

Comparison of Risk Factor Profiles for Primary Open-Angle Glaucoma Subtypes Defined by Pattern of Visual Field Loss: A Prospective Study

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PURPOSE. We explored whether risk factor associations differed by primary open-angle glaucoma (POAG) subtypes defined by visual field (VF) loss pattern (i.e., paracentral or peripheral).

METHODS. We included 77,157 women in the Nurses' Health Study (NHS) and 42,773 men in the Health Professionals Follow-up Study (HPFS 1986–2010), and incident medical record confirmed cases of paracentral ($n = 440$) and peripheral ($n = 865$) POAG subtypes. We evaluated African heritage, glaucoma family history, body mass index (BMI), mean arterial blood pressure, diabetes mellitus, physical activity, smoking, caffeine intake, and alcohol intake. We used competing risk Cox regression analyses modeling age as the metatime and stratified by age, cohort, and event type. We sequentially identified factors with the least significant differences in associations with POAG subtypes ("stepwise down" approach with P for heterogeneity [P -het] < 0.10 as threshold).

RESULTS. Body mass index was more inversely associated with the POAG paracentral VF loss subtype than the peripheral VF loss subtype (per 10 kg/m²; hazard ratio [HR] = 0.67 [95% confidence interval (CI): 0.52, 0.86] versus HR = 0.93 [95% CI: 0.78, 1.10]; P -het = 0.03) as was smoking (per 10 pack-years; HR = 0.92 [95% CI: 0.87, 0.98] versus HR = 0.98 [95% CI: 0.94, 1.01]; P -het = 0.09). These findings were robust in sensitivity analyses using a "stepwise up" approach (identify factors that showed the most significant differences). Nonheterogeneous (P -het > 0.10) adverse associations with both POAG subtypes were observed with glaucoma family history, diabetes, African heritage, greater caffeine intake, and higher mean arterial pressure.

CONCLUSIONS. These data indicate that POAG with early paracentral VF loss has distinct as well as common determinants compared with POAG with peripheral VF loss.

Keywords: glaucoma, visual field, epidemiology

Primary open-angle glaucoma (POAG) involves optic nerve fiber layer dropout that produces visual field (VF) loss, which can show heterogeneous patterns. The optic nerve contains distinct retinal ganglion cell populations that serve peripheral and paracentral visual function. Because the vulnerability of retinal ganglion cell subtypes may vary,^{1,2} the etiology of POAG may differ by the pattern of early VF loss. Inferior paracentral fibers are in the "macula vulnerability zone,"³ as the fovea lies below the disc, and accompanying blood vessels make more acute arcuate turns, creating shear forces that could compromise local blood flow. These features make them particularly vulnerable when there is dysfunction of endothelial cells, mitochondria, or the autonomic nervous system. In hereditary diseases with such dysfunctions like Leber's hereditary optic neuropathy or familial dysautonomia, there is maculopapillary bundle pathology with visual function deficits similar to early paracentral VF loss in POAG ("para-POAG").^{4–6} Also, genetic studies have identified loci that are more strongly

associated with para-POAG (e.g., in the intergenic *CAVI/CAV2* region,⁷ *p53* region,⁸ and the intergenic *GUCY1A3/GUCY1B3* region⁹) than peripheral VF loss subtype ("peri-POAG"). Thus, there is compelling evidence that the vulnerability of central fibers versus that of peripheral fibers may differ in POAG.

To further test this hypothesis, we used data from two population-based studies and conducted a competing risk analysis to assess whether POAG subtypes defined by VF loss may have unique determinants.

METHODS

Study Design and Population

The Nurses' Health Study (NHS)^{10,11} is a cohort of female registered nurses established in 1976 when 121,700 US women completed a lifestyle and health questionnaire. The Health Professionals Follow-up Study (HPFS)¹² is a cohort begun in

1986 when 51,529 male healthcare providers (e.g., dentists, veterinarians, pharmacists) completed a similar questionnaire. Participants provided updated information on mailed biennial questionnaires; the follow-up has been >85%. Informed consent was implied from voluntary completion of questionnaires; participants were free to discontinue participating at any time. The research adhered to the tenets of the Declaration of Helsinki. The Human Research Committees of Brigham & Women's Hospital, Massachusetts Eye and Ear Infirmary, and Harvard School of Public Health approved this study.

The study period was from 1986 (baseline) to 2010. The following were excluded at baseline:

1. Participants (NHS: $n = 29,233$) who did not respond to the initial semiquantitative food frequency questionnaires (SFFQs) or had inadequate dietary information (adequate dietary information consisted of >50 of 61 items completed yielding 500–3500 kcal/day);
2. Participants with prevalent cancers excluding nonmelanoma skin cancer, as cancer could profoundly affect risk factors (NHS: $n = 6297$; HPFS: $n = 1998$);
3. Participants with prevalent glaucoma (NHS: $n = 1388$; HPFS: $n = 1075$);
4. Participants (NHS: $n = 2096$; HPFS: $n = 1354$) lost to follow-up from 1976 to 1986 (NHS) or within 2 years of baseline (NHS/HPFS); and
5. Participants who never reported an eye exam during follow-up (NHS: $n = 3679$; HPFS: $n = 3441$).

