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Demographic, Comorbid, and Clinical Variables Associated With Pointwise Visual Field Damage in Glaucoma: Data From the AGIS and CIGTS Clinical Trials

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Purpose: To investigate differences across the visual field (VF) in the rate of glaucomatous progression, the likelihood of defect in four disease severity cross-sections, and comparisons of subgroups in each of between 12 demographic, comorbid, and clinical variables.

Methods: Two long-term glaucoma clinical trials used Humphrey Field Analyzer 24-2 VFs to calculate pointwise deviations from age-matched normal controls. Slopes of glaucomatous progression over time were calculated per participant using linear mixed models. Pointwise differences between subgroups in slopes and cross-sectional categories were tested, adjusting for multiple comparisons using false discovery rate (FDR) and *Q* values.

Results: Pointwise data were available for 1118 patients who had 15,073 VFs. On average, defects were seen at all VF points. Of the 12 variables, six had average pointwise slopes where Subgroup 1 had significantly faster progression than Subgroup 2 at all or many of the 52 VF points: participants who were older (≥65 vs. younger), 52/52; were male, 13/52; had diabetes, 29/52; had hypertension, 46/52; had a larger cup-to-disc ratio (≥0.7), 36/52; or had larger differences in absolute mean deviation (MD) between eyes (>3 dB), 52/52. Cross-sectional patterns at MD severity of −12 to −6.1 dB showed strong midline effects for gender and other patterns for hypertension, cup-to-disc ratio, absolute difference in MD between eyes, and disc notching.

Conclusions: The approach used provides new longitudinal and cross-sectional insights into variation across the VF associated with demographic, comorbid, and clinical variables.

Translational Relevance: This exploration and characterization of variable effects in the setting of pointwise VF testing may enable clinicians to anticipate patterns of VF loss based on demographic, comorbid, and clinical associations.

Introduction

Patterns of visual field (VF) damage and progression in patients with glaucoma have been thoroughly described. In a major review article, Brusini and Johnson[1] identified numerous ways to stage functional damage in glaucoma. These include Aulhorn and Karmeyer's five stages from only relative defects to central island collapse,[2] the Advanced Glaucoma Intervention Study (AGIS) score weighting where depressed tests were located,[3] and the Ocular Hypertension

Treatment Study (OHTS) finding that 17 different classifications characterized the shapes of VF defects.[4] Other areas of the VF have been defined based on thinning of the retinal nerve fiber layer.[5] Building upon the identification of central VF loss in glaucoma by Hood et al.,[6] a recent investigation used artificial intelligence to identify patterns of central VF loss.[7] This body of research has enabled clinicians to identify and characterize the typical and the unusual forms of glaucoma progression and has advanced understanding of the origin and progression of glaucoma damage over time.[8]

The current study takes a different approach. Rather than identifying patient-specific patterns, we summarize point-specific patterns of defect across the VF as functions of demographic, comorbid, and clinical variables. The AGIS and the Collaborative Initial Glaucoma Treatment Study (CIGTS) together enrolled 1198 glaucoma patients with a range of disease severity measured over years of follow-up. VF and patient data from both trials were used to address questions on the pointwise longitudinal rates of progression, as well as the pointwise cross-sectional patterns of defect. These questions are as follows: (1) Does the pointwise rate of progression differ between the VF locations and by baseline demographic, comorbid, or clinical variables? (2) Does the likelihood of defects change by VF location as the patient progresses through the no damage and mild, moderate, and severe damage course of glaucoma, and do the cross-sectional pointwise VF patterns differ by baseline demographic, comorbid, or clinical variables? Noting that longitudinal and cross-sectional results can reveal distinctly different features, our goal was to use a data-driven approach to allow results to emerge without assumptions, possibly shedding new light on previously described concepts.

Methods

The AGIS and CIGTS were multi-center, randomized clinical trials of interventions for open-angle glaucoma that began in 1988 and 1993, respectively. The AGIS compared intervention sequences starting with either trabeculectomy or argon-laser trabeculoplasty in a sample of previously diagnosed glaucoma patients with advanced disease. The CIGTS compared medication and trabeculectomy interventions in a sample of newly diagnosed glaucoma patients. The CIGTS protocol development was guided by the AGIS protocol, including patient visit schedule, data collection forms, and use of the Humphrey Field Analyzer (HFA) 24-2 test procedure.

The AGIS enrolled 591 participants (789 eyes) between 1988 and 1992 at 11 US centers, with follow-up through 2002.[9] When only one eye was enrolled (n = 393 participants), randomization was to one of the two surgical treatment sequences. When both eyes were enrolled (n = 198 participants), one eye was randomized, and the other eye received the alternate treatment sequence. The CIGTS enrolled 607 participants between 1993 and 1997 at 14 US centers, with follow-up through 2004.[10] For each CIGTS participant, a study eye was chosen at baseline and randomized. Both trials collected clinical data on both eyes of each participant at baseline, 3 months, and 6 months and then every 6 months thereafter. At each visit, VF testing was performed by a certified ophthalmic technician who followed a standardized VF testing protocol. The AGIS performed one VF to screen for eligibility and a second to serve as the baseline reference VF. AGIS was missing digitized VF data at baseline for 40 subjects. The CIGTS required at least two baseline VFs; the second was used in this study as the baseline reference VF. Both CIGTS and AGIS adhered to the tenets of the Declaration of Helsinki and received institutional review board approval at individual clinical centers and study operations centers.

The HFA 24-2 VF test, used in both trials, assesses sensitivity at 54 VF points. VF test results are displayed with several metrics, including the threshold value plot (raw data) and the total deviation plot (age-adjusted deviations from normal). To calculate total deviation plot values, pointwise values from the threshold value plot are age standardized at each VF point using a large sample of subjects without eye disease. Total deviation plots are automatically generated in the Humphrey VF output, but these values were not data entered in the CIGTS or AGIS. However, point-specific digital data from the threshold value plot were available for 599 CIGTS participants (99%) and 519 AGIS participants (88%). Because the Humphrey age-adjusted coefficients are proprietary, we used published age-adjusted coefficients from the visualFields package in R (R Foundation for Statistical Computing, Vienna, Austria) based on a sample of 263 fields from 91 healthy subjects.[11] We calculated a visualFields mean deviation (vF-MD) by averaging the pointwise values and used the vF-MD for field-wide analyses. The Humphrey MD and vF-MD have a correlation of 0.99 in the 15,073 VFs from 1118 participants for whom both MDs were available (Supplementary Fig. S1). VF data were omitted within 1 year prior to and 6 weeks after a cataract extraction, as well as visits in which both central lens opacity and visual acuity of <20/40 were noted. We also omitted 22 fields with all zero threshold values, possibly due to instrument errors or participant inattention.

Rate of Progression

Of the two questions posed in the Introduction, Question 1 assessed the rate of progression (slope) over time at each point in the VF for each participant and whether the pointwise slopes differed by baseline demographic, comorbid, or clinical variables. To avoid biasing the slope estimate with repeated floor effects (i.e., points that decreased and then flattened near the minimum observed deviation, −33 dB), we excluded follow-up points after a second value of <−30 dB, a method similar to Tobit (censored) regression.[12–14] We also excluded VF points where the first value was ≤−20 dB to allow for meaningful decline (Supplementary Table S1, which for completeness includes points starting at >−20 dB and ≤−20 dB). We required at least six follow-up visits over 3 years for the calculation of slopes (12% of participants were excluded). The distribution of patient-specific estimated slopes is illustrated with a boxplot for each VF point.

We then tested whether the pointwise slopes differed by subgroups of baseline variables and further descriptively examined heatmap patterns of pointwise slope differences between subgroups. Demographic variables included sex (male vs. female), age (<65 vs. ≥65 years), race (white vs. black), and education (<high school vs. ≥high school). Self-reported comorbid variables (all dichotomized as yes vs. no) included hypertension, diabetes, cardiovascular disease, and immediate family history of glaucoma. Clinical variables included vertical cup-to-disc ratio (CDR; <0.7 vs. ≥0.7),[15] absolute difference in MD between eyes (within 3 dB vs. >3 dB),[16] disc hemorrhage (yes vs. no), and optic disc notching (yes vs. no).

Overall Disease Severity

For Question 2, we considered four categories of overall disease severity across the field based on MD: no damage (MD ≥ −2 dB), mild damage (MD between −6 and −2.1 dB), moderate damage (MD between −12 and −6.1 dB), and severe damage (MD ≤ −12.1 dB), a modification of the McKean–Cowdin et al.[17] severity scale. For each participant, we identified the first VF (over time) that met the criterion for the given MD category, without consideration of time since detection or enrollment; each participant could contribute only one VF at each of the four MD levels. For an overview of each VF point at each MD category, we plotted the 25th, 50th (median), and 75th percentiles of defect using heatmaps. At each cross-sectional MD severity level and each VF point, we tested subgroup differences between baseline demographic, comorbid, and clinical variables. VF heatmap plots facilitated descriptive visualization of subgroup comparisons.

Statistical Methods

Participant characteristics were summarized with descriptive statistics (mean, standard deviation [SD], frequency, percentage). Differences between AGIS and CIGTS participant characteristics were tested with two-sample *t*-tests, two-sample Wilcoxon tests, χ^2 tests, or Fisher exact tests. We also tested for differences in participant characteristics between those with any pointwise VF data versus those without (who were excluded) and between those who had sufficient VF points for the slope analyses versus those who did not (and were excluded).

Analyses were limited to one eye per participant. In the CIGTS, we used the clinician-defined study eye (the worse eye by intraocular pressure [IOP], Humphrey MD, or CDR). In AGIS, if both eyes were eligible at baseline, the worse eye by Humphrey MD was designated as the study eye. Pointwise age-adjusted deviations from normal and slopes of these deviations over time were summarized using boxplots, heatmap plots, and descriptive statistics. For display purposes, all left eye VFs were flipped to right-eye orientation. The 54 points were numbered left to right (nasal to temporal) and top to bottom (superior, 1–27; inferior, 28–54). Blind spot points 26 and 35 were excluded from all analyses.

