*

Effect Modification	Categories Of Cumulatively Updated Caffeine Intake (mg/d)					<i>P</i> -trend	<i>P</i> -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	0.58
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	
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	0.54
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	
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	0.43
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	
POAG with IOP ≥ 22 mm Hg							
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	0.15
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	
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	0.11
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	
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	0.04
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	

* 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 a biological parent or any siblings.

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 effect 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 sexes 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 the mechanistic studies that show that high levels of caffeine, in doses found in approximately one to three cups of caffeinated coffee, causes transient elevations of ~1 to 3 mm Hg^{7,11-13,40} that lasts for ~2 hours.

We observed a suggestive inverse association with consumption of an average of 1 cup of tea consumption with the risk of development of POAG. Although this may be due to chance, recent studies have shown that flavonoids, rich in tea, lower IOP.⁴¹ 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. The study was large, with more 1000 incident cases, and 79,120 women and 42,052 men observed 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 FFQs, 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 percentage 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 >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 U.S. men and women, and 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 would differ greatly from those 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 broad-based U.S. 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 examinations 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 RRs 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 examinations 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 (RR = 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 POAG, we found that overall caffeine consumption was not associated with the increased risk of POAG. The effect modification by family history on the association with caffeine deserves further study.

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