After these exclusions, there were 79,007 NHS and 43,661 HPFS participants eligible for contributing person-time; however, at each 2-year risk period (from the return of one questionnaire to the next), we applied additional provisional exclusions for age, eye exam status, and covariate outlying values (see later section that defines outliers). For example, for the 1986 to 1988 risk period, only 53,052 NHS and 29,987 HPFS participants were allowed to contribute person-time after we provisionally excluded an additional 25,955 NHS and 13,674 HPFS participants for age <40 years (0 NHS and 246 HPFS); covariate outliers (774 NHS and 290 HPFS); and no eye exam (25,181 NHS and 13,138 HPFS). In later periods, those provisionally excluded were allowed in analyses if they newly met these criteria while still meeting the main eligibility criteria during follow-up: no prior report of glaucoma, no prevalent cancer, alive, and actively participating. Thus, during follow-up, the number of participants who ever contributed person-time was 77,157 in NHS and 42,773 in HPFS. Among cases, exclusions were not differential ($P = 0.58$) by POAG subtype. Among potential peri-POAG (618 NHS, 271 HPFS) versus para-POAG cases (303 NHS, 146 HPFS), those excluded due to prevalent cancer or covariate outliers were 2.7% (12 NHS, 12 HPFS) for peri-POAG and 2.0% (3 NHS, 6 HPFS) for para-POAG, leaving 865 peri-POAG cases (606 NHS and 259 HPFS) and 440 para-POAG cases (300 NHS and 140 HPFS) in analyses.

Ascertainment of POAG Cases and Classification of POAG by VF Loss Pattern

From participants self-reporting glaucoma, we obtained permission to retrieve medical information. Diagnosing eye care providers were sent a glaucoma questionnaire about maximum intraocular pressure (IOP), optic nerve features, filtration apparatus status, and any secondary causes for elevated IOP and were asked to send all VF reports; alternatively, they could send complete medical records. For

confirmation, a glaucoma specialist evaluated the available medical information in a standardized manner.

The case definition of POAG was the presence of a VF defect on a reliable test that was subsequently reproduced and was consistent with optic nerve fiber layer dropout, without slit lamp biomicroscopic findings showing secondary causes for elevated IOP. Those who could not be confirmed, had unreliable VFs, or had secondary glaucomas were censored in analyses (secondary glaucomas were censored as our goal was to better understand POAG etiology).

During the study, 8032 NHS and 3422 HPFS participants reported new glaucoma diagnoses. This was confirmed in 65% and 56% (NHS and HPFS, respectively): POAG (27% NHS, 27% HPFS), only elevated IOP or optic disc cupping (19% NHS, 16% HPFS), and other types of glaucoma/glaucoma suspect (19% NHS, 13% HPFS). The remaining (35% NHS, 44% HPFS) were unconfirmed, as the participants (7% NHS, 14% HPFS) or their eye care providers (4% NHS, 4% HPFS) could not be contacted; participants did not give permission for record review (12% NHS, 10% HPFS); participants indicated the initial report was erroneous (10% NHS, 14% HPFS); or eye care providers refuted the glaucoma diagnosis (2% NHS, 2% HPFS).

The Figure shows the various VF loss patterns and specific details of how peri-POAG and para-POAG were classified. Of note, para-POAG was defined as the earliest abnormal VF showing either isolated paracentral loss only or paracentral loss accompanied with VF loss in the Bjerrum area and nasal step area in the same hemifield, but without any loss in the temporal wedge region. We included the latter paracentral group as those with only isolated paracentral loss at diagnosis were uncommon (~21% of para-POAG cases; Table 1), whereas those with clear early paracentral loss frequently also showed peripheral loss. Primary open-angle glaucoma cases ($n = 209$) that could not be subtyped (paracentral VF loss with VF loss in any temporal wedge region in the same eye or paracentral VF loss in one hemifield with peripheral loss only in the other hemifield) were censored in analyses.