For each of the 12 demographic, comorbid, and clinical variables, the dichotomous subgroups were tested for differences in VF slope over time at each VF point. Slopes were estimated with a linear mixed regression model using eye-level random effects for intercept and time. Subgroup differences were tested with a covariate by time interaction. For each of the four cross-sectional MD severity levels, subgroup differences were tested at each VF point using both two-sample *t*-tests and Wilcoxon tests. Rather than establishing which test was more appropriate for each of the 2496 comparisons (52 VF points × 4 MD categories × 12 variables), we present results from both tests. Considering the 52 statistical tests performed for each subgroup comparison, we would expect 2.6 points (5%) in the VF to be significant by chance alone. For each of the 52 comparisons within the slope and cross-sectional analyses, we used the Benjamini–Yekutieli procedure to control, at alpha = 0.05, the false discovery rate (FDR).[18] FDR *Q* values[19, 20] (hereafter, *Q* values) were included to balance a penalty for false discovery and an advantage for true discovery. In addition to statistical tests, descriptive comparisons between subgroups for both slope and cross-sectional data are displayed in

VF heatmaps. All analyses used SAS 9.4 (SAS Institute, Cary, NC); the multtest procedure was used for FDR and Q value calculations.

Results

Baseline demographic, comorbid, and clinical characteristics in AGIS ($n = 519$) and CIGTS ($n = 599$) participants are shown in Table 1. Compared with the CIGTS participants, the AGIS participants were on average older (mean ± SD, 65.3 ± 9.3 vs. 57.9 ± 11.0 years; $P < 0.0001$), and a larger percentage were female (54% vs. 45%; $P = 0.0032$), black (55% vs. 38%; $P < 0.0001$), had less than a high school education (37% vs. 21%; $P < 0.0001$), self-reported hypertension (51% vs. 37%; $P < 0.0001$), and had a ≥3 dB difference in MD between eyes at baseline (68% vs. 36%; $P < 0.0001$). Differing eligibility criteria in the AGIS and CIGTS, respectively, led to different baseline values for Humphrey MD (−11.1 ± 5.8 vs. −5.4 ± 4.3 dB; $P < 0.0001$) and IOP (24.2 ± 5.2 vs. 27.5 ± 5.6 mmHg; $P < 0.0001$).

We further compared participants who had pointwise VF data versus those who did not (AGIS, $n = 519$ vs. $n = 72$; CIGTS, $n = 599$ vs. $n = 8$) and those who had sufficient follow-up for the slope analysis (AGIS + CIGTS, $n = 980$) versus those who did not ($n = 138$). Those without pointwise VF or slope data were older and had worse baseline MD (details in Supplementary Tables S2a, S2b, S2c).

Question 1a: Does the Pointwise Rate of Progression Differ Among the VF Locations?

The rates of progression (estimated slopes) are illustrated with a boxplot for each of the 52 VF locations, showing the distribution of slopes for all participants at that VF point (Fig. 1). The means and medians of all 52 boxplots were similar and slightly below zero, but the full distributions captured wide variability between patients in the rates of progression (dB/yr). The narrow interquartile range (which includes 50% of participants) showed little progression of disease (less than approximately 0.5 dB of progression per year) during

Table 1. Comparison of Baseline Demographic, Comorbid, and Clinical Variables Between CIGTS and AGIS Patients Who Had Pointwise Data From at Least One Visual Field

	CIGTS ($n = 599$)			AGIS ($n = 519$)			
Continuous Variables	*n*	Mean (SD)	Min, Max	*n*	Mean (SD)	Min, Max	P[a]
Age at randomization (yr)	599	57.9 (11.0)	28.8, 75.8	519	65.3 (9.3)	36.0, 80.0	<0.0001
Humphrey MD (dB)	599	−5.4 (4.3)	−23.5, 3.4	513	−11.1 (5.8)	−24.7, 0.5	<0.0001
IOP (mmHg)	599	27.5 (5.6)	19.0, 50.0	511	24.2 (5.2)	14.0, 50.0	<0.0001
Vertical CDR	599	0.7 (0.2)	0.1, 1.0	519	0.8 (0.1)	0.2, 1.0	<0.0001
ETDRS visual acuity	599	85.8 (5.7)	70, 99	519	79.4 (8.7)	56, 100	<0.0001
Absolute difference in MD between eyes (dB)	599	3.2 (3.4)	0.0, 23.1	479	6.6 (5.6)	0.0, 26.1	<0.0001
Categorical Variables	Frequency (%)			Frequency (%)			P[b]
Gender: male; female	330 (55.1); 269 (44.9)			240 (46.2); 279 (53.8)			0.0032
Race: white; black; other[c]	335 (55.9); 225 (37.6); 39 (6.5)			225 (43.4); 286 (55.1); 8 (1.5)			<0.0001
Education: <high school; ≥high school	124 (21.0); 473 (79.0)			193 (37.2); 326 (62.8)			<0.0001
Diabetes: yes; no	100 (16.7); 499 (83.3)			105 (20.2); 414 (79.8)			0.1275
Hypertension: yes; no	222 (37.1); 377 (62.9)			264 (50.9); 255 (49.1)			<0.0001
Cardiovascular disease: yes; no	89 (14.9); 510 (85.1)			95 (18.3); 424 (81.7)			0.1212
Glaucoma family history[d]: yes; no	197 (36.7); 340 (63.3)[e]			200 (38.5); 319 (61.5)			0.5349
MD between eyes: ≥3 dB; ±3 dB	215 (35.9); 384 (64.1)			324 (67.6); 155 (81.3)[f]			<0.0001
Disc hemorrhage: yes; no	20 (3.3); 579 (96.7)			13 (2.5); 506 (97.5)			0.4112
Notching: yes; no	305 (50.9); 294 (49.1)			183 (35.3); 335 (64.7)[g]			<0.0001

ETDRS, Early Treatment Diabetic Retinopathy Score.
[a]Two-sample Wilcoxon test (absolute difference in MD between eyes) or two-sample *t*-test (all other variables).
[b]Fisher's exact test or χ^2 test.
[c]Other races were not included in any analyses in this paper.
[d]Parent, sibling, and children.
[e]Due to missing data, percentages were calculated from a sample size of 537.
[f]Due to missing data, percentages were calculated from a sample size of 479.
[g]Due to missing data, percentages were calculated from a sample size of 518.

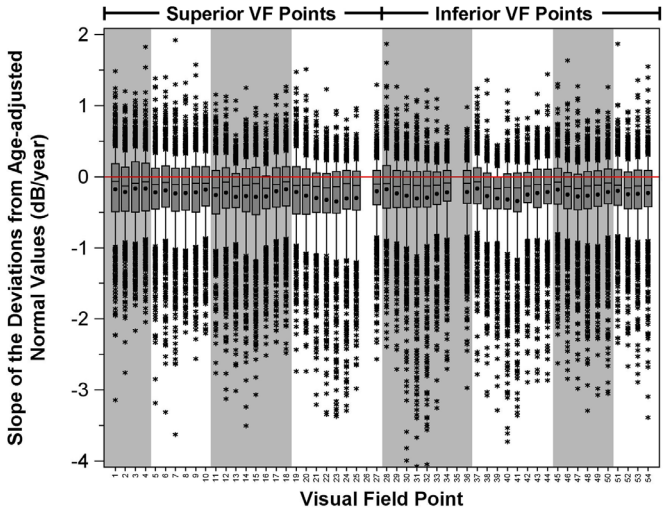

Figure 1. Side-by-side boxplots displaying the distribution of slopes over time at each VF point for the deviations from age-adjusted normal values (dB). The 54 points are numbered left to right, with the *gray and white alternating bands* showing each VF row, from the most nasal to the most temporal. Points 1 to 27 are in the superior hemifield, and points 28 to 54 are in the inferior hemifield. Blind-spot points 26 and 35 are excluded (shown as gaps). *Boxes* enclose the 25th to 75th percentiles and show that approximately 50% of slopes are between −0.5 and +0.3 dB/yr; the *horizontal line* within a box represents the median value; a *black dot* represents the mean value; *whiskers* extend to the 10th percentiles below and the 90th percentile above; and *asterisks* represent outlying values. Plots include points with starting pointwise deviation values > -20 dB. All left-eye VFs are flipped to right-eye orientation.

the study course. At each of the 52 VF points, <1% of participants showed improvement of 1 dB/yr or more. Long tails of negative slopes are present at all VF points, indicating substantial pointwise progression for the lower 25% of participants, particularly for the lowest 10% (below the lower whisker). Based on the distribution of lower outliers, the most severe damage appeared to occur in the region from just above the horizontal midline to the bottom of the VF. The undulating pattern of the boxes across the VF rows, particularly near the midline, shows slightly less peripheral and more central point progression (Supplementary Table S1).

