tvst

Glaucoma

Cohort Study of Race/Ethnicity and Incident Primary Open-Angle Glaucoma Characterized by Autonomously Determined Visual Field Loss Patterns

Jae H. Kang[1,*], Mengyu Wang[2,3,*], Lisa Frueh[1,4], Bernard Rosner[1,4], Janey L. Wiggs[3], Tobias Elze[2], and Louis R. Pasquale[5]

[1] Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[2] Harvard Ophthalmology AI Lab, Schepens Research Eye Institute of Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, USA
[3] Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, USA
[4] Harvard T.H. Chan School of Public Health, Boston, MA, USA
[5] Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Correspondence: Jae H. Kang, Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, 181 Longwood Avenue, Boston, MA 02114, USA.
e-mail: nhjhk@channing.harvard.edu

Received: January 17, 2022
Accepted: May 23, 2022
Published: July 25, 2022

Keywords: race; ethnicity; epidemiology; glaucoma; visual field loss

Citation: Kang JH, Wang M, Frueh L, Rosner B, Wiggs JL, Elze T, Pasquale LR. Cohort study of race/ethnicity and incident primary open-angle glaucoma characterized by autonomously determined visual field loss patterns. Transl Vis Sci Technol. 2022;11(7):21, https://doi.org/10.1167/tvst.11.7.21

Purpose: We evaluated racial/ethnic differences in primary open-angle glaucoma (POAG) defined by machine-learning–derived regional visual field (VF) loss patterns.

Methods: Participants ($N = 209{,}036$) from the Nurses' Health Study (NHS; 1980–2018), Nurses' Health Study II (NHS2; 1989–2019), and Health Professionals Follow-Up Study (HPFS; 1986–2018) who were ≥40 years of age and free of glaucoma were followed biennially. Incident POAG cases ($n = 1946$) with reproducible VF loss were confirmed with medical records. Total deviation information from the earliest reliable glaucomatous VF for each POAG eye ($n = 2564$) was extracted, and machine learning analyses were used to identify optimal solutions ("archetypes") for regional VF loss patterns. Each POAG eye was assigned a VF archetype based on the highest weighting coefficient. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using per-eye Cox proportional hazards models.

Results: We identified 14 archetypes: four representing advanced loss patterns, nine of early loss, and one of no VF loss. Compared to non-Hispanic whites, black participants had higher risk of early VF loss archetypes (HR = 1.98; 95% CI, 1.48–2.66) and even higher risk for advanced loss archetypes (HR = 6.17; 95% CI, 3.69–10.32; *P*-contrast = 0.0002); no differences were observed for Asians or Hispanic whites. Hispanic white participants had significantly higher risks of POAG with paracentral defects and advanced superior loss; black participants had significantly higher risks of all advanced loss archetypes and three early loss patterns, including paracentral defects.

Conclusions: Blacks, compared to non-Hispanic whites, had higher risks of POAG with early central and advanced VF loss.

Translational Relevance: In POAG, risks of VF loss regional patterns derived from machine learning algorithms showed racial differences.

Introduction

Primary open-angle glaucoma (POAG) is a complex, multifactorial chronic optic neuropathy that manifests as distinct visual field (VF) loss patterns localizing to the nerve fiber layer.[1] Previous studies have manually documented patterns of new onset of glaucomatous VF loss among patients with ocular hypertension, and from such studies it is clear that multiple distinct loss patterns exist,[2,3] suggesting that both the patterns of underlying optic nerve damage and the etiology in POAG are heterogeneous.[4,5] In contrast to evaluating all POAG or POAG stratified by intraocular pressure (IOP) levels, studies of POAG incorporating the heterogeneity in VF loss patterns representing different types of optic nerve damage may provide new etiologic insights. For example, optic disc

changes associated with glaucomatous paracentral scotomas were more proximal to the papillomacular bundle than those associated with peripheral VF loss,[6–10] and having such a VF loss pattern was associated with more systemic risk factors compared to peripheral VF loss.[11–13]

Automated VF data are a spatial array of retinal sensitivities reflecting the functional integrity of the entire visual pathway.[14] VF mean deviation (MD), pattern standard deviation, and the glaucoma hemifield test represent useful indices, but the outputs provide little information regarding which specific region in the VF shows glaucomatous loss.[15,16] Archetype analysis is an artificial intelligence (AI) algorithm that analyzes data clustered on the edges of the data space to ascertain dimensional patterns in a dataset.[17] For example, when applied to Humphrey VF data from a tertiary care glaucoma clinic, archetype analysis objectively identified weighted patterns of VF loss that were strikingly similar to manually documented VF patterns for patients with new-onset POAG.[2,18] The weighting coefficients derived from archetype analysis can contribute to a more accurate assessment of the functional status of glaucoma suspects[19] and aid in determining and quantifying glaucomatous VF progression.[20]

We applied archetype analysis to new-onset POAG in three prospective US population-based health professional cohorts who were free of glaucoma at baseline to ascertain risk of POAG with different VF loss patterns. Because early disease tends to be asymmetric, we also assessed the inter-eye correlation between patterns of VF loss.[21,22] Finally, self-reported race/ethnicity may be a strong POAG risk factor,[23–25] but race/ethnic differences in risk by regional VF loss have been little investigated. We evaluated whether there were differences in the risk of POAG defined by specific VF loss patterns by race/ethnic differences.

Methods

Study Population

The Nurses' Health Study (NHS) began in 1976 when 121,700 female nurses 30 to 55 years of age were recruited. The Nurses' Health Study II (NHS2) was initiated in 1989 with 116,429 female nurses 25 to 42 years of age. In 1986, the Health Professionals Follow-Up Study (HPFS) enrolled 51,529 male health professionals 40 to 75 years of age. Since the initial recruitment health questionnaires, biennial follow-up surveys have been administered to collect information on lifestyle, diet, and medical status, including information about physician-diagnosed glaucoma. A total of 209,036 participants from the NHS (N = 79,895; follow-up period, 1980–2018), NHS2 (N = 86,795; follow-up period, 1989–2019), and the HPFS (N = 42,346; follow-up period, 1986–2018) were included. We excluded participants with prevalent glaucoma and prevalent cancer (as cancer profoundly changes lifestyle), those without a baseline food frequency questionnaire in the NHS and HPFS (because dietary exposures were of main interest in the initial glaucoma studies, those without baseline food frequency questionnaires were not followed), and those who only completed the baseline (1980, 1989, 1986) questionnaires and were lost to follow-up. Follow-up response rates have been >85%. The institutional review boards of the Brigham and Women's Hospital, Harvard T. H. Chan School of Public Health, and Icahn School of Medicine at Mount Sinai approved the study protocol; participants' completion of the questionnaires was considered to be implied consent by the institutional review boards. This study adhered to the tenets of the Declaration of Helsinki.