Assessment of Risk Factors

We focused on hypothesized POAG risk factors: African heritage,¹³ glaucoma family history,¹³ body mass index (BMI),¹⁴ mean arterial blood pressure,¹⁵ diabetes mellitus,^{16,17} physical activity,¹⁸ cigarette smoking,^{19,20} caffeine,²¹ and alcohol intake.²² All risk factors were assessed by self-report on questionnaires; validation studies have found a high degree of reliability and accuracy of information.^{11,23–27} Age was calculated as years from birthdate until the return of each questionnaire. Weight was assessed biennially and, along with height (assessed in 1976 in NHS and 1986 in HPFS), was used to calculate updated cumulatively averaged BMI (kg/m^2). With cumulative averaging every two years, the average of all available information was used (e.g., in 1986, the 1986 BMI values were used; in 1988, the average of 1986 and 1988 values was used; in 1990, the average of 1986, 1988, and 1990 values was used). This approach was used because glaucoma is a chronic disease, and cumulative averages represent participants' long-term exposure; also, with this approach, no participants had missing data. Cigarette smoking details were assessed biennially and pack-years of smoking was updated. Participants' reported time spent per week on eight to ten selected activities was multiplied by each activity's energy expenditure requirements (metabolic equivalents [METs]) and summed to yield MET hours per week.^{28,29} Diet was assessed in 1986 (also in 1980 and 1984 in NHS) and every 4 years thereafter using SFFQs. Participants reported the average consumption frequency of a portion size of specific foods/beverages containing alcohol (beer, wine, spirits) or caffeine

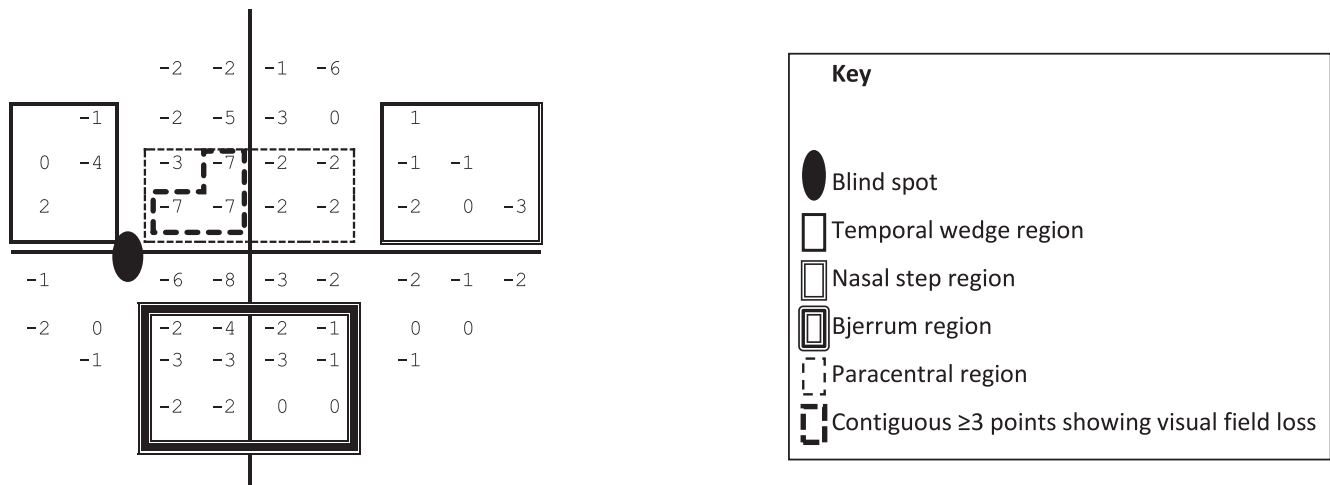


FIGURE. Paracentral and peripheral visual field loss definitions. A representative pattern deviation (PD) plot used to define the type of VF loss for the left eye is depicted. The different boxed areas represent the various regions that can show glaucomatous VF defects; defects were defined as ≥ 3 contiguous points that are < -5 decibels. The box with a dashed line indicates the paracentral region in the superior hemifield (the mirror-image region below the horizontal line indicates the corresponding inferior paracentral region). The boxes with solid lines indicate the peripheral loss regions: the nasal step region and temporal wedge regions in the superior hemifield and the Bjerrum region in the inferior hemifield. There is overlap between the Bjerrum region and the second row of the paracentral region. This was because the superior Bjerrum region evaluated had to be restricted as during VF review, we omitted the superior-most row of points in the upper visual field, which could be affected by ptosis; for symmetry, we applied the same overlap in the inferior hemifield. For a case to be defined as having peripheral loss, VF loss in the superior or inferior nasal step, temporal wedge, or Bjerrum regions had to be present with no loss in the paracentral regions. For a case to be defined as having early paracentral loss, VF loss in the superior or inferior paracentral zones had to be present without any peripheral VF loss or with peripheral VF loss, except for temporal wedge VF loss, in the same hemifield as the paracentral VF loss (those with advanced loss not meeting these criteria were censored at diagnosis). Here, the PD plot shows superior paracentral VF loss only (thick dashed lines).