We next show AGIS and CIGTS data with overlaid distributions for both vF-MD values (Fig. 2a) and pointwise deviations from normal (Fig. 2b). Histograms of all baseline and follow-up vF-MD values show less damage in the CIGTS than in the AGIS, but with substantial overlap. The distribution of pointwise deviations from age-adjusted normal subjects (dB) shows a bimodal distribution for both the AGIS and the CIGTS, with a sizeable minority of VF points having extensive damage, particularly in the AGIS, which enrolled those with advanced

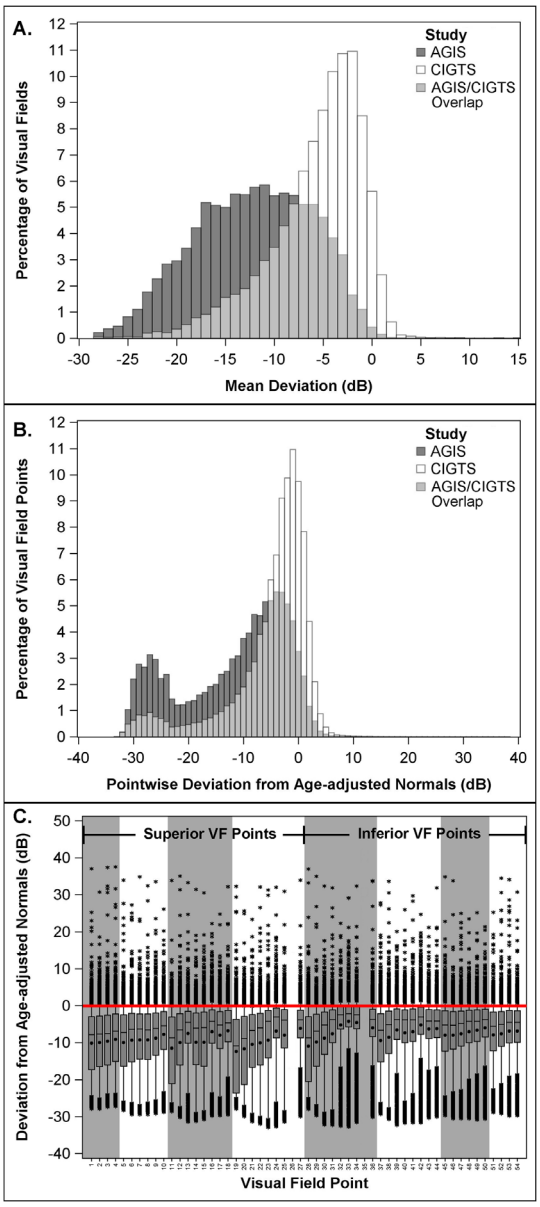

Figure 2. (a) Distribution of mean deviation values (dB) for AGIS and CIGTS participants including baseline and all follow-up visual fields (n = 15,107). Values greater than +3 dB (n = 29) are barely visible. (b) Distribution of pointwise deviations from age-adjusted normal values (dB) for AGIS and CIGTS participants including baseline and all follow-up visual fields. Deviations greater than 10 dB (n = 576 of 785,540) are barely visible. (c) Side-by-side boxplots displaying the distribution of pointwise deviations from age-adjusted normal values (dB) at each VF point, at baseline, and at all follow-up visits. The 54 points are numbered left to right, with the *gray and white alternating bands* showing each VF row, from the most nasal to the most temporal. Points 1 to 27 are in the superior hemifield, and points 28 to 54 are in the inferior hemifield. Blind-spot points 26 and 35 are excluded (shown as gaps). *Boxes* enclose the 25th to 75th percentiles; horizontal lines within boxes represent median values; *black dots* represent mean values; *whiskers* extend to the 10th percentile below and the 90th percentile above; and *asterisks* represent outlying values. All left eyes are flipped to right-eye orientation.

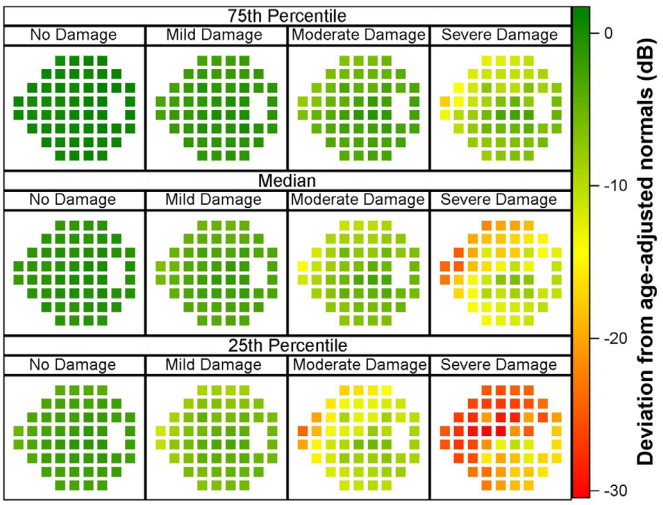

Figure 3. Heatmap plots showing the 25th, 50th (median), and 75th percentiles of pointwise deviations from age-adjusted normal values (dB), shown for the four MD severity categories: no damage (≥−2 dB), $n = 375$; mild damage (−6 to −2.1 dB), $n = 656$; moderate damage (−12 to −6.1 dB), $n = 695$; and severe damage (≤−12.1 dB), $n = 508$. Large differences across the visual field can be seen, especially with moderate and/or severe damage. Only a subject's first field in each severity category is included.

disease whereas the CIGTS enrolled newly diagnosed participants. Figure 2c displays side-by-side boxplots showing the distribution of deviations from age-adjusted normal for each point in the VF pooled over time. The pattern within each VF row (alternately shaded blocks) shows more damage in the nasal and less in the temporal region, with substantial variability. In general, correlations between adjacent points within the same hemifield had the largest magnitude and dampened with distance; cross-hemifield correlations were smaller or negative. Correlations were generally stronger with increasing damage (Supplementary Figs. S3A, S3B; Spreadsheet of Pairwise Correlations).

Heatmap plots (Fig. 3) show wide variability by MD severity categories (columns) and across the 25th, 50th (median), and 75th percentiles (rows) of the distribution of pointwise deviations from age-adjusted normal values. Field-wide deficits from normal started as early as mild MDs (−2.1 to −6 dB), and pointwise damage increased with MD severity (see Supplementary Table S3 for descriptive statistics).

Question 1b: Does the Pointwise Rate of Progression Differ by Baseline Demographic, Comorbid, or Clinical Variables?

For each of the 12 variables, differences between subgroups in slopes of age-adjusted deviations from normal (Subgroup 1 minus Subgroup 2) were tested at each VF point (Table 2). Statistical significance is indicated by black outlined squares, either thin (by P values or Q values) or bold (by FDR-adjusted or Q values); Q values aligned with P values when the probability of false detection was low, and otherwise aligned with FDR-adjusted values (Table 2). The heatmap colors allow visual descriptions of subgroup differences (Figs. 4–6) without regard to statistical significance. The differences can be negative or positive.

Table 2. Significant Pointwise Differences in Slopes of Age-Adjusted Deviations From Normal Among Subgroups of Demographic, Comorbid, and Clinical Variables

Variable Tested for Differences in Slopes (Subgroup 1 vs. Subgroup 2)	Slope (dB/yr), Mean[a] (Range)		Difference (dB/yr)	Significant Points, *n*/52		
	Subgroup 1[b]	Subgroup 2[b]	Mean (Range)	Raw *P*	FDR *P*	*Q*
Gender: male vs. female	−0.30 (−0.45, −0.21)	−0.18 (−0.29, −0.09)	−0.12 (−0.22, −0.04)	30	13	30
Age: ≥65 yr vs. <65 yr	−0.39 (−0.49, −0.28)	−0.14 (−0.25, −0.03)	−0.25 (−0.34, −0.17)	52	52	52
Race: black vs. white	−0.28 (−0.38, −0.13)	−0.22 (−0.35, −0.12)	−0.06 (−0.18, 0.07)	10	1	1
Education: <high school vs. ≥high school	−0.29 (−0.41, −0.15)	−0.23 (−0.34, −0.14)	−0.06 (−0.16, 0.03)	6	0	0
Hypertension: yes vs. none	−0.33 (−0.45, −0.23)	−0.18 (−0.31, −0.10)	−0.15 (−0.21, −0.08)	47	46	47
Diabetes: yes vs. none	−0.39 (−0.53, −0.26)	−0.21 (−0.33, −0.12)	−0.18 (−0.28, −0.02)	34	29	34
Cardiovascular disease: yes vs. none	−0.37 (−0.66, −0.25)	−0.22 (−0.34, −0.14)	−0.15 (−0.39, −0.04)	17	1	17
Immediate family history of glaucoma: yes vs. none	−0.29 (−0.45, −0.16)	−0.23 (−0.36, −0.14)	−0.05 (−0.14, 0.03)	0	0	0
CDR: ≥0.7 vs. <0.7	−0.29 (−0.42, −0.20)	−0.14 (−0.25, −0.02)	−0.15 (−0.24, −0.05)	38	36	38
Mean deviation difference between eyes: >3 dB vs. ≤3 dB	−0.35 (−0.51, −0.24)	−0.15 (−0.23, −0.09)	−0.21 (−0.31, −0.13)	52	52	52
Disc hemorrhage: yes vs. none	−0.31 (−0.68, −0.10)	−0.24 (−0.35, −0.17)	−0.07 (−0.40, 0.12)	0	0	0
Notching: yes vs. no	−0.26 (−0.38, −0.15)	−0.23 (−0.33, −0.16)	−0.03 (−0.11, 0.07)	0	0	0

The last three columns show the number of VF points with significant differences between subgroups, based on raw *P*-values, FDR-adjusted *P*-values, and Q values. (Only points with starting deviations > −20 dB were included.)

[a]Mean value is the average of the mean slope over 52 points.

[b]In the Variable column, Subgroup 1 is listed before Subgroup 2; e.g., for gender, Subgroup 1 is male and Subgroup 2 is female.