Assessment of Race/Ethnicity and Potential Risk Factors for POAG

Race and ethnicity were assessed in 1992 and 2004 in the NHS, in 1989 and 2005 in the NHS2, and in 1986 and 2014 in the HPFS. Due to the small categories and for simplicity, those self-reporting any African ancestry were first categorized as blacks, then among those remaining those self-reporting any Asian ancestry were categorized as Asians, and then among those remaining those self-reporting Hispanic ethnicity were categorized as Hispanic white; all others were categorized as non-Hispanic white. We used participants' self-reported information on biennial questionnaires for covariates potentially related to POAG in prior studies (Supplementary Methods S1): age; socioeconomic status; glaucoma family history; body mass index (BMI); mean arterial blood pressure; hypertension; diabetes mellitus; hypercholesterolemia; myocardial infarction; total cholesterol level; physical activity; cigarette smoking; beta-blocker and other antihypertensives use; statin and other cholesterol-lowering drug use; healthy eating index; dietary intakes of caffeine, alcohol, and nitrate; markers of access to eye care (e.g., self-reports of cataract, cataract extraction, age-related macular degeneration, number of eye exams); number of other physician visits; and, among women, age at menopause and postmenopausal hormone use. Validation studies have found a high reliability and accuracy of information from our health professional participants.[26] If missingness was <5%, values were imputed to the median (for continu-

ous variables); if missingness was greater, missingness indicators were created for covariates.

Assessment of POAG Cases and Extraction of VF Data

When participants reported new-onset glaucoma on biennial questionnaires, we asked them for permission to obtain confirmatory medical data from their eyecare providers. We obtained medical records or a completed glaucoma questionnaire with items including maximal IOP, filtration apparatus status, optic nerve structural information, ophthalmic surgery, and all VF data. Then, a glaucoma specialist (LRP) reviewed the medical records to confirm a diagnosis of POAG using standardized criteria.

For POAG confirmation, we required: (1) gonioscopy indicating that the trabecular meshwork was visible in both eyes (70% of cases) or slit-lamp biomicroscopy demonstrating normal anterior chamber depth plus pharmacological dilation (30% of cases); (2) slit-lamp biomicroscopy demonstrating no signs in either eye of pigment dispersion syndrome, uveitis, exfoliation syndrome, trauma, or rubeosis; and (3) reproducible VF defects consistent with glaucoma on two or more reliable tests. To determine glaucomatous VF loss, we required three contiguous points on the pattern deviation plot that were –5 dB or greater in a pattern consistent with retinal nerve fiber layer topology. The type of perimetry was restricted to 24-2 or 30-2 Humphrey VFs performed with full thresholding or the Swedish Interactive Thresholding Algorithm strategy.

A total of 1957 participants (Supplementary Table S1) were diagnosed with incident POAG (NHS, 1251 cases; NHS2, 223 cases; HPFS, 483 cases). In eyes with POAG ($n = 2581$), all included eyes had to have documentation of reproducible glaucomatous VF loss on two or more reliable VFs; those that did not meet this criterion were censored in analyses. The total deviation (dB) values from the earliest VF test indicating glaucomatous loss were extracted, and VF loss patterns were determined; to use data from the date most proximal to the date of diagnosis, we extracted data from the earliest glaucomatous VF test results. For those with bilateral POAG, the worse eye was defined as the one with the lower MD value; for those with unilateral POAG, the worse eye was the eye with POAG, and data from the non-affected eye were not used. The median time between the earliest date of any of IOP > 21 mmHg, cup-to-disc ratio (CDR) > 0.6, or asymmetry > 0.1 or documentation of glaucomatous VF loss by the diagnosing eye care provider and the extracted VF test in the worse eye was 1 year, and this did not differ by race ($P > 0.10$).

Statistical Analyses

Determining Archetypal VF Loss Patterns

Archetypal analysis (an unsupervised AI technique) on extracted total deviation (dB) data was applied to determine VF loss patterns for each POAG-affected eye. Archetypal analysis reduces dataset dimensionality by anchoring datapoints to values on the edges of a data cluster, autonomously generating and quantifying VF patterns that are clinically recognizable, valid, and useful[19,20,27] (for an example, see Supplementary Methods S2 and Supplementary Fig. S1).

Inter-Eye Analysis of Archetypal VF Loss Patterns

There were 624 pairs of eyes with bilateral POAG available on which to conduct inter-eye association analyses. We calculated the inter-eye Spearman correlations for the weighting coefficients of the archetypal VF loss patterns between the worse and better eyes. *P* values were corrected for multiple comparisons using false discovery rate (FDR).[28] We further evaluated the relation between the weighting coefficients of the archetypal VF loss patterns in the worse eye with the weighting coefficients of each archetypal VF loss pattern in the better eye using the stepwise Bayesian information criterion (BIC) method. The statistical importance of each parameter was measured by the magnitude of BIC increase when a parameter was removed from the optimal model. When the BIC increase for a parameter was at least 6 higher than another parameter in the model, the former parameter was considered more strongly associated with the outcome than the latter parameter.[29]

Prospective Per-Eye Analysis of Race/Ethnicity of POAG Subtypes Defined by Archetypes

For the prospective analysis, to maximize power and because early POAG can be asymmetrical, we used the eye as the unit of analysis, with "eye-years" accrued over time as has been previously described.[30,31] For each eye with POAG, the archetype with the highest weighting coefficient was used for assigning POAG subtypes based on regional VF loss (Supplementary Fig. S1). For eyes where the highest weighting coefficient was for the normal VF pattern (Fig. 1) (archetype 1, as may happen, for example, with early glaucomatous VF loss featuring an isolated shallow superior nasal step but most of the entire VF is normal), we assigned the archetype with the second highest weighting coefficient. The diagnosis date was the earliest date of any of IOP > 21 mmHg, CDR > 0.6, or asymmetry > 0.1 or documentation of glaucomatous VF loss by the diagnosing eye care provider; we stopped follow-up at this date to minimize incorporating post-diagnosis changes in covariates. For each eye, eye-years