(coffee, tea, cola, chocolate)³⁰ during the previous year. Nutrient values were calculated by multiplying the consumption frequency of each food/beverage portion by the nutrient content, summing these products across all items, and then adjusting for total energy intake³¹ and cumulatively averaged. Diabetes, systolic and diastolic blood pressure, hypertension, and various types of blood pressure-lowering medications were repeatedly asked in questionnaires. Mean arterial blood pressure was derived by using the updated cumulatively averaged values for systolic blood pressure and diastolic blood pressure in the following equation: $(1/3 \times \text{systolic blood pressure}) + (2/3 \times \text{diastolic blood pressure})$. To reduce the influence of outliers, we excluded outliers identified using the extreme studentized deviate many-outlier detection approach, assuming an upper limit of 2% of values being outliers.³² For each variable, at most 1.5% of person-time and cases with extreme values were excluded as outliers.

Statistical Analysis

We treated individuals as the unit of analysis rather than eyes, as eyes were not considered independently. Participants were classified according to the status of the eye(s) with reproducible VF loss, and the diagnosis date was the earliest date of any glaucomatous sign (IOP, cup to disc ratio, VF loss) in affected eye(s). Person-years of follow-up were accrued from the return of the 1986 questionnaire until glaucoma diagnosis, cancer, loss to follow-up, death, or 2010, whichever came first. Risk factors that showed linear associations with POAG risk (caffeine and alcohol intake, mean arterial blood pressure, systolic and diastolic blood pressure, physical activity, pack-years of smoking, and BMI) were modeled as continuous variables, with clinically meaningful units, while glaucoma family history, African ancestry, diabetes, hypertension, and use of antihypertensive medications were modeled as categorical variables.

We fit an extension of the Cox proportional hazards models for competing risks survival analyses to compute hazard ratios (HRs) and 95% confidence intervals (CIs). We used age as the time metameter,^{28,29} and we further stratified analyses by age (in months) to minimize confounding. We combined the data from the two cohorts into one dataset and then evaluated Cox proportional hazards models that stratified on cohort to allow for different hazards in the two cohorts. Competing risk modeling involved data augmentation where each subject had a separate observation for each outcome, with each observation having the same follow-up time but with a separate indicator variable for each POAG subtype. We stratified on event subtype to estimate separate associations of each risk factor to each outcome under a proportional hazard assumption in a single model.^{33,34} Separate subtype-specific covariates were constructed where they were defined to be equal to the value of the covariate in the observation corresponding to that subtype and to be equal to zero in observations corresponding to other subtypes.³⁵

We took the “stepwise down approach”³³⁻³⁵ where we started with an initial multivariable model that simultaneously adjusted for all factors but allowed different associations for each risk factor in relation to the two outcomes. We then iteratively fit a series of reduced models in which one risk factor at a time was allowed to have a single common estimate across the two outcomes. In each of these reduced models, the associations with the remaining risk factors were allowed to be different, so that the reduced model differed from the initial model by only one variable. We used likelihood ratio tests for heterogeneity to compare the initial model to each reduced model. Because these tests for heterogeneity are low powered, we used a conservative *P* value for heterogeneity (*P*-het) of < 0.10 as the threshold for the likelihood ratio test to indicate that the associations with a risk factor were different for the two outcomes. We set the risk factor with the largest *P*-het that was ≥ 0.10 to have a single estimate across the two outcomes,

TABLE 1. Age and Age-Adjusted Characteristics* of All Person-Time and of Cases of POAG Subtypes Defined by Pattern of VF Loss, NHS, and HPFS (1986–2010), United States