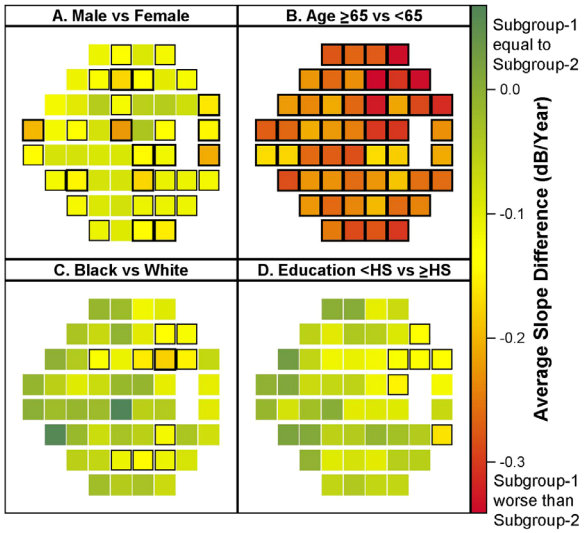

Figure 4. Dichotomous subgroups of demographic variables are shown in heatmap plots to display average pointwise differences (dB/yr) in slopes over time of age-adjusted deviations from normal. (A) Gender (males vs. females). (B) Age (≥65 years vs. <65 years). (C) Race (black vs. white). (D) Education (<high school [HS] vs. ≥high school). The *color scale* on the right shows the magnitude, by color, of the difference between subgroups (Subgroup 1 minus Subgroup 2). Significant pointwise differences by *t*-test are denoted by *thin-line squares* and after FDR adjustment by *bold squares*. A difference of zero indicates that the subgroup means are equal (*light green*). The relative differences between the dichotomous subgroups can range from positive (*solid green*) to negative (*yellow* to *solid red*). For example, males (Subgroup 1) had an average progression from −0.22 to −0.04 dB/yr faster than females (Subgroup 2). (Table 2 shows data ranges for all four panels.)

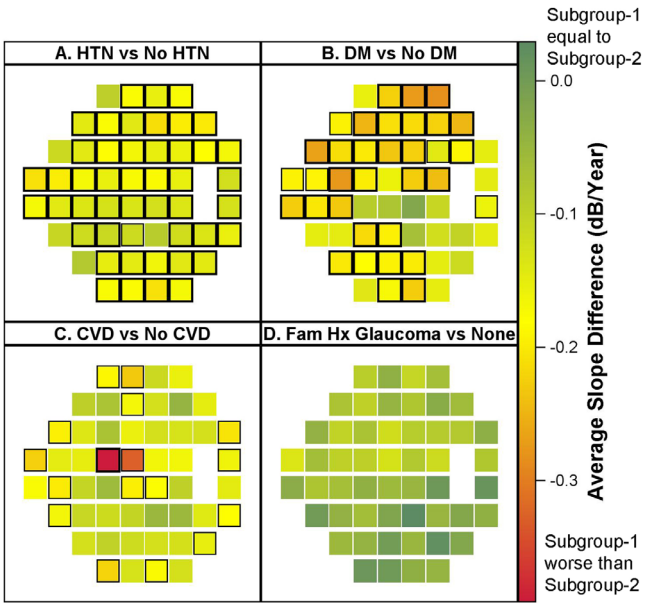

Figure 5. Dichotomous subgroups of comorbid variables are shown in heatmap plots to display average pointwise differences (dB/yr) in slopes over time of age-adjusted deviations from normal. (A) Hypertension (HTN; yes vs. no). (B) Diabetes (DM; yes vs. no). (C) Cardiovascular disease (CVD; yes vs. no). (D) Immediate family history (Fam Hx) of glaucoma (yes vs. no). The *color scale* on the right shows the magnitude, by color, of the difference between subgroups (Subgroup 1 minus Subgroup 2). Significant pointwise differences by *t*-test are denoted by *thin-line squares* and after FDR adjustment by *bold squares*. A difference of zero indicates that the subgroup means are equal (*light green*). The relative difference between the dichotomous subgroups can range from positive (*solid green*) to negative (*yellow* to *solid red*). For example, those with HTN (Subgroup 1) had "worse" (faster) progression by −0.21 to −0.08 dB/yr than those without HTN (Subgroup 2), as shown by all visual field points less than zero. (Table 2 shows data ranges for all four panels.)

Gender

Each point in the VF shows that the slopes for males were always either slightly or much steeper, but never less steep, on average, than the slopes for females. Statistically significant slope differences were seen in 30 VF points out of 52, with 13/52 points being significant after FDR adjustment and 30/52 by Q value (Table 2). The average slopes over the VF points ranged from −0.45 to −0.21 (mean, −0.30 dB/yr) for males and −0.29 to −0.09 (mean, −0.18 dB/yr) for females; the pointwise differences between slopes of males and females ranged from −0.22 to −0.04 dB/yr (Fig. 4A).

Age

At all VF points, participants who were ≥65 years old showed faster disease progression than those <65 years old. These differences were statistically significant for all 52 points, as well as after FDR adjustment (Table 2). The range of slopes over the VF points was −0.49 to −0.28 (mean, −0.39 dB/yr) for those ≥65 years old and −0.25 to −0.03 (mean, −0.14 dB/yr) for those <65 years old; pointwise differences between the slopes of those older versus younger ranged from −0.34 to −0.17 dB/yr (Fig. 4B). A tendency for faster progression in the superior/temporal region between those ≥65 years old was seen.

Race and Education

There were few VF points with slope differences between black and white participants or between subgroups differing by less versus more than high school education (Figs. 4C, 4D; Table 2).

Hypertension

Participants with hypertension showed significantly faster progression than those without hypertension (Fig. 5A) at 47/52 points and at 46/52 after FDR adjustment (Table 2). Average slopes were steeper at all 52 points for participants with hypertension (mean, −0.33 dB/yr; range, −0.45 to −0.23) compared with

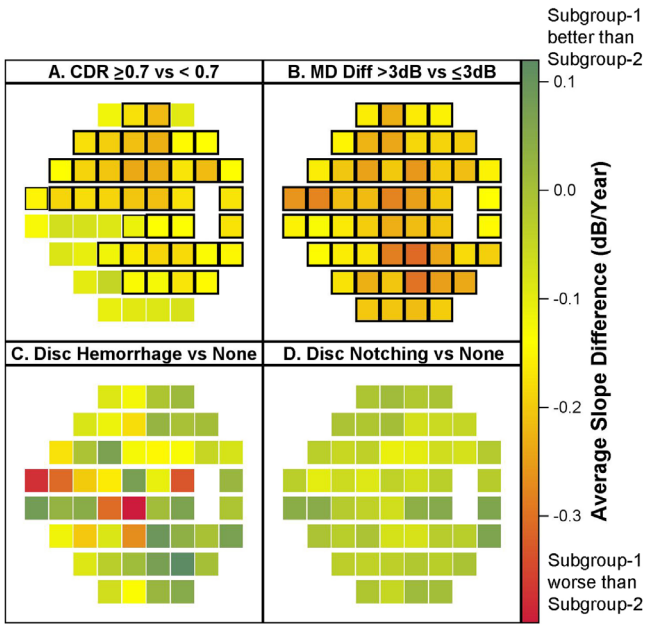

Figure 6. Dichotomous subgroups of clinical variables are shown in heatmap plots to display average pointwise differences (dB/yr) in slopes over time of age-adjusted deviations from normal. (A) CDR (≥0.7 vs. <0.7). (B) Baseline difference in MD between eyes (>3 dB vs. ≤3 dB). (C) Disc hemorrhage versus none. (D) Optic disc notching versus none. The *color scale* on the right shows the magnitude, by color, of the difference between subgroups (Subgroup 1 minus Subgroup 2). Significant pointwise differences by *t*-test are denoted by *thin-line squares* and after FDR adjustment by *bold squares*. A difference of zero indicates that the subgroup means are equal (*yellow–green*). The relative difference between the dichotomous subgroups can range from positive (*solid green*) to negative (*yellow* to *solid red*). For example, those with CDR ≥ 0.7 (Subgroup 1) had "worse" (faster) progression by −0.24 to −0.05 dB/yr than those with CDR < 0.7 (Subgroup 2), especially above the midline. (Table 2 shows data ranges for all four panels.)

those without hypertension (mean, −0.18 dB/yr; range, −0.31 to −0.10), with average pointwise differences of −0.15 dB/yr.

Diabetes

Participants with diabetes showed faster progression of disease at all points in the VF compared with those without diabetes (Fig. 5B); these differences were statistically significant at 34/52 points and at 29/52 after FDR adjustment (Table 2). Over all of the VF points, those with diabetes declined faster (mean, −0.39 dB/yr; range, −0.53 to −0.26) than those without diabetes (mean, −0.21 dB/yr; range, −0.33 to −0.12), with average pointwise differences of −0.18 dB/yr. Slope differences were more evident in the peripheral and paracentral points of the superior, nasal, and inferior regions.

Cardiovascular Disease

Participants with cardiovascular disease versus those without showed on average faster progression at all VF points (Fig. 5C), with significance at 17/52 points by *Q* values, but only 1/52 with FDR adjustment.

Immediate Family History of Glaucoma

Those with an immediate family history of glaucoma versus without showed no significant differences in slopes (Fig. 5D).

Cup-to-Disc Ratio

Faster disease progression across the VF was found for those with worse CDR (≥0.7) (Fig. 6A). Of the 38/52 VF points showing significant differences between subgroups, 36/52 remained significant after FDR adjustment (Table 2). Participants with CDR ≥ 0.7 declined faster (mean, −0.29 dB/yr; range, −0.42 to −0.20) than those with CDR < 0.7 (mean, −0.14 dB/yr; range, −0.25 to −0.02), with an average pointwise difference of −0.15 dB/yr.

Absolute Difference in MD Between Eyes

Faster disease progression at all points in the VF was also observed for participants who had more versus less than a 3-dB difference (in absolute value) in MD between eyes at baseline. Of the 52/52 VF points that showed significant subgroup differences, all remained significant after FDR adjustment (Fig. 6b, Table 2). Participants with a >3-dB difference between eyes declined faster (mean, −0.35 dB/yr; range, −0.51 to −0.24) than those with a ≤3-dB MD difference between eyes (mean, −0.15 dB/yr; range, −0.23 to −0.09), with an average pointwise difference between groups of −0.21 dB/yr. We also estimated the correlation between pointwise VF slopes and absolute MD differences between eyes as a continuous measure; the results are consistent with those using dichotomous subgroups but provide additional detail (Supplementary Figs. S2A, S2B).