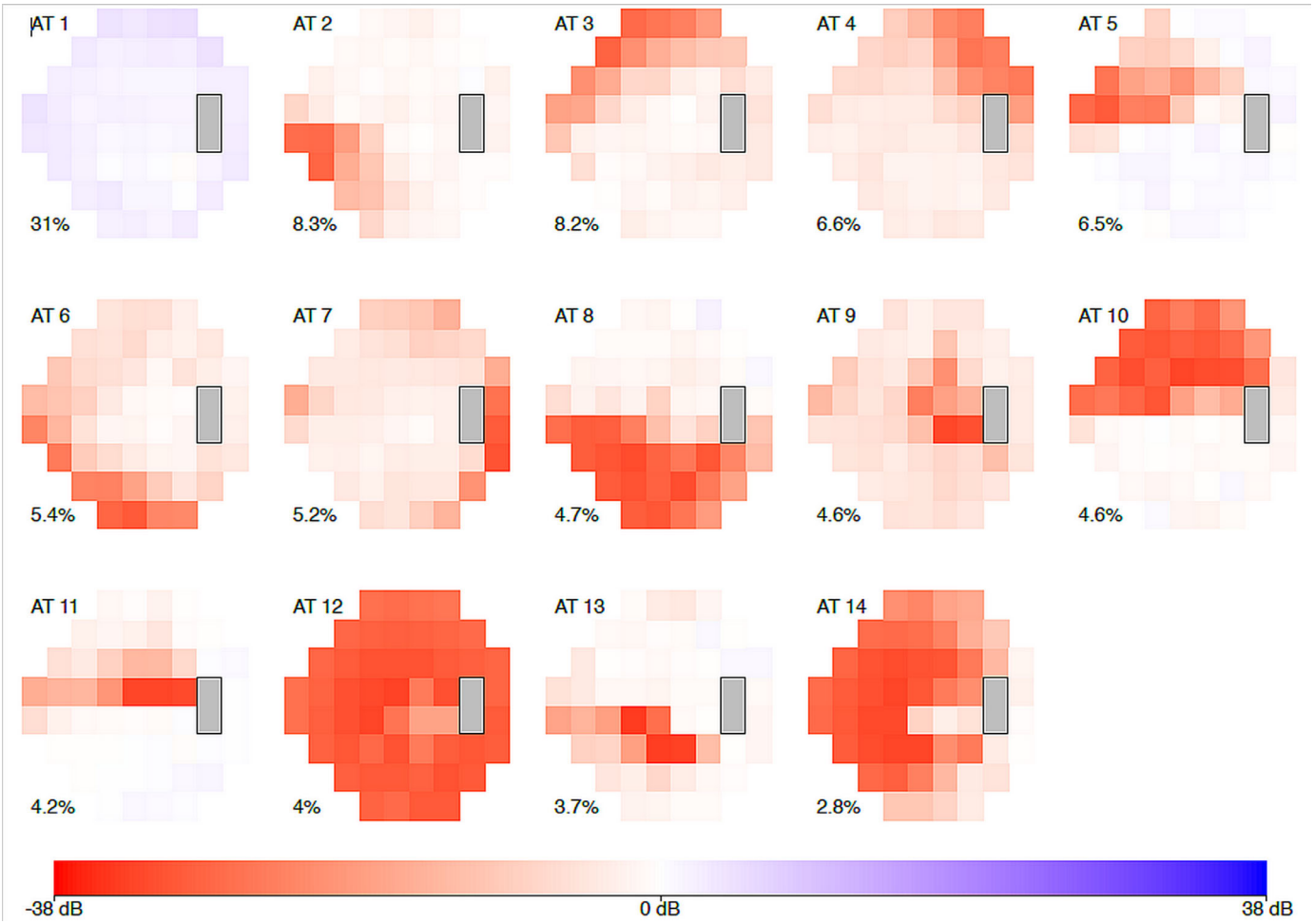

Figure 1. The 14 archetypal visual field loss patterns (ATs) derived from visual fields of the 1957 incident primary open-angle glaucoma cases (2581 affected eyes). The integer at the *top left* of each archetype denotes the archetype number. The percentage at the *bottom left* of each archetype indicates the respective average decomposition weight for this pattern.

of follow-up were accrued from the return of the baseline questionnaire until glaucoma diagnosis, cancer, loss to follow-up, death, or study completion, whichever came first.

We combined the data from our three cohorts and then evaluated per-eye Cox proportional hazards models[30,31] using age as the time metameter with time-varying covariates that stratified on age in months,[32] 2-year risk period, and cohort, adjusting for the correlation of VF loss in the two eyes, to estimate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Importantly, we applied the Firth penalized likelihood method[33] for Cox proportional hazard modeling, which in a simulation study has been found to substantially improve the ability to obtain accurate estimates over the usual maximum-likelihood–based standard Cox model in instances of sparse case numbers in survival data.[34] Analyses were performed with SAS 9.4 (SAS Institute, Cary, NC). For associations with individual POAG subtypes defined by VF archetypes, $P < 0.05$ based on FDR[28] was considered statistically significant to address multiple comparisons. We used the contrast test method[35] to evaluate whether the association with at least one archetype was different from the others.

Results

Determining Archetypal VF Loss Patterns and Inter-Eye Analysis of Archetypal VF Loss Patterns

Archetype analyses identified 14 archetypal VF loss patterns (ATs) in 2581 eyes with incident POAG (Fig. 1). AT 1 (normal VF pattern) was the most heavily weighted AT, followed by patterns resembling superior (AT 2) and inferior (AT 3) nasal steps. Most patterns

resembled pathology affecting the retinal nerve fiber layer except for ATs 4 and 9, which were possibly non-glaucomatous VF loss patterns.