	NHS (All Women)			HPFS (All Men)		
	All Person-Time,† n = 1,161,616	POAG Cases With Paracentral VF Loss, n = 300	POAG Cases With Peripheral VF Loss, n = 606	All Person-Time,† n = 554,598	POAG Cases With Paracentral VF Loss, n = 140	POAG Cases With Peripheral VF Loss, n = 259
Age in years, mean (SD)	62.3 (9.3)	66.5 (7.6)	65.0 (7.9)	62.1 (10.4)	67.5 (8.9)	67.9 (8.3)
Family history of glaucoma, %	12.6	26.4	31.9	10.6	32.7	22.8
African ancestry, %	1.2	2.5	2.1	0.7	0.0	3.3
Diabetes, %	7.3	8.6	8.9	6.4	6.6	13.5
Hypertension: treated, %	34.0	40.1	38.6	27.1	33.1	32.8
Hypertension: no report of pharmacological treatment, %	8.3	6.8	9.0	8.2	8.1	8.8
Systolic blood pressure (mm Hg)‡, mean (SD)	127.3 (11.1)	128.3 (11.2)	130.0 (11.7)	128.8 (9.9)	129.7 (9.1)	130.8 (9.9)
Diastolic blood pressure (mm Hg)‡, mean (SD)	78.7 (6.6)	79.4 (6.9)	79.5 (6.5)	80.3 (6.1)	80.7 (5.6)	81.4 (5.9)
Mean arterial blood pressure (mm Hg)‡, mean (SD)	94.9 (7.5)	95.7 (7.8)	96.3 (7.5)	96.5 (6.5)	97.0 (6.0)	97.9 (6.4)
Ever smoking history, %	53.3	48.1	51.3	47.4	45.8	51.5
Pack years among ever smokers, mean (SD)	22.9 (19.9)	20.9 (19.1)	23.4 (21.5)	23.7 (18.0)	24.9 (16.3)	24.5 (19.2)
Alcohol intake as drinks per day,‡§ mean (SD)	0.5 (0.7)	0.5 (0.7)	0.5 (0.7)	0.9 (1.0)	0.8 (0.9)	1.1 (1.2)
Caffeine intake as cups of caffeinated coffee per day,‡ mean (SD)	2.2 (1.4)	2.1 (1.2)	2.2 (1.4)	1.7 (1.5)	1.6 (1.5)	1.7 (1.5)
Physical activity (MET-hours/wk),‡ mean (SD)	15.9 (14.7)	18.6 (17.2)	16.5 (14.2)	30.0 (25.7)	30.8 (21.8)	28.5 (23.4)
BMI (kg/m ²),‡ mean (SD)	25.8 (4.7)	25.3 (4.5)	25.9 (4.9)	25.7 (3.1)	25.3 (2.6)	25.6 (2.9)
Clinical characteristics of cases						
Maximum untreated IOP (mm Hg),¶ mean (SD)	N/A	21.7 (4.3)	22.7 (5.0)	N/A	23.2 (5.1)	24.6 (5.3)
Vertical cup to disc ratio,¶ mean (SD)	N/A	0.7 (0.2)	0.6 (0.2)	N/A	0.7 (0.2)	0.6 (0.2)
VF pattern standard Deviation (dB),¶ mean (SD)	N/A	7.0 (3.9)	4.4 (2.2)	N/A	7.4 (3.6)	4.7 (2.4)
Age at diagnosis, mean (SD)	N/A	67.6 (7.6)	66.1 (7.8)	N/A	68.7 (8.8)	69.0 (8.3)
Affected in only one eye, n (%)	N/A	188 (62.7)	430 (71.0)	N/A	86 (61.4)	193 (74.5)
Paracentral VF loss pattern by affected eye, n (%):						
1 eye affected with paracentral loss only	N/A	59 (19.7)	N/A	N/A	28 (20.0)	N/A
1 eye with paracentral + peripheral loss	N/A	129 (43.0)	N/A	N/A	58 (41.4)	N/A
Both eyes with paracentral loss only	N/A	5 (1.7)	N/A	N/A	1 (0.7)	N/A
1 eye: paracentral; 1 eye: paracentral + peripheral	N/A	14 (4.7)	N/A	N/A	6 (4.3)	N/A
Both eyes: paracentral + peripheral	N/A	16 (5.3)	N/A	N/A	11 (7.9)	N/A
1 eye: paracentral; 1 eye: peripheral	N/A	16 (5.3)	N/A	N/A	8 (5.7)	N/A
1 eye: paracentral + peripheral; 1 eye: peripheral	N/A	61 (20.3)	N/A	N/A	28 (20.0)	N/A

* Values are mean with standard deviations in parentheses or percentages or percentages and are standardized to the age distribution of the study population.

† Person-time accrued from 77,157 women in the NHS and 42,773 men in the HPFS from 1986 to 2010.

‡ Variables were cumulatively updated using the data from all the prior available questionnaires as of each risk period.

§ One alcoholic drink was considered equivalent to intake of 10.8 g of alcohol.

|| One cup of caffeinated coffee was considered equivalent to intake of 137 mg of caffeine.

¶|| Values are as of diagnosis. If only one eye is diseased, values are the maximum values from that eye. If both eyes are diseased, values are the greater value from either eye.

and this became the new comparison model for the next iteration. For factors represented by multiple variables (e.g., no hypertension, hypertension with no report of treatment, hypertension with treatment), a single test compared the associations of all variables across subtypes. We repeated these steps until we obtained a final parsimonious model that equated those relationships of a risk factor with different outcomes when there was little statistical evidence for differences and that estimated different associations for different outcomes for those risk factors that showed P -het < 0.10.³⁵

In secondary analyses, we explored the associations with various vascular risk factors, as vascular factors have been implicated in para-POAG.¹ We evaluated separate competing risk survival analysis models that assessed four different vascular risk factors in place of mean arterial blood pressure: systolic blood pressure, diastolic blood pressure, hypertension status (history of treatment or no report of treatment), and hypertension status by diuretic drug use (currently treated with diuretics, currently treated with other blood pressure-lowering drugs, or no current treatment), as diuretic drugs have been previously associated with POAG.³⁶

In sensitivity analyses to evaluate the internal validity, we used a “stepwise up approach” where we started with an initial multivariable model that assumed similar associations for every risk factor in relation to the two outcomes. We then iteratively fit a series of expanded models in which one risk factor at a time had two different estimates for the two outcomes, while the remaining risk factors had the same estimate for the two outcomes, and we used P -het < 0.10 as the threshold.