Disc Hemorrhage and Notching

Disc hemorrhage and notching showed no pointwise slope differences between subgroups (Figs. 6c, 6d; Table 2).

Question 2a: Considering the Four Categories of Glaucomatous Damage (None, Mild, Moderate, and Severe), What Is the Likelihood of Defect at Each VF Location?

Figure 3 shows fairly uniform patterns in the earliest stages of glaucoma across the three VF

Table 3. Significant Pointwise Differences in Age-Adjusted Deviations From Normal Among Subgroups of Demographic, Comorbid, and Clinical Variables

Variable Tested, Subgroup 1 vs. Subgroup 2	Deviation (dB), Mean (Range)		Difference (dB), Subgroup 1 – Subgroup 2, Mean (Range)	Significant Points[a]		Deviation (dB), Mean (Range)		Difference (dB), Subgroup 1 – Subgroup 2, Mean (Range)	Significant Points[a]	
	Subgroup 1	Subgroup 2		*t*-Test, FDR	Wilcoxon Test, FDR	Subgroup 1	Subgroup 2		*t*-Test, FDR	Wilcoxon Text, FDR
	No Damage (Iowa MD, ≥−2 dB; $n = 375$)					Mild Damage (Iowa MD, −6 dB to −2.1 dB; $n = 656$)				
Gender: male vs. female	−0.8 (−2.0, 0.2)	−1.1 (−3.3, 0.2)	0.3 (−0.5, 1.3)	7, 0[b]	5, 0[b]	−4.1 (−7.7, −2.0)	−4.2 (−8.8, −1.6)	0.0 (−0.9, 1.5)	19[c], 0	14, 1[b]
Age: ≥65 yr vs. <65 yr	−1.0 (−2.3, 0.3)	−0.9 (−2.9, 0.2)	−0.1 (−0.8, 0.9)	4, 0[b]	3, 0[b]	−4.3 (−7.5, −2.0)	−4.0 (−8.3, −1.7)	−0.3 (−1.4, 0.8)	10[c], 0	12, 2[c]
Race: black vs. white	−0.9 (−3.7, 0.4)	−0.9 (−2.0, 0.0)	−0.1 (−1.8, 0.7)	2, 0[b]	7, 1[c]	−4.3 (−8.2, −1.8)	−4.1 (−7.9, −1.8)	−0.2 (−1.4, 0.8)	8, 2[c]	14, 5[c]
Education: <high school vs. ≥high school	−1.1 (−3.9, 0.6)	−0.9 (−2.3, 0.2)	−0.2 (−1.5, 1.2)	4, 0[c]	11[c], 1[c]	−4.2 (−8.0, −2.1)	−4.1 (−8.4, −1.7)	−0.1 (−1.5, 1.5)	14[b], 6	18, 9[c]
Hypertension: yes vs. none	−0.9 (−2.7, 0.3)	−0.9 (−2.6, 0.1)	0.0 (−0.7, 0.7)	1, 0[b]	4, 0[b]	−4.2 (−7.6, −1.9)	−4.1 (−8.4, −1.7)	−0.1 (−0.8, 1.0)	3, 0[b]	7, 1[b]
Diabetes: yes vs. none	−0.9 (−2.4, 0.3)	−0.9 (−2.7, 0.1)	0.0 (−1.1, 0.8)	2, 0[b]	1, 0[b]	−4.1 (−7.3, −1.8)	−4.2 (−8.3, −1.8)	0.0 (−0.9, 1.4)	5, 0[b]	4, 0[b]
Cardiovascular disease: yes vs. none	−1.0 (−3.7, 0.5)	−0.9 (−2.5, 0.1)	−0.1 (−1.6, 1.0)	1, 0[b]	1, 0[b]	−4.3 (−8.2, −1.8)	−4.1 (−8.0, −1.7)	−0.2 (−1.4, 0.8)	0, 0[b]	3, 0[b]
Immediate family history of glaucoma: yes vs. none	−0.9 (−3.6, 0.5)	−1.0 (−2.7, 0.3)	0.1 (−1.1, 1.2)	7, 2[b]	6, 2[b]	−4.3 (−8.3, −2.2)	−4.1 (−8.0, −1.6)	−0.2 (−1.5, 0.7)	5, 0[b]	6, 0[b]
CDR: ≥0.7 vs. <0.7	−1.1 (−3.4, 0.1)	−0.7 (−2.5, 0.3)	−0.4 (−1.7, 0.9)	13[c], 4	20[c], 8	−4.3 (−8.5, −1.9)	−3.9 (−7.8, −1.6)	−0.4 (−2.4, 1.0)	25[b], 17	18, 9[c]
MD difference between eyes: >3 dB vs. ≤3 dB	−1.0 (−3.8, 0.4)	−0.9 (−2.4, 0.1)	−0.1 (−1.6, 1.4)	5, 0[b]	8, 0[c]	−4.7 (−9.2, −2.1)	−3.8 (−7.4, −1.5)	−0.8 (−2.4, 1.2)	29[b], 28	26[b], 22
Disc hemorrhage: yes vs. none	−1.2 (−4.6, 1.7)	−0.9 (−2.6, 0.1)	−0.2 (−2.3, 2.4)	2, 0[b]	2, 0[b]	−3.7 (−9.9, −0.7)	−4.2 (−7.9, −1.8)	0.4 (−3.1, 1.9)	10, 0[b]	4, 0[b]
Notching: yes vs. no	−1.1 (−3.9, 0.3)	−0.8 (−2.4, 0.1)	−0.2 (−2.0, 0.8)	8, 0[c]	9, 3[b]	−4.2 (−9.1, −1.8)	−4.1 (−7.7, −1.8)	0.0 (−1.9, 1.2)	15[b], 14	19[b], 10
	Moderate Damage (Iowa MD, −12 to −6.1 dB; $n = 695$)					Severe Damage (Iowa MD, ≤12.1 dB; $n = 508$)				
Gender: male vs. female	−8.4 (−13.8, −3.8)	−8.6 (−16.2, −3.6)	0.2 (−1.9, 2.8)	38[b], 35	31[b] 27	−15.1 (−20.3, −8.8)	−15.2 (−21.6, −7.3)	0.1 (−2.2, 3.1)	22[b], 0	19[b], 0
Age: ≥65 yr vs. <65 yr	−8.6 (−14.1, −4.2)	−8.4 (−16.0, −3.2)	−0.1 (−1.2, 1.9)	8, 0[b]	11, 4[c]	−15.1 (−20.4, −8.4)	−15.2 (−21.7, −7.4)	0.1 (−2.0, 2.1)	5, 0[b]	19[b], 15
Race: black vs. white	−8.7 (−15.3, −3.9)	−8.4 (−14.6, −3.5)	−0.3 (−1.4, 1.6)	9, 0[b]	14, 4[b]	−15.6 (−20.7, −9.0)	−14.5 (−20.7, −7.0)	−1.1 (−3.7, 1.0)	17, 9[b]	17[b], 11
Education: <high school vs. ≥high school	−8.7 (−14.6, −4.3)	−8.4 (−15.2, −3.4)	−0.3 (−3.0, 2.1)	31[b], 24	30[b], 23	−15.6 (−20.4, −9.3)	−14.9 (−21.1, −7.3)	−0.7 (−3.5, 2.2)	20[b], 15	24[b], 17
Hypertension: yes vs. none	−8.7 (−14.5, −4.1)	−8.3 (−15.4, −3.4)	−0.4 (−1.6, 1.0)	12[c], 7	16, 12[c]	−15.4 (−20.9, −8.4)	−15.0 (−20.9, −7.6)	−0.4 (−2.0, 1.5)	3, 0[b]	4, 0[b]
Diabetes: yes vs. none	−8.4 (−14.4, −4.0)	−8.5 (−15.1, −3.6)	0.1 (−1.7, 1.7)	5, 0[c]	10, 2[c]	−15.1 (−20.3, −8.2)	−15.2 (−21.0, −8.0)	0.0 (−2.1, 2.4)	5, 0[b]	7, 0[b]
Cardiovascular disease: yes vs. none	−8.7 (−14.3, −4.2)	−8.5 (−15.2, −3.6)	−0.3 (−1.5, 1.7)	7, 0[b]	6, 0[c]	−15.3 (−20.2, −9.1)	−15.1 (−21.0, −7.7)	−0.2 (−2.1, 1.9)	3, 0[b]	10, 0[b]
Immediate family history of glaucoma: yes vs. none	−8.6 (−15.0, −3.9)	−8.5 (−15.0, −3.7)	−0.1 (−1.4, 0.9)	1, 0[b]	2, 0[b]	−15.2 (−20.9, −8.0)	−15.1 (−20.8, −8.1)	−0.1 (−1.9, 1.9)	3, 0[b]	5, 0[b]
CDR: ≥0.7 vs. <0.7	−8.7 (−15.3, −3.9)	−8.0 (−14.0, −3.1)	−0.7 (−3.7, 2.4)	25[b], 20	25[b], 21	−15.3 (−20.8, −8.2)	−14.6 (−20.8, −7.2)	−0.6 (−4.0, 3.8)	11, 3[c]	12, 2[c]
MD difference between eyes: >3 dB vs. ≤3 dB	−8.9 (−15.8, −3.6)	−7.9 (−14.0, −3.8)	−1.0 (−3.5, 2.1)	32[b], 32	23[b], 21	−15.2 (−21.1, −7.8)	−15.1 (−21.2, −8.1)	0.0 (−2.9, 4.0)	19[b], 6	13[b], 5
Disc hemorrhage: yes vs. none	−7.9 (−19.0, −1.9)	−8.5 (−14.9, −3.8)	0.7 (−4.7, 4.0)	22[b], 13	16[c], 3	−15.0 (−23.3, −5.5)	−15.2 (−20.8, −8.0)	0.2 (−7.9, 5.9)	13, 6[c]	6, 0[b]
Notching: yes vs. no	−8.6 (−16.1, −3.6)	−8.4 (−14.0, −3.7)	−0.1 (−3.5, 1.8)	24[b], 18	29[b], 21	−15.2 (−21.5, −7.8)	−15.1 (−20.5, −8.1)	−0.1 (−3.9, 2.3)	13, 4[c]	20[b], 9

Results are stratified by the four mean deviation categories, from no damage to severe damage.