In inter-eye analyses (Fig. 2), the highest Spearman correlation coefficients between the weighting coefficients in the worse (horizontal axis) and better (vertical axis) eyes were found between the same archetypal VF loss patterns (r range, 0.13–0.63; $P < 0.003$). Comparable results were observed in stepwise regression analyses that evaluated the relation between the archetypal VF loss patterns in the worse eye with each of the 14 archetypal VF loss patterns in the better eye (Supplementary Fig. S2) or when, instead of worse-better eye comparisons, we evaluated correlations (Supplementary Fig. S3) or regression analyses (Supplementary Fig. S4) between the right and left eyes.

Per-Eye Prospective Analysis of Race/Ethnicity of POAG Subtypes Defined by Archetypes

For the per-eye analyses of POAG subtypes defined by VF archetypes, we censored 10 cases because they developed cancer during follow-up and one case whose highest weighting coefficient was for the normal VF pattern and did not have a second highest coefficient. This left 2564 eyes with VF loss from 1946 incident POAG cases (1250 NHS cases, 216 NHS2 cases, 480 HPFS cases) for analyses.

Compared to non-Hispanic whites, blacks were younger and more frequently reported a glaucoma family history. Blacks had more diabetes, hypertension, higher BMI, and lower socioeconomic status

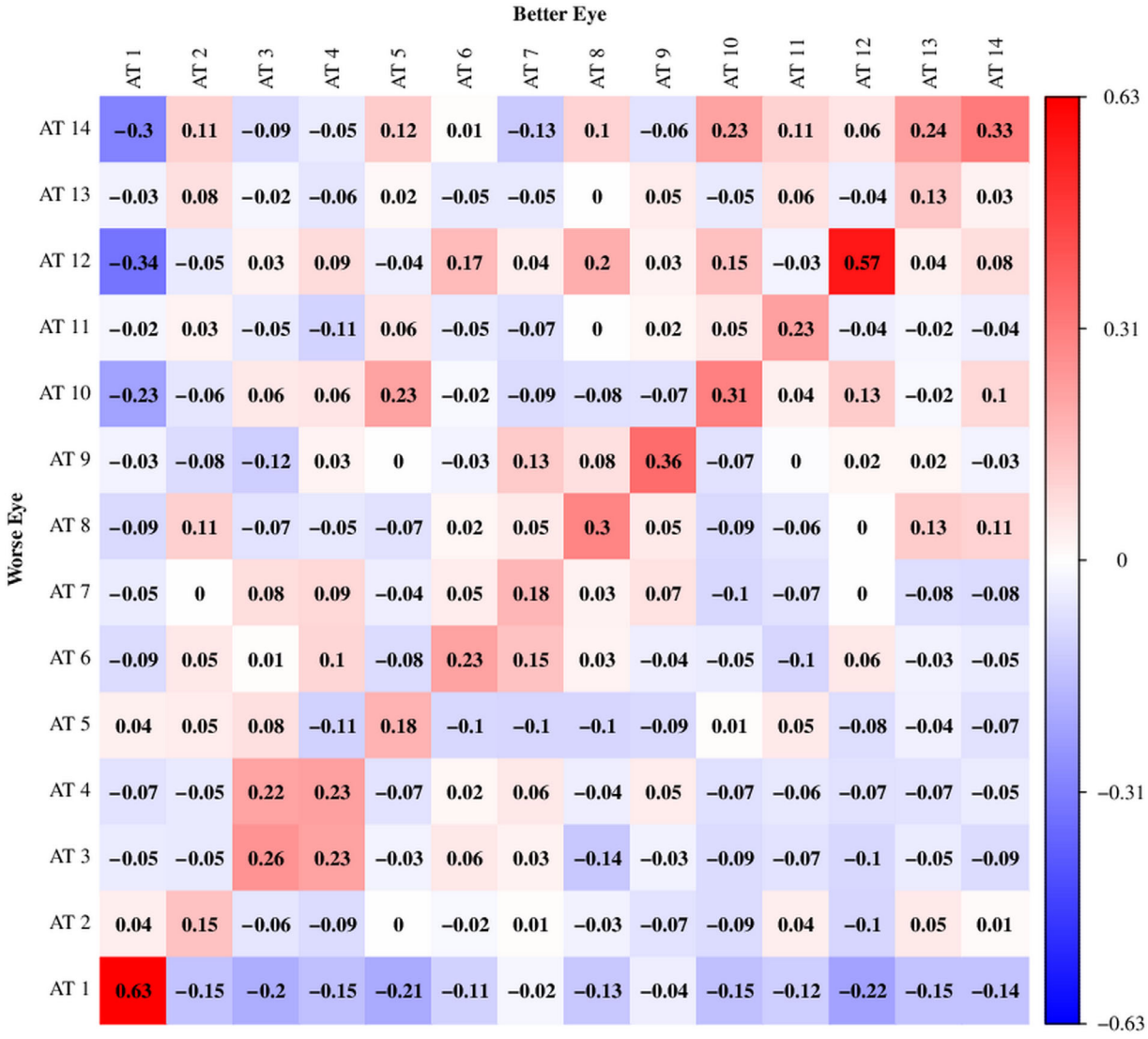

Figure 2. Spearman correlation coefficients between the weight coefficients of the 14 archetypal VF loss patterns in the better (vertical axis) and worse (horizontal axis) eyes among 624 incident POAG cases who were affected in both eyes. *Blue* and *red* denote positive and negative correlations, respectively.

Table 1. Age and Age-Adjusted Characteristics of Eye-Years of Follow-Up by Race/Ethnicity in the NHS (1980–2018; $N = 79,895$), NHS2 (1989–2019; $N = 86,795$), and HPFS (1986–2018; $N = 42,346$)[a]