RESULTS

Participants' mean age was 62 years, and their mean BMI was 26 kg/m² (Table 1). Participants in NHS were more likely than HPFS participants to have been treated for hypertension, smoked, and consumed more caffeine, while they drank less alcohol, exercised less, and had somewhat lower systolic, diastolic, and mean arterial blood pressure. Cohort participants had similar frequencies of glaucoma family history (11%–13%), African ancestry (1%), and diabetes (6%–7%).

We observed 1305 incident POAG cases: 440 para-POAG cases (300 women and 140 men) and 865 peri-POAG cases (606 women and 259 men). Compared with peri-POAG cases, para-POAG cases were less likely to smoke, had lower BMI, exercised more, and had lower systolic, diastolic, and mean arterial blood pressures; they also had worse mean pattern standard deviations (PSD) but lower mean IOP.

In arriving at the final reduced model in competing risk analyses, we observed two factors differ in their magnitude of association (not direction) with the two outcomes (Table 2): pack-years of smoking and BMI. In the final reduced model, BMI was significantly more strongly inversely associated with risk of para-POAG than with risk of peri-POAG (per 10 kg/m²; HR = 0.67 [95% CI: 0.52, 0.86] versus HR = 0.93 [95% CI: 0.78, 1.10]; P -het = 0.03). Greater pack-years of cigarette smoking was significantly more inversely associated with risk of para-POAG (per 10 pack-years; HR = 0.92 [95% CI: 0.87, 0.98] versus HR = 0.98 [95% CI: 0.94, 1.01]; P -het = 0.09). Other risk factors of African ancestry, glaucoma family history, diabetes, higher mean arterial blood pressure, and greater caffeine intake were significantly adversely associated with both outcomes, and in the final reduced model, these risk factors had common estimates for the two subtypes (Table 2). In sensitivity analyses, the results were essentially unchanged when mean arterial blood

pressure was taken out of analyses to address the possibility that BMI and smoking may influence risk through altering blood pressure (data not shown).

In analyses of other vascular risk factors as alternatives to mean arterial blood pressure, higher diastolic blood pressure significantly increased the risk of both subtypes (P -het = 0.71; Table 3). However, there were no associations with the other vascular risk factors and either outcome.

In sensitivity analyses, where the stepwise up approach was used, we identified the same risk factors, BMI, and cigarette smoking, as having different estimates for the two outcomes. This provided support for internal validity.

DISCUSSION

In this large prospective study, consistent with another study,¹ para-POAG was associated with lower IOP and more pronounced focal VF defects as indicated by higher PSD values than peri-POAG. Higher BMI and greater pack-years of smoking were significantly more inversely associated with para-POAG than with peri-POAG, while other risk factors, such as family history and African ancestry, showed similar associations with the two outcomes. These results were robust in sensitivity analyses and underscore the notion that para-POAG and peri-POAG may have different etiologies.

Cigarette smoking was more strongly inversely associated with para-POAG. The relation between cigarette smoking and POAG overall has been conflicting,^{37–40} and no study, to our knowledge, has evaluated the association between cigarette smoking and POAG subtypes defined by VF loss pattern. The mechanism underlying this differential association is unknown. However, cigarette smoking or nicotine ingestion may have vascular effects that may preferentially affect paracentral fibers. Vascular effect may include increasing blood velocity in the macula,⁴¹ optic nerve head⁴² and ophthalmic artery, although effects on the actual blood flow in relevant vascular beds are unknown.⁴³ Also, cigarette smoke/nicotine may be directly neuroprotective as a source of nitric oxides,⁴⁴ as an agonist of the nicotinic acetylcholine receptors⁴⁵ or be indirectly neuroprotective by increasing blood flow to the optic nerve via nicotine-induced dilatation mediated by nitric oxide liberated from perivascular nitrergic neurons.^{46,47}

The mechanism underlying the inverse relation between higher BMI and POAG, particularly with para-POAG, is also unknown. Those with low BMI (e.g., BMI < 18.5) may have impaired endothelium-dependent vasodilation⁴⁸ or have low cerebrospinal fluid (CSF) pressure,^{49,50} which has been consistently adversely associated with POAG risk.^{51–56} Thus, lower BMI and resulting lower CSF may translate into a higher translaminal cribriform pressure gradient^{57,58} that may be deleterious, particularly for the axonal transport in the paracentral fibers.