[a]Number of significant points by *t*-test or Wilcoxon test before and after adjustment for FDR.

[b]*Q* equals the number given.

[c]*Q* is between the unadjusted (*t*-test or Wilcoxon test) and FDR-adjusted values but closer to the number given.

percentiles (column 1). However, variability across the VF increases dramatically from the mild through severe MD categories (columns 2–4).

Question 2b: Considering the Four MD Severity Categories, Do Patterns Differ by Baseline Demographic, Comorbid, or Clinical Variables?

Differences in age-adjusted deviations from normal between dichotomous subgroups of demographic, comorbid, and clinical variables were tested at each VF point within each of the four MD categories. Statistically significant subgroup differences, which can be negative or positive, are reported in Table 3, along with significance tests (expressed as number significant per 52 points; Supplementary Table S4 gives subgroup sample sizes). Significant P values and/or Q values are indicated on heatmap plots by black outlined squares (t-test) or triangles (Wilcoxon test); significant P values after FDR adjustment and/or Q values are indicated by bold outlined squares (t-test) or filled triangles (Wilcoxon test). In addition to the statistical comparisons, subgroup comparisons are visualized descriptively with color heatmaps that can show novel patterns not identifiable in the tabled data (Figs. 7–9).

Gender

In the comparison of males versus females, the strongest pointwise FDR-adjusted differences were seen in category 3 (moderate; 35/52 by t-test; 27/52 by

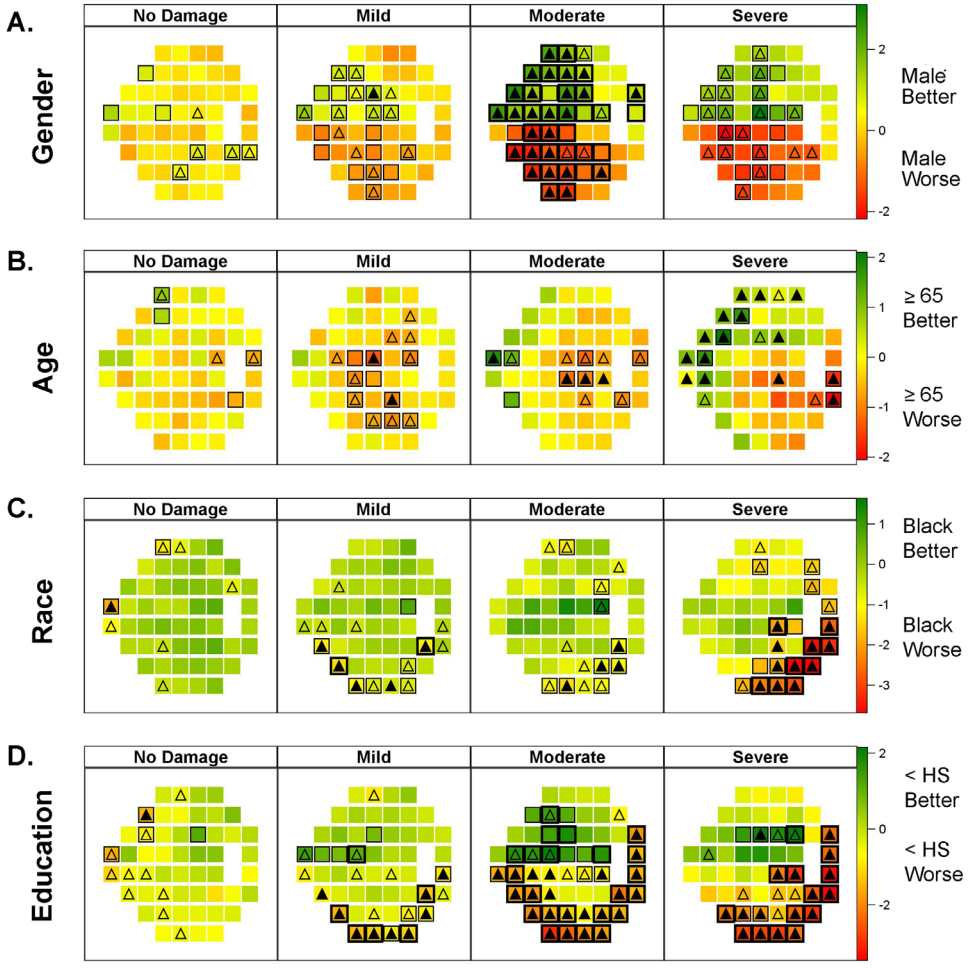

Figure 7. Dichotomous subgroups of demographic variables across each of the four mean MD categories (no damage or mild, moderate, or severe damage) are shown. Heatmap plots display average pointwise differences in age-adjusted deviations from normal between (A) gender (males vs. females), (B) age (≥65 years vs. <65 years), (C) race (black vs. white), and (D) education (<high school vs. ≥high school). Significant pointwise differences are denoted by *thin squares* (t-tests) or *open triangles* (Wilcoxon tests); differences after FDR adjustment are shown as *bold squares* (t-tests) or *filled triangles* (Wilcoxon tests). A difference of zero indicates that the subgroup means are equal. The relative difference (Subgroup 1 minus Subgroup 2) can range from positive (*green*) to negative (*red*). Subgroup labels can also be reversed, e.g., "males better" (*green*) and "males worse" (*red*) are equivalent to the reverse being true for females. (Table 3 shows data ranges for all four panels.)

Wilcoxon test), with similar relationships in category 4 (Fig. 7A). Although field-wide average values were quite similar in males and females, the within-field patterns show a prominent horizontal midline effect, with males having better superior points and females having better inferior points. This pointwise gender difference, even visible in category 1, increased over each MD category.

Age

For categories 2 and 3, participants who were older experienced significantly more damage in the central region of the VF compared with those who were younger (Fig. 7B). In category 4, older participants showed significantly less damage in the peripheral nasal points and more damage in the peripheral temporal points of the VF than did younger participants (15/52 by FDR-adjusted Wilcoxon test).

Race

Although VFs in MD categories 1 to 3 were similar between races, black participants in category 4 showed significantly worse damage than white participants at the temporal inferior points (9/52 by FDR-adjusted *t*-test; 11/52 by FDR-adjusted Wilcoxon test) (Fig. 7C).

Education

In MD categories 2 to 4, participants with less than a high school education showed less damage in the superior field and significantly more damage in the inferior periphery than those with a high school education or better (category 2, 6/52 and 9/52; category 3, 24/52 and 23/52; category 4, 15/52 and 17/52 by FDR-adjusted *t*-test and Wilcoxon test, respectively) (Fig. 7D).

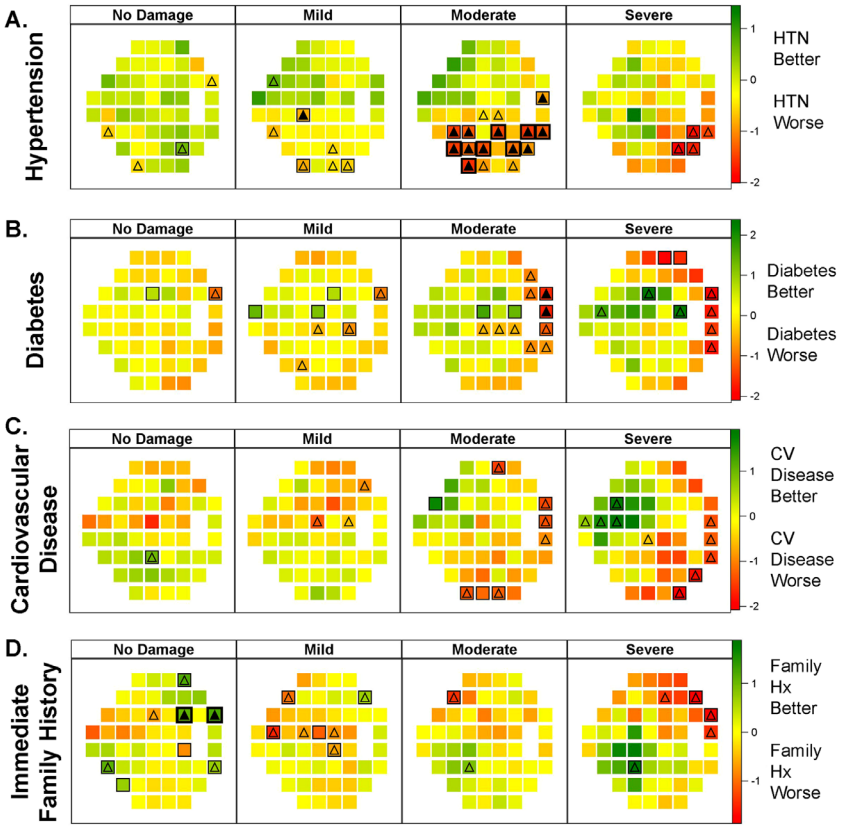

Figure 8. Dichotomous subgroups of comorbidity variables across each of the four MD categories (no damage or mild, moderate, or severe damage) are shown. Heatmap plots display average pointwise differences in age-adjusted deviations from normal between (A) hypertension (yes vs. no), (B) diabetes (yes vs. no), (C) cardiovascular disease (yes vs. no), and (D) immediate family history of glaucoma (yes vs. no). Significant pointwise differences are denoted by *thin squares* (*t*-tests) or *open triangles* (Wilcoxon tests); differences after FDR adjustment are shown as *bold squares* (*t*-tests) or *filled triangles* (Wilcoxon tests). A difference of zero indicates that the subgroup means are equal. The relative difference (Subgroup 1 minus Subgroup 2) can range from positive (*green*) to negative (*red*). Subgroup labels can also be reversed, e.g., "hypertension better" and "hypertension worse" are equivalent to the reverse being true for no hypertension. (Table 3 shows data ranges for all four panels.)