	Non-Hispanic White[b] (ey = 7,638,258)	Black[b] (ey = 100,022)	Asian[b] (ey = 97,943)	Hispanic White[b] (ey = 86,617)
Persons, *n*	201,073	2,930	2,761	2,272
Percent of total eye-years, %	96.4	1.3	1.2	1.1
Age (y), mean (SD)	58.1 (11.2)	56.8 (10.6)	56.8 (10.9)	55.8 (10.5)
Female, %	83.8	91.3	78.6	89.7
Family history of glaucoma, %	18.6	28.9	18.3	24.9
Self-reported diabetes, %	6.3	12.9	9.7	9.8
Self-reported hypertension, %	34.7	52.4	39.0	36.0
Self-reported cataract diagnosis, %	14.6	14.6	14.3	15.3
Self-reported cataract extraction, %	7.8	6.1	7.6	7.6
Self-reported age-related macular degeneration, %	2.7	1.7	2.1	2.2
Body mass index (kg/m^2), mean (SD)	25.4 (4.7)	27.6 (5.3)	23.6 (3.5)	25.9 (4.7)
Physical activity (MET-h/wk), mean (SD)	21.2 (22.6)	18.0 (22.7)	21.3 (24.1)	21.7 (24.0)
Pack-years of smoking, mean (SD)	9.5 (19.4)	6.7 (16.0)	4.6 (18.3)	5.8 (17.1)
Caffeine intake (mg/d), mean (SD)	261.5 (199.7)	172.2 (157.0)	203.9 (175.5)	227.1 (178.1)
Alcohol intake (g/d), mean (SD)	6.1 (9.3)	3.1 (6.2)	2.8 (6.8)	4.6 (7.5)
AHEI score (without alcohol), mean (SD)	47.3 (9.7)	49.1 (10.1)	51.2 (9.7)	50.1 (9.6)
Age at menopause (y), mean (SD)[c]	49.1 (4.8)	48.8 (4.9)	49.5 (4.2)	48.9 (4.7)
Current postmenopausal hormone use,[c] %	20.8	14.4	17.8	20.6
Number of eye exams reported during follow-up, mean (SD)	5.3 (4.1)	4.6 (3.9)	4.9 (4.1)	5.2 (4.2)
Number of physician visits reported during follow-up, mean (SD)	7.9 (3.8)	7.2 (3.8)	7.5 (3.8)	8.3 (3.6)
Socioeconomic status score based on census tract,[d] mean (SD)	0.2 (4.7)	−5.2 (6.6)	0.6 (5.3)	−0.6 (5.6)

ey, eye-years of follow-up; MET-h, metabolic equivalent-hours; AHEI, Alternate Healthy Eating Index score (without alcohol; range, 0–100).

[a]Values are standardized to the age distribution of the study population.

[b]Due to the small categories and for simplicity, those self-reporting any African ancestry were first categorized as blacks, then among those remaining those self-reporting any Asian ancestry were categorized as Asians, and then among those remaining those self-reporting Hispanic ethnicity were categorized as Hispanic white; all others were categorized as non-Hispanic white.

[c]Among women only.

[d]This score is based on the sum of the *z*-scores of census tract indicators based on participants' zip codes (median household income, home value, percentage with college degree, percentage of families with interest or dividends, percentage occupied housing, percentage living in poverty, percentage white).

than non-Hispanic whites, and, among women, they were less likely to take postmenopausal hormones (Table 1). Compared to non-Hispanic whites, Asians were younger and had more diabetes, more hypertension, and lower BMI. Asians smoked and drank alcohol less than non-Hispanic whites, and, among women, were less likely to take postmenopausal hormones. Hispanic whites were younger than non-Hispanic whites, had more frequent family history of glaucoma and more diabetes, but smoked less. Overall, blacks and Asians had the fewest eye and physician exams (Table 1). Among cases (Supplementary Table S2), black and Hispanic white POAG cases were the youngest at diagnosis and were the most likely to have both eyes affected, whereas Asian POAG cases had the lowest IOP and highest CDR.

Of the 13 ATs showing loss, four (ATs 8, 10, 12, and 14) represented advanced VF loss, and the other

Table 2. Hazard Ratios of POAG With Early VF Loss Versus Advanced VF Loss Archetypes Based on the Highest Weighting Coefficients of the Affected Eye(s)[a] by Race Compared to Not Developing Any POAG

Type of Glaucomatous Visual Field Loss	Race/Ethnicity Categories (Eyes with POAG)	Multivariable-Adjusted HR (95% CI)		
		Model 1[b]	Model 2[c]	Model 3[d]
Early loss[a] (eyes with POAG, $n = 2225$)	Black ($n = 49$)	1.92 (1.44–2.56)	1.98 (1.48–2.66)	1.98 (1.48–2.66)[e]
	Asian ($n = 45$)	2.01 (1.49, 2.72)	1.85 (1.37–2.50)	1.85 (1.37–2.50)
	Hispanic white ($n = 26$)	1.46 (0.99–2.16)	1.43 (0.97–2.10)	1.43 (0.97–2.10)
	Non-Hispanic white ($n = 2105$)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Advanced loss[a] (eyes with POAG, $n = 339$)	Black ($n = 19$)	5.67 (3.51–9.16)	6.23 (3.75–10.35)	6.17 (3.69–10.32)[e]
	Asian ($n = 8$)	1.72 (0.81–3.67)	1.82 (0.85–3.91)	1.75 (0.82–3.76)
	Hispanic white ($n = 5$)	2.27 (0.96–5.36)	2.22 (0.94–5.28)	2.22 (0.93–5.28)
	Non-Hispanic white ($n = 307$)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)

[a]Advanced VF loss was defined as having being assigned to the archetype with the highest weighing coefficients and those archetypes were ATs 8, 10, 12, and 14. Early VF loss was defined as having been assigned to all other archetypes.

[b]Model 1 was stratified by age in months, 2-year risk period, and cohort and adjusted for family history of glaucoma.

[c]Model 2 included model 1 plus socioeconomic status score (based on census tract information), number of eye exams reported, number of physician exams, physical activity (metabolic equivalents-hours/week), pack-years of smoking, caffeine intake (mg/d), alcohol intake (g/d), nitrate intake (mg/d), caloric intake (kcal/d), Alternate Healthy Eating Index (excluding alcohol), and, among women, age at menopause (<45, 45–49, 50–53, 54+ years) and postmenopausal hormone use (premenopausal, never, current, past use).

[d]Model 3 included model 2 plus body mass index (kg/m^2), self-reported history of diabetes, heart disease, cataract, cataract extraction, age-related macular degeneration, mean arterial blood pressure, hypercholesterolemia, serum total cholesterol, statin use, non-statin cholesterol lowering drug use, hypertension treated with beta blockers, hypertension treated with diuretics, hypertension treated with other blood pressure lowering drugs, and hypertension with no treatment.