Many studies have evaluated blood pressure-related parameters and POAG risk, and the results have been inconsistent.^{59–63} The one parameter where there is some consistency has been lower ocular perfusion pressure,^{59–61} which we could not measure. Mean arterial pressure, which is a component of ocular perfusion pressure, and diastolic blood pressure were associated with higher POAG risk, regardless of POAG subtype. No associations were observed with systolic blood pressure and hypertension, whether treated or untreated, which is consistent with prior studies.^{59,62} However, our data need to be interpreted with caution, as true relations between blood pressure and POAG risk are likely complex and may depend on factors we could not measure (e.g., genetics,⁶⁴ nocturnal blood

TABLE 2. Hazard Ratios of Various Risk Factors and Their Differential Relations With POAG Subtypes Defined by VF Loss Pattern (Paracentral and Peripheral): Results of Stepwise Competing Risk Analysis,* Using Data From the NHS and HPFS (1986–2010), United States

Variable	Initial Full Model*†‡		Final Reduced Model*†‡§	
	POAG With Paracentral VF Loss HR (95% CI)	POAG With Peripheral VF Loss HR (95% CI)	POAG With Paracentral VF Loss HR (95% CI)	POAG With Peripheral VF Loss HR (95% CI)
Mean arterial blood pressure (per 5 mm Hg)	1.04 (0.96, 1.11)	1.06 (1.01, 1.11)		1.05 (1.01, 1.09)
Caffeine intake (per cup of caffeinated coffee/d) ¶	1.04 (0.96, 1.11)	1.07 (1.02, 1.12)		1.06 (1.02, 1.10)
African ancestry	1.70 (0.83, 3.47)	2.31 (1.49, 3.56)	0.66	2.10 (1.45, 3.05)
Family history of glaucoma	2.98 (2.41, 3.70)	3.32 (2.86, 3.86)	0.46	3.20 (2.83, 3.62)
Physical activity (per 1.75 MET-h/wk) #	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	0.42	1.00 (1.00, 1.01)
Alcohol intake (per alcoholic drink/d) ¶	0.97 (0.86, 1.09)	1.04 (0.96, 1.12)	0.40	1.02 (0.95, 1.08)
Diabetics	1.15 (0.80, 1.64)	1.44 (1.14, 1.81)	0.35	1.34 (1.11, 1.63)
Pack-years of smoking (per 10 pack-years)	0.93 (0.88, 0.99)	0.97 (0.94, 1.01)	0.28	0.98 (0.94, 1.01)
BMI (per 10 units, kg/m ²)	0.70 (0.54, 0.91)	0.91 (0.76, 1.08)	0.21	0.67 (0.52, 0.86)

* Stepwise down competing risk Cox regression modeling was conducted. The initial full model assumed different associations of each risk factor with the two outcomes. Sex was set to provide different estimates for the two outcomes given the differences in the cohorts. A series of reduced models in which one risk factor at a time was constrained to have a single estimate for the two outcomes were fit. The values of *P* for heterogeneity presented are the results of this procedure of testing against the initial full model. In successive iterations, the risk factor with the largest *P* value for heterogeneity based on likelihood ratio tests was set to have a single estimate across the two outcomes (if *P* > 0.10), and this became the new model for the next round of testing. These steps were repeated until a final reduced model was obtained in which the only risk factors with different estimates across the two outcomes were those with *P* for heterogeneity < 0.10.

† Age was the time metamer in all Cox regression models with stratification for age (in months), cohort, and glaucoma subtype stratum.

‡ In the initial full model, all nine variables were simultaneously adjusted for and were modeled to provide different estimates for each outcome; therefore, there are two estimates for each outcome.

§ In the final reduced model, all variables, except for smoking and BMI, that showed nonsignificant (*P* < 0.10) heterogeneity in the estimates for the two outcomes were modeled to provide a common estimate for parsimony, and the two risk factors that showed significant heterogeneity in associations with the two outcomes were modeled to yield two different estimates for each outcome.

|| Variables were cumulatively updated using the data from all the prior available questionnaires as of each risk period.

¶ One cup of caffeinated coffee was considered equivalent to intake of 137 mg of caffeine; one alcoholic drink was considered equivalent to intake of 10.8 g of alcohol.

A unit of 1.75 MET-hours/week was considered equivalent to an increase of 30 minutes of brisk walking per week.

TABLE 3. Hazard Ratios of Various Vascular Risk Factors and Their Differential Relations With POAG Subtypes Defined by VF Loss Pattern (Paracentral and Peripheral): Results of Stepwise Competing Risk Analysis,* Using Data From the NHS and HPS (1986–2010), United States

Variable	Initial Full Model†‡		Final Reduced Model†‡§	
	POAG With Paracentral VF Loss HR (95% CI)	POAG With Peripheral VF Loss HR (95% CI)	POAG With Paracentral VF Loss HR (95% CI)	POAG With Peripheral VF Loss HR (95% CI)
Hypertension, history of treatment	1.08 (0.87, 1.34)	1.00 (0.86, 1.17)	1.03 (0.90, 1.17)	1.05 (0.85, 1.29)
Hypertension, no report of any treatment	0.98 (0.68, 1.42)	1.08 (0.84, 1.39)		
Hypertension, currently being treated with diuretics	1.03 (0.74, 1.44)	1.11 (0.88, 1.39)	0.72	1.08 (0.90, 1.31)
Hypertension, currently being treated with other drugs¶	1.10 (0.84, 1.45)	0.95 (0.77, 1.17)		1.00 (0.85, 1.18)
Hypertension, no current treatment¶	1.04 (0.79, 1.36)	1.03 (0.85, 1.25)		1.03 (0.88, 1.21)
Diastolic blood pressure (per 5 mm Hg)#	1.08 (1.00, 1.17)	1.06 (1.01, 1.13)	0.71	1.07 (1.02, 1.12)
Systolic blood pressure (per 5 mm Hg)#	0.99 (0.94, 1.04)	1.03 (1.00, 1.06)	0.17	1.02 (0.99, 1.04)