Hypertension

In MD category 3, those with hypertension had significantly worse damage across much of the inferior field compared with those without hypertension (7/52 and 12/52 by FDR-adjusted *t*-test and Wilcoxon test, respectively) (Fig. 8A).

Diabetes, Cardiovascular Disease, and Immediate Family History of Glaucoma

In all four categories, few significant pointwise differences were seen between dichotomous subgroups (Figs. 8B–8D).

Cup-to-Disc Ratio

Participants with CDR ≥ 0.7 showed significantly worse pointwise damage in the central region of the VF and significantly less damage in the temporal periphery than those with CDR < 0.7, particularly in MD categories 2 to 3 (category 1, 4/52 and 8/52; category 2, 17/52 and 9/52; category 3, 20/52 and 21/52; category 4, 3/52 and 2/52 by FDR-adjusted *t*-test and Wilcoxon test, respectively) (Fig. 9A).

Absolute Difference in MD Between Eyes

In MD categories 2 and 3, participants with MD differences > 3 dB between eyes at baseline (vs. ≤3 dB) showed significantly more damage in the central and nasal points of the field and less in the extreme temporal and superior periphery (category 2, 28/52 and 22/52; category 3, 32/52 and 21/52 by FDR-adjusted *t*-test and Wilcoxon test, respectively) (Fig. 9B). Supplementary Figures S2C and S2D display the relationship between pointwise VF deviations and the continuous, not dichotomized, measure of absolute difference between eyes in MD. Results were similar but provide additional detail.

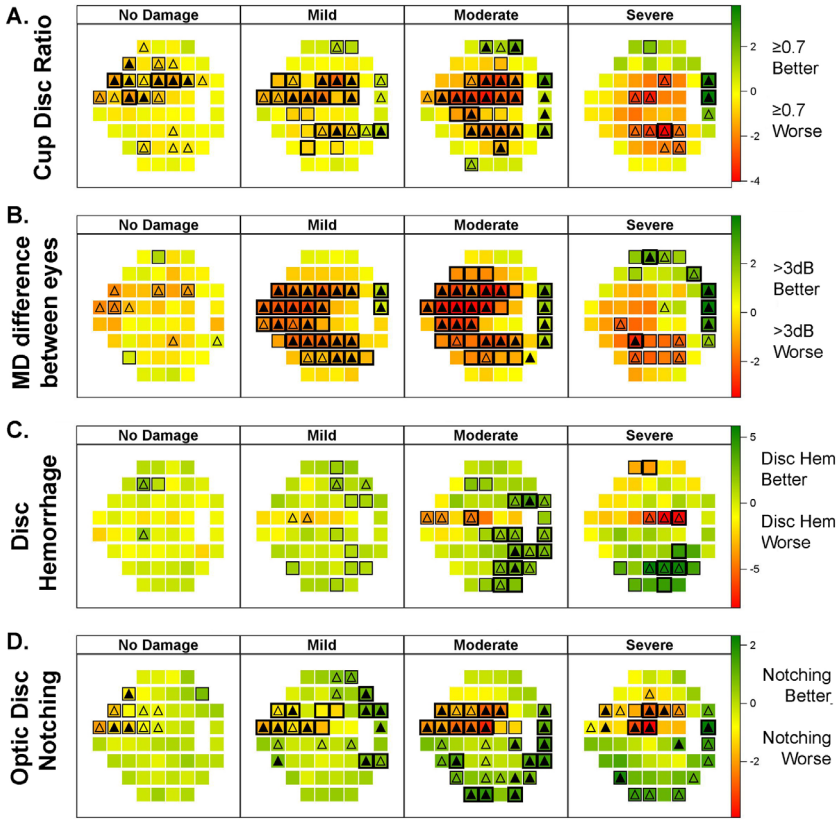

Figure 9. Dichotomous subgroups of clinical variables across each of the four MD categories (no damage or mild, moderate, or severe damage) are shown. Heatmap plots display average pointwise differences in age-adjusted deviations from normal between (A) CDR (≥0.7 vs. <0.7), (B) baseline absolute difference in MD between eyes (>3 dB vs. ≤3 dB), (C) disc hemorrhage (Disc Hem; yes vs. no), and (D) optic disc notching (yes vs. no). Significant pointwise differences are denoted by *thin squares* (*t*-tests) or *open triangles* (Wilcoxon tests); differences after FDR adjustment are shown as *bold squares* (*t*-tests) or *filled triangles* (Wilcoxon tests). A difference of zero indicates that subgroup means are equal. The relative difference (Subgroup 1 minus Subgroup 2) can range from positive (*green*) to negative (*red*). Subgroup labels can also be reversed, e.g., "CDR ≥ 0.7 better" (*green*) and "CDR ≥ 0.7 worse" are equivalent to the reverse being true for CDR < 0.7. (Table 3 shows data ranges for all four panels.)

Disc Hemorrhage

In MD categories 2 to 4, participants with disc hemorrhage versus without showed increasing damage in the single VF row above the midline but short of the blind spot and significantly less damage than those without disc hemorrhage for points in the temporal inferior region of the VF (category 3, 13/52 and 3/52; category 4, 6/52 and 0/52 by FDR-adjusted *t*-test and Wilcoxon test, respectively) (Fig. 9C).

Notching

In MD categories 2 to 4, participants with optic disc notching showed significantly more damage than those without notching for points from the nasal periphery to the central field above the midline, but not beyond the blind spot (category 2, 14/52 and 10/52; category 3, 18/52 and 20/52; category 4, 4/52 and 9/52 by FDR-adjusted *t*-test and Wilcoxon test, respectively) (Fig. 9D).

Discussion

This novel exploration of each of the 52 non–blind-spot points in the HFA 24-2 VF found surprisingly many differences between dichotomous subgroups of 12 demographic, comorbid, or clinical variables. Our longitudinal outcomes included both rates of progression (slope) at each VF point, which are largely stable or decreasing, and tests for subgroup differences in the rates of progression for each of the 12 variables. Cross-sectional outcomes show the likelihood of defect at each VF point in four MD severity categories and the pointwise tests for subgroup differences in each category. Consistent with prior research, VF improvement of ≥1 dB/yr at one or more VF points was observed in 5% of participants.[21–23]

Pointwise slope trajectories over time and cross-sectional pattern analyses answer different questions and yield different results. Slopes are measured across the entire multi-year time frame and reflect cumulative damage over time. The cross-sectional analyses separately consider each of the four MD severity categories, where defects may develop slowly over time and only fully exhibit, if at all, in the moderate or severe levels. For subgroup comparisons, slope differences tended to have broad effects across the VF, consistent with widespread loss observed in the OHTS,[24] whereas cross-sectional results tended to have distinct patterns in various VF regions such as nasal and temporal, consistent with previously observed individual patterns.[25]

Longitudinal results revealed significant subgroup differences in six of the 12 variables tested. Each of the first (vs. second) subgroups below showed faster progression, on average, at every point in the VF, with statistical significance by FDR at all or many of the VF locations: older versus younger age (52/52); male versus female gender (13/52; 30/52 by *Q* values); hypertension, yes versus no (46/52); diabetes, yes versus no (29/52); absolute MD difference between eyes, larger versus smaller (52/52); and CDR, high versus low (36/52).

Cross-sectional results showed that each of the 52 VF points displayed defects from normal, starting field-wide as early as "mild" glaucoma severity (MDs of −2.1 to −6 dB). Further, patterns of loss could differ by specific demographic, comorbid, or clinical characteristics, some strongly informative and others mildly or non-informative. Nine of the 12 variables revealed significant subgroup differences in at least one of the four MD severity categories. These included differences by gender, age, race, education, hypertension, CDR, absolute MD difference between eyes, disc hemorrhage, and optic disc notching.

The association of patient demographic characteristics with field-wide glaucoma severity have been explored,[26–28] but associations of these characteristics with pointwise deficits and progression have been limited. Our results showing that males (vs. females) had faster glaucoma progression at all VF points and worse defects in the inferior versus superior portion of the field, particularly in the moderate severity category, are novel. Our results are consistent with the gender differences between eye regions observed by Tobe et al.[29] using measurements of ocular perfusion pressure (OPP) and retinal capillary flow (with confocal scanning laser Doppler flowmetry). A positive association between retinal capillary flow and OPP was found in females, with a corresponding negative association found in males, suggesting gender differences in vascular autoregulation in response to changes in OPP. It has also been suggested that ophthalmic gender differences may be related to sex hormones.[30,31]

It is well known that the risks of glaucoma and disease progression increase with age.[27] We further found that those ≥65 years of age had steeper regression slopes than those <65 years of age at every point in the VF. A novel finding was that, between those with severe glaucoma damage, those ≥65 years old versus younger patients showed less deficit from normal in the superior nasal periphery.

Several studies reviewed by Tham et al.[32] have looked at the effects of chronic systemic diseases on incident glaucoma and glaucoma progression, with varying results. Both hypertension and glaucoma increase with age, with complex relationships between

blood pressure and ocular perfusion pressure. Antihypertension drugs taken in the evening have been associated with lower nocturnal blood pressure, more pronounced nocturnal blood pressure dipping, lower nocturnal ocular perfusion pressure, and greater VF loss,[33] showing that strict hypertension control may be at odds with efforts to slow glaucoma progression. The connection between glaucoma and hypertension requires further study and would benefit from joint medical management of these two diseases.[33] Cardiovascular disease has also been examined as a predictor of progression in glaucoma,[34] with conflicting results likely due to modest sample sizes. Similar to Chan et al.,[35] who found rapid progression in those with cardiovascular disease, we found faster mean pointwise progression in those with cardiovascular disease versus without at all 52 VF points, significant with Q values at 17/52 points. Diabetes was previously associated with field-wide open-angle glaucoma progression in both the AGIS and the CIGTS[36,37]; evidence was similar in our pointwise analysis. The advent of metformin around 1995 likely moderated the effect of diabetes. Along with small sample size, this could explain the results of Hou et al.,[38] whose 1995 study of 32 diabetics and 111 non-diabetics found no significant field-wide difference in progression but did find significant differences in the rate of retinal nerve fiber layer thinning.