[e]The global contrast test of whether the estimates for black versus non-Hispanic white race/ethnicity was different by early versus advanced loss was significant ($P = 0.0002$) but not for Asians ($P = 0.90$) or Hispanic whites ($P = 0.36$).

nine were considered early VF loss (Fig. 1). "Advanced VF loss" was defined as those archetypes showing VF loss patterns affecting an entire hemifield or both hemifields; ATs 11 and 13 were considered early loss as the large portions of the macular regions were not affected. We identified 1836 POAG affected eyes in non-Hispanic whites, 50 in blacks, 39 in Asians, and 21 in Hispanic white participants. Compared to non-Hispanic whites, blacks were significantly more likely to develop POAG with early VF loss, with the various nested models showing similar associations (Table 2) (for model 3, black HR = 1.98; 95% CI, 1.48–2.66); for POAG with advanced VF loss, blacks were at even higher risk (HR = 6.17; 95% CI, 3.69–10.32). Notably, the difference in the associations for POAG with advanced VF loss versus POAG with early VF loss in blacks versus non-Hispanic whites was statistically significant (P for difference in estimates = 0.0002); the elevated risks were not different for the two subtypes of POAG for Asians ($P = 0.90$) or Hispanic whites ($P = 0.36$). Indeed, in multivariable-adjusted linear regression analyses of MD among POAG eyes only, compared to non-Hispanic whites, blacks had a significantly worse MD (difference in MD = −2.18; 95% CI, −3.21 to −1.15); this was not observed for Asians or Hispanic whites ($P \geq 0.23$).

In a secondary exploratory analysis, when the 13 ATs were evaluated individually by race/ethnicity (Supplementary Table S3), we observed that globally there were no significant differences in associations for Asians ($P = 0.90$) or Hispanic whites ($P = 0.17$) compared to non-Hispanic whites; however, we observed globally significant differences ($P = 0.01$) across archetypes for blacks compared to non-Hispanic whites, although many of the analyses were underpowered. Specifically, in model 3, blacks had FDR significantly higher risks of developing POAG for three of nine early VF loss archetypes—AT 3 (HR = 2.91; 95% CI, 1.67–5.09), AT 5 (HR = 2.55; 95% CI, 1.23–5.30), and AT 11 (HR = 3.97; 95% CI, 1.61–9.80)—and all four advanced VF loss archetypes—AT 8 (HR = 7.72; 95% CI, 3.25–18.38), AT 10 (HR = 3.86; 95% CI, 1.38–10.84), AT 12 (HR = 14.72; 95% CI, 5.29–40.95), and AT 14 (HR = 7.19; 95% CI, 1.59–32.54). Hispanic whites had FDR significantly higher risk of the advanced VF loss archetype, AT 10 (HR = 5.23; 95% CI, 1.88–14.56) and AT 11 (HR = 4.91; 95% CI, 2.00–12.06), consistent with

paracentral VF loss; however, the statistical power was low.

Discussion

Using an unsupervised AI algorithm, we identified 14 ATs in incident POAG from three population-based cohorts. In case-only analyses, in general, the best predictors of the weighting coefficients of each archetype in the better eye were those of the same archetype in the worse eye. Also, although recognizing that race is an inexact proxy for multiple attributes including cultural, societal, environmental, biological, and other factors,[36] we observed that, even after adjusting for many factors, compared with non-Hispanic whites the black participants were at significantly increased risk of POAG with advanced and central VF loss. This is notable given that our participants were health professionals with high levels of education and similar access to health care.

The ATs observed were like those generated by Elze et al.[18] in a tertiary glaucoma clinic. Both studies found that the normal VF pattern was the most heavily weighted, that superior and inferior nasal steps were common early defects, and that both solutions autonomously recognized a dense superior paracentral VF loss pattern. Like Teng et al.,[37] we found a strong inter-eye association in the patterns of VF loss, indicating the within-person consistency and possibly implicating systemic susceptibilities caused by genetics and environmental exposures shared between eyes of the same patient.

Other population-based POAG studies have observed a higher prevalence, earlier POAG onset, and more severe VF loss at diagnosis in blacks and among Hispanics.[23,38–42] These findings may be due to less access to or utilization of eye care, higher prevalence of risk factors, genetic differences, chronic stress, or a combination of factors. One proposed explanation for racial/ethnic health disparities is that minorities experience higher allostatic load (i.e., physiological burden of stress measured using biomarkers pertinent to cardiovascular, metabolic, inflammatory, and neuroendocrine systems[43]) and health deterioration earlier in life than non-Hispanic whites due to the cumulative impact of marginalization and discrimination, a concept known as "weathering."[44] Although our multivariable-adjusted model adjusted for several of these downstream biomarkers (i.e., age, diabetes, blood pressure), stress and inflammatory biomarkers related to discrimination or early life factors that we did not account for may have contributed to higher incidence of glaucoma and greater glaucoma disease severity at diagnosis.[45]

Eye care utilization differs among racial/ethnic groups, with blacks being least likely to have regular eye exams in the United States.[46] However, given that our cohort consists of health professionals, that we allowed in analyses only those who reported eye exams in the past 2 years, and that racial/ethnic differences were observed even after adjustment for number of eye exams during follow-up, it is unlikely that eye care access differences drove the racial/ethnic differences observed. Black participants were more likely to have diabetes and a family history of glaucoma; thus, it is not likely that the quality of the eye exams was very different from the quality of those received by other groups.

Genetic factors may also have played a role. Genetically determined African ancestry has been independently associated with greater glaucoma risk,[47] and, in Latinos, having more African ancestry informativity genetic markers was associated with higher IOP.[48]

A strength of our study was the use of a novel archetype analysis to generate quantitative measures of regional patterns of VF loss. This was a large prospective study with 1946 incident cases (2564 eyes with POAG) and 209,036 participants followed for 30+ years, with high follow-up rates. Due to the wealth of information available, particularly repeated health and behavior information and markers of socioeconomic status,[41] and the homogeneity of the study population in education and healthcare access, we were able to minimize the possibility of major confounding biases.