* From the model in Table 2, the variable mean arterial blood pressure was substituted with each of the four groups of vascular variables above; only the results for the vascular risk factors from four different competing risks models are presented. Stepwise down competing risk Cox regression modeling was conducted. The initial full model assumed different associations of each risk factor with the two outcomes. Sex was set to provide different estimates for the two outcomes given the differences in the cohorts. A series of reduced models in which one risk factor at a time was constrained to have a single estimate for the two outcomes were fit. The values of P for heterogeneity presented are the results of this procedure of testing against the initial full model. In successive iterations, the risk factor with the largest P for heterogeneity based on likelihood ratio tests was set to have a single estimate across the two outcomes (if $P > 0.10$), and this became the new model for the next round of testing. These steps were repeated until a final reduced model was obtained in which the only risk factors with different estimates across the two outcomes were those with P for heterogeneity < 0.10 .

† Age was the time metameter in all Cox regression models with stratification for age (in months), cohort, and glaucoma subtype stratum.

‡ In the initial full model, all nine variables were simultaneously adjusted for and were modeled to provide different estimates for each outcome; therefore, there are two estimates for each outcome.

§ In the final reduced model, all variables, except for smoking and body mass index, that showed no significant ($P < 0.10$) heterogeneity in the estimates for the two outcomes were modeled to provide a common estimate for parsimony, and the two risk factors that showed significant heterogeneity in associations with the two outcomes were modeled to yield two different estimates for each outcome.

|| The parameters of treated hypertension and hypertension with no report of treatment were tested together in the likelihood ratio test (2 degrees of freedom [DOF]).

¶ The parameters of hypertension treated with diuretics, hypertension treated with other drugs, and hypertension with no report of treatment were tested together in the likelihood ratio test (3 DOF).

Variables were cumulatively updated using the data from all the prior available questionnaires as of each risk period.

pressure dips,^{65,66} simultaneous IOP levels,^{59,61} and systemic treatment³⁶).

Study limitations included the lack of standardized eye exams, which may have led to case under-ascertainment. In studies with case under-ascertainment, biases are minimized if the case definition is specific and if the ascertainment is uniform across risk factors evaluated. It is possible that peripheral VF damage was less likely to be noticed by POAG cases early in the disease process as it has less impact on daily living versus paracentral loss and that this could lead to differential ascertainment for the two outcomes depending on risk factor levels. However, in our data, the opposite seemed to be true in that those with peri-POAG came to eye care providers' attention earlier: 62% of those with para-POAG and 72% of those with peri-POAG had only one eye affected at diagnosis. Cases of para-POAG may not have been detected earlier as when one eye is affected with para-POAG, the fellow eye may compensate.^{67,68} Although this potential differential under-ascertainment of para-POAG may explain some of the inverse associations observed with higher BMI and cigarette smoking, it is unlikely to explain all of the results. In our previous studies, greater BMI and smoking were adversely associated with cataract extractions and macular degeneration,⁶⁹⁻⁷³ which also affect central vision and impair daily functioning, indicating that the associations likely represent biologic mechanisms rather than biases. Also, cases of peri-POAG had higher untreated IOP than para-POAG cases, and these tonometric readings may have prompted them to seek eye care earlier. Thus, given the specificity of our case definition, the standardized classification of POAG cases by VF pattern, the restriction of the person-time to participants who reported eye exams, and the adjustment for many confounders, it is unlikely that detection biases explain all of our results.

Another limitation was the lack of information on IOP, an important covariate, for all participants. Also, there may have been misclassification of POAG subtypes, but it is unlikely that the misclassification was differential by BMI or smoking status; however, the inclusion in the para-POAG group of those with both paracentral and peripheral VF loss may have biased results toward the null. Also, the generalizability of the results might be limited, as our participants were mostly healthy, screened, and highly educated European-derived Caucasians; thus, associations may differ in other populations. Finally, this was a data-driven analysis, involving multiple comparisons; thus, the results need confirmation in other large studies for external validity.

Study strengths include the 20+ years of follow-up on a large number of study participants in a prospective population-based setting. Also, multiple risk factors of interest could be simultaneously evaluated.

In conclusion, cigarette smoking and BMI had statistically different magnitude of associations with POAG subtypes defined by early VF loss pattern. Identifying unique determinants of each subtype may improve our approach to studying POAG etiology.

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