Limitations of this study include the fact that all 12 study variables were dichotomized for simplicity. Although the dichotomies used are standard within ophthalmology (e.g., CDR < 0.7 vs. ≥ 0.7), different cut points could have yielded different results. Future analyses could use more categories or continuous measures. Second, individual tests were performed without considering potential confounding effects of other variables, such as confounding effects of hypertension when testing the effect of diabetes (Supplementary Table S5). Third, significance testing was FDR-adjusted within each VF set of 52 points but not across the 12 unique variables. This strategy was deemed appropriate for this first exploratory investigation, where accepting a false effect was considered less concerning than missing a true effect. Fourth, we used the visualFields MD rather than the more standard Humphrey MD, although the two measures are highly correlated. Fifth, we had no data on the location of optic disc notching and sparse data on corneal thickness or retinal nerve fiber layer, potentially important variables. Finally, we did not consider treatment regimens (medications, trabeculectomy, or argon laser trabeculoplasty) at randomization or follow-up.

Strengths of this study include the large datasets from both the AGIS and the CIGTS, each with wide ranges of severity at baseline. Both clinical trials used nearly identical standardized VF testing, follow-up visit schedules, and case report forms, and both had long-term follow-up, facilitating the combining of data. With 9 years of chronological overlap, any temporal effects should be similar between studies. Extensive time was devoted to data entry and cleaning and merging datasets, yielding a robust and largely complete dataset for analyses. The final analyses, by design, were based on averages of VF values over hundreds of unique participants. Our novel epidemiological approach was intended to yield new findings in the study of glaucomatous progression.

Conclusions

The approaches used in this study give new insights into variation across the visual field connected to demographic, comorbid, and clinical variables. The exploration of covariate effects in the setting of pointwise visual field testing may lead to new pursuits in the exploration of disease mechanisms,[7] such as testing variables for association with the nerve fiber layer. Both our quantitative and descriptive results have yielded novel findings, including gender differences in progression rates, intriguing patterns by hemifield, and the strong pointwise effects of age, hypertension, diabetes, cup-to-disc ratio, and absolute difference in mean deviation between eyes. These findings and the associated methods provide motivation for future investigations.

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References

1. Brusini P, Johnson CA. Staging functional damage in glaucoma: review of different classification methods. *Surv Ophthalmol*. 2007;52(2):156–179.
2. Aulhorn E, Karmeyer H. Frequency distribution in early glaucomatous visual field defects. *Doc Ophthalmol Proc Series*. 1977;14:75–83.
3. Advanced Glaucoma Intervention Study Investigators. Advanced Glaucoma Intervention Study. 2. Visual field test scoring and reliability. *Ophthalmology*. 1994;101(8):1445–1455.
4. Keltner JL, Johnson CA, Cello KE, et al. Classification of visual field abnormalities in the ocular hypertension treatment study. *Arch Ophthalmol*. 2003;121(5):643–650.
5. Lin C, Mak H, Yu M, Leung CK. Trend-based progression analysis for examination of the topography of rates of retinal nerve fiber layer thinning in glaucoma. *JAMA Ophthalmol*. 2017;135(3):189–195.
6. Hood DC, Raza AS, de Moraes CG, Liebmann JM, Ritch R. Glaucomatous damage of the macula. *Prog Retin Eye Res*. 2013;32:1–21.
7. Wang M, Shen LQ, Pasquale LR, et al. Artificial intelligence classification of central visual field patterns in glaucoma. *Ophthalmology*. 2020;127(6):731–738.
8. Rabiolo A, Morales E, Mohamed L, et al. Comparison of methods to detect and measure glaucomatous visual field progression. *Transl Vis Sci Technol*. 2019;8(5):2.
9. Ederer F, Gaasterland DE, Sullivan EK, AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 1. Study design and methods and baseline characteristics of study patients. *Control Clin Trials*. 1994;15(4):299–325.
10. Musch DC, Lichter PR, Guire KE, Standardi CL. The Collaborative Initial Glaucoma Treatment Study: study design, methods, and baseline characteristics of enrolled patients. *Ophthalmology*. 1999;106(4):653–662.
11. Marín-Franch I, Swanson WH. The visualFields package: a tool for analysis and visualization of visual fields. *J Vis*. 2013;13(4):10.
12. Russell RA, Crabb DP. On alternative methods for measuring visual field decay: Tobit linear regression. *Invest Ophthalmol Vis Sci*. 2011;52(13):9539–9540.
13. Caprioli J, Mock D, Bitrian E, et al. Author response: on alternative methods for measuring visual field decay: Tobit linear regression. *Invest Ophthalmol Vis Sci*. 2012;53(1):118.
14. Caprioli J, Mohamed L, Morales E, et al. A method to measure the rate of glaucomatous visual field change. *Transl Vis Sci Technol*. 2018;7(6):14.
15. Gloster J. Quantitative relationship between cupping of the optic disc and visual field loss in chronic simple glaucoma. *Br J Ophthalmol*. 1978;62(10):665–669.
16. Musch DC, Gillespie BW, Lichter PR, Niziol LM, Janz NK, CIGTS Study Investigators. Visual field progression in the Collaborative Initial Glaucoma Treatment Study: the impact of treatment and other baseline factors. *Ophthalmology*. 2009;116(2):200–207.
17. McKean-Cowdin R, Varma R, Wu J, Hays RD, Azen SP, Los Angeles Latino Eye Study Group. Severity of visual field loss and health-related quality of life. *Am J Ophthalmol*. 2007;143(6):1013–1023.
18. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. *Ann. Statist.* 2001;29(4):1165–1188.
19. Storey JD, Taylor JE, Siegmund D. Strong control, conservative point estimation and simultaneous conservative consistency of false discovery rates: a unified approach. *J R Stat Soc Series B Stat Methodol*. 2004;66(1):187–205.
20. Storey JD. False discovery rates. In: Lovric M, ed., *International Encyclopedia of Statistical Science*. Heidelberg: Springer-Verlag; 2011:504–508.
21. Musch DC, Gillespie BW, Palmberg PF, Spaeth G, Niziol LM, Lichter PR. Visual field improvement in the Collaborative Initial Glaucoma Treatment Study. *Am J Ophthalmol*. 2014;158(1):96–104.e2.
22. Gardiner SK, Demirel S, Johnson CA. Is there evidence for continued learning over multiple years in perimetry?. *Optom Vis Sci*. 2008;85(11):1043–1048.
23. Caprioli J, de Leon JM, Azarbod P, et al. Trabeculectomy can improve long-term visual function in glaucoma. *Ophthalmology*. 2016;123(1):117–128.
24. Artes PH, Chauhan BC, Keltner JL, et al. Longitudinal and cross-sectional analyses of visual field progression in participants of the Ocular Hypertension Treatment Study. *Arch Ophthalmol*. 2010;128(12):1528–1532.

25. Sample PA, Chan K, Boden C, et al. Using unsupervised learning with variational Bayesian mixture of factor analysis to identify patterns of glaucomatous visual field defects. *Invest Ophthalmol Vis Sci*. 2004;45(8):2596–2605.
26. Kim JH, Rabiolo A, Morales E, et al. Risk factors for fast visual field progression in glaucoma. *Am J Ophthalmol*. 2019;207:268–278.
27. Ernest PJ, Schouten JS, Beckers HJ, Hendrikse F, Prins MH, Webers CA. An evidence-based review of prognostic factors for glaucomatous visual field progression. *Ophthalmology*. 2013;120(3):512–519.
28. Blumberg D, Skaat A, Liebmann JM. Emerging risk factors for glaucoma onset and progression. *Prog Brain Res*. 2015;221:81–101.
29. Tobe LA, Harris A, Trinidad J, et al. Should men and women be managed differently in glaucoma? *Ophthalmol Ther*. 2012;1(1):1.
30. Schmidl D, Schmetterer L, Garhöfer G, Popa-Cherecheanu A. Gender differences in ocular blood flow, *Curr Eye Res*, 2015;40(2):201–212,
31. Vajaranant TS, Nayak S, Wilensky JT, Joslin CE. Gender and glaucoma: what we know and what we need to know. *Curr Opin Ophthalmol*. 2010;21(2):91–99.
32. Tham YC, Cheng CY. Associations between chronic systemic diseases and primary open angle glaucoma: an epidemiological perspective. *Clin Exp Ophthalmol*. 2017;45(1):24–32.
33. Leeman M, Kestelyn P. Glaucoma and blood pressure. *Hypertension*. 2019;73(5):944–950.
34. Chauhan BC, Mikelberg FS, Balaszi AG, et al. Canadian Glaucoma Study: 2. Risk factors for the progression of open-angle glaucoma. *Arch Ophthalmol.* 2008;126(8):1030–1036.
35. Chan TCW, Bala Siu A, Wan F, White A. Risk factors for rapid glaucoma disease progression. *Am J Ophthalmol*. 2017;180:151–157.
36. AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 12. Baseline risk factors for sustained loss of visual field and visual acuity in patients with advanced glaucoma. *Am J Ophthalmol*. 2002;134(4):499–512.
37. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology*. 2001;108(11):1943–1953.
38. Hou H, Shoji T, Zangwill LM, et al. Progression of primary open-angle glaucoma in diabetic and nondiabetic patients. *Am J Ophthalmol*. 2018;189:1–9.