Our study had several limitations. Repeated in-person eye exams were not possible; thus, we relied on questionnaire and medical record information for disease confirmation, a method that had low sensitivity. However, methodologically, hazard ratios can still be valid if the case definition is highly specific (e.g., reproducible VF loss) and the ascertainment method was unrelated to exposure (we required reports of eye exams at each follow-up cycle).[49] A major limitation was that we had relatively few POAG-affected eyes from those who were black, Asian, or Hispanic white; thus, although some results were statistically significant, our confidence intervals were wide for certain estimates, so the results should be interpreted with ample caution and replicated in another study with a greater number of cases from various races and ethnicities. More broadly, we acknowledge that the NHS, NHS2, and HPFS were cohorts that were not ideally suited for this research question due to the low representation of black, Asian, and Hispanic white populations. Although our study supports the prior work of others that have also reported on racial differences

in VF loss development in POAG,[50,51] future studies of VF loss patterns in POAG in much more diverse populations are needed to further substantiate our findings. Furthermore, on all participants, we did not have regularly updated information on IOP information and central corneal thickness. Yet, central corneal thickness is not considered a strong POAG risk factor[52] in the general population, and in the Baltimore Eye Study (and among our cases; Supplementary Table S2), untreated IOP among cases was similar in prevalent POAG cases among blacks and whites.[15] Also, because our study participants were health professionals, our results may not be generalizable to general populations, where racial/ethnic disparities in POAG may be larger. Finally, although all of our participants were health professionals, there may have been residual confounding by factors that we were not able to adjust for, such as quality of eye exams, early childhood environment, and social treatment, which may have accounted for some of the race / ethnic differences.

In summary, in this prospective study of incident POAG among health professionals, archetype analyses were able to identify and quantify major specific regional patterns of VF loss; when compared to non-Hispanic whites, blacks had higher risks of incident POAG with central and advanced loss. The subtyping of glaucoma using machine-learning–based approaches and identifying unique risk factors may help researchers fine-tune and improve the discovery of POAG risk factors.

Acknowledgments

Supported by grants from the National Cancer Institute, National Institutes of Health (UM1 CA186107, U01 CA176726, and U01 CA167552 to LRP); by grants from the National Eye Institute, National Institutes of Health (R01 EY015473 to LRP; K99 EY028631 and R00 EY028631 to MW; R01 EY030575 to TE); by an unrestricted challenge grant to the Icahn School of Medicine at Mount Sinai, Department of Ophthalmology from Research to Prevent Blindness (LRP); by The Glaucoma Foundation (LRP); and by an unrestricted challenge grant to Harvard Medical School, Department of Ophthalmology, from Research to Prevent Blindness (MW); by an Alcon Young Investigator Grant (MW). The sponsors had no role in the design or conduct of this research.

Disclosure: **J.H. Kang**, None; **M. Wang**, Alcon (F), Genentech (F); **L. Frueh**, None; **B. Rosner**, None; **J.L. Wiggs**, Aerpio Pharmaceuticals (F), Allergan (C), Avellino (C), Editas (C), Maze (C), Regenxbio (C); **T. Elze**, None; **L.R. Pasquale**, Eyenovia (C), Twenty Twenty (C), and Skye Biosciences (C)

* JHK and MW contributed equally to this work.

References

1. Caprioli J, Sears M. Patterns of early visual field loss in open-angle glaucoma. *Trans Am Ophthalmol Soc*. 1986;84:133–145.
2. Keltner JL, Johnson CA, Cello KE, et al. Classification of visual field abnormalities in the ocular hypertension treatment study. *Arch Ophthalmol*. 2003;121:643–650.
3. Carreras FJ, Rica R, Delgado AV. Modeling the patterns of visual field loss in glaucoma. *Optom Vis Sci*. 2011;88:E63–E79.
4. Craig JE, Han X, Qassim A, et al. Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression. *Nat Genet*. 2020;52:160–166.
5. Caprioli J, Miller JM. Correlation of structure and function in glaucoma. Quantitative measurements of disc and field. *Ophthalmology*. 1988;95:723–727.
6. Gardiner SK, Johnson CA, Cioffi GA. Evaluation of the structure-function relationship in glaucoma. *Invest Ophthalmol Vis Sci*. 2005;46:3712–3717.
7. Horn FK, Mardin CY, Laemmer R, et al. Correlation between local glaucomatous visual field defects and loss of nerve fiber layer thickness measured with polarimetry and spectral domain OCT. *Invest Ophthalmol Vis Sci*. 2009;50:1971–1977.
8. Kanamori A, Naka M, Nagai-Kusuhara A, Yamada Y, Nakamura M, Negi A. Regional relationship between retinal nerve fiber layer thickness and corresponding visual field sensitivity in glaucomatous eyes. *Arch Ophthalmol*. 2008;126:1500–1506.
9. Ferreras A, Pablo LE, Garway-Heath DF, Fogagnolo P, Garcia-Feijoo J. Mapping standard automated perimetry to the peripapillary retinal nerve fiber layer in glaucoma. *Invest Ophthalmol Vis Sci*. 2008;49:3018–3025.
10. Garway-Heath DF, Poinoosawmy D, Fitzke FW, Hitchings RA. Mapping the visual field to the optic disc in normal tension glaucoma eyes. *Ophthalmology*. 2000;107:1809–1815.
11. Kang JW, Park B, Cho BJ. Comparison of risk factors for initial central scotoma versus initial peripheral scotoma in normal-tension glaucoma. *Korean J Ophthalmol*. 2015;29:102–108.
12. Kim JM, Kyung H, Shim SH, Azarbod P, Caprioli J. Location of initial visual field defects in

glaucoma and their modes of deterioration. *Invest Ophthalmol Vis Sci*. 2015;56:7956–7962.
13. Park SC, De Moraes CG, Teng CC, Tello C, Liebmann JM, Ritch R. Initial parafoveal versus peripheral scotomas in glaucoma: risk factors and visual field characteristics. *Ophthalmology*. 2011;118:1782–1789.
14. Larkin M. Visual fields interpretation. *J Am Optom Assoc*. 1980;51:837–842.
15. Yang L, Shi X, Tang X. Associations of subjective and objective clinical outcomes of visual functions with quality of life in Chinese glaucoma patients: a cross-sectional study. *BMC Ophthalmol*. 2019;19:166.
16. Jones PR, Philippin H, Makupa WU, Burton MJ, Crabb DP. Severity of visual field loss at first presentation to glaucoma clinics in England and Tanzania. *Ophthalmic Epidemiol*. 2020;27:10–18.
17. Cutler A, Breiman L. Archetypal analysis. *Technometrics*. 1994;36:338–347.
18. Elze T, Pasquale LR, Shen LQ, Chen TC, Wiggs JL, Bex PJ. Patterns of functional vision loss in glaucoma determined with archetypal analysis. *J R Soc Interface*. 2015;12:20141118.
19. Wang M, Pasquale LR, Shen LQ, et al. Reversal of glaucoma hemifield test results and visual field features in glaucoma. *Ophthalmology*. 2018;125:352–360.
20. Wang M, Shen LQ, Pasquale LR, et al. An artificial intelligence approach to detect visual field progression in glaucoma based on spatial pattern analysis. *Invest Ophthalmol Vis Sci*. 2019;60:365–375.
21. Greenfield DS, Liebmann JM, Ritch R, Krupin T, Low-Pressure Glaucoma Study Group. Visual field and intraocular pressure asymmetry in the low-pressure glaucoma treatment study. *Ophthalmology*. 2007;114:460–465.
22. Wang JC, Gazzard G, Foster PJ, et al. Interocular asymmetry of visual field defects in primary open angle glaucoma and primary angle-closure glaucoma. *Eye (Lond)*. 2004;18:365–368.
23. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *JAMA*. 1991;266:369–374.
24. Kang JH, Willett WC, Rosner BA, Hankinson SE, Pasquale LR. Prospective study of alcohol consumption and the risk of primary open-angle glaucoma. *Ophthalmic Epidemiol*. 2007;14:141–147.
25. Wilson MR, Hertzmark E, Walker AM, Childs-Shaw K, Epstein DL. A case-control study of risk factors in open angle glaucoma. *Arch Ophthalmol*. 1987;105:1066–1071.
26. Bao Y, Bertoia ML, Lenart EB, et al. Origin, methods, and evolution of the three Nurses' Health Studies. *Am J Public Health*. 2016;106:1573–1581.
27. Cai S, Elze T, Bex PJ, Wiggs JL, Pasquale LR, Shen LQ. Clinical correlates of computationally derived visual field defect archetypes in patients from a glaucoma clinic. *Curr Eye Res*. 2017;42:568–574.
28. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Statist Soc B*. 1995;57:289–300.
29. Schwarz G. Estimating dimension of a model. *Ann Statist*. 1978;6:461–464.
30. Merle BMJ, Rosner B, Seddon JM. Genetic susceptibility, diet quality, and two-step progression in drusen size. *Invest Ophthalmol Vis Sci*. 2020;61:17.
31. Seddon JM, Widjajahakim R, Rosner B. Rare and common genetic variants, smoking, and body mass index: progression and earlier age of developing advanced age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2020;61:32.
32. Cox DR, Oakes D. *The Analysis of Survival Data.* London: Chapman & Hall; 1984.
33. Firth D. Bias reduction of maximum likelihood estimates. *Biometrika*. 1993;80:27–38.
34. Adhikary AC, Shafiqur Rahman M. Firth's penalized method in Cox proportional hazard framework for developing predictive models for sparse or heavily censored survival data. *J Stat Comput Simul*. 2021;91:445–463.
35. Wang M, Spiegelman D, Kuchiba A, et al. Statistical methods for studying disease subtype heterogeneity. *Stat Med*. 2016;35:782–800.
36. Wilson MR. The use of "race" for classification in medicine: is it valid? *J Glaucoma*. 2003;12:293–294.
37. Teng B, Li D, Choi EY, et al. Inter-eye association of visual field defects in glaucoma and its clinical utility. *Transl Vis Sci Technol*. 2020;9:22.
38. Varma R, Ying-Lai M, Francis BA, et al. Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. *Ophthalmology*. 2004;111:1439–1448.
39. Leske MC, Connell AM, Wu SY, et al. Incidence of open-angle glaucoma: the Barbados Eye Studies. The Barbados Eye Studies Group. *Arch Ophthalmol*. 2001;119:89–95.
40. Wilson R, Richardson TM, Hertzmark E, Grant WM. Race as a risk factor for progressive glaucomatous damage. *Ann Ophthalmol*. 1985;17:653–659.
41. Fraser S, Bunce C, Wormald R. Retrospective analysis of risk factors for late presentation of chronic glaucoma. *Br J Ophthalmol*. 1999;83:24–28.

42. AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 3. Baseline characteristics of black and white patients. *Ophthalmology*. 1998;105:1137–1145.
43. Rodriquez EJ, Kim EN, Sumner AE, Napoles AM, Perez-Stable EJ. Allostatic load: importance, markers, and score determination in minority and disparity populations. *J Urban Health*. 2019;96:3–11.
44. Williams DR, Mohammed SA. Racism and health I: pathways and scientific evidence. *Am Behav Sci*. 2013;57, doi:10.1177/0002764213487340.
45. Kershaw KN, Lewis TT, Diez Roux AV, et al. Self-reported experiences of discrimination and inflammation among men and women: the multiethnic study of atherosclerosis. *Health Psychol*. 2016;35:343–350.
46. Schneider EC, Zaslavsky AM, Epstein AM. Racial disparities in the quality of care for enrollees in Medicare managed care. *JAMA*. 2002;287:1288–1294.
47. Cole BS, Gudiseva HV, Pistilli M, et al. The role of genetic ancestry as a risk factor for primary open-angle glaucoma in African Americans. *Invest Ophthalmol Vis Sci*. 2021;62:28.
48. Nannini D, Torres M, Chen YD, et al. African ancestry is associated with higher intraocular pressure in Latinos. *Ophthalmology*. 2016;123:102–108.
49. Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia, PA: Lippincott-Raven Publisher; 1998:130–131.
50. Khachatryan N, Medeiros FA, Sharpsten L, et al. The African Descent and Glaucoma Evaluation Study (ADAGES): predictors of visual field damage in glaucoma suspects. *Am J Ophthalmol*. 2015;159:777–787.
51. Taylor KD, Guo X, Zangwill LM, et al. Genetic Architecture of primary open-angle glaucoma in individuals of African descent: the African Descent and Glaucoma Evaluation Study III. *Ophthalmology*. 2019;126:38–48.
52. Belovay GW, Goldberg I. The thick and thin of the central corneal thickness in glaucoma. *Eye (Lond)*. 2018;32:915–923.