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Association between Intraocular Pressure and Rates of Retinal Nerve Fiber Layer Loss Measured by Optical Coherence Tomography

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Abstract

Purpose—To evaluate the relationship between intraocular pressure (IOP) and rates of retinal nerve fiber layer (RNFL) thickness change over time measured by spectral-domain (SD) optical coherence tomography (OCT).

Design—Observational cohort study.

Participants—The study involved 547 eyes of 339 patients followed for an average period of 3.9 ± 0.9 years. Three hundred and eight (56.3%) had a diagnosis of glaucoma and 239 (43.7%) were considered glaucoma suspects.

Methods—All eyes underwent imaging using the Spectralis® SD OCT (Heidelberg Engineering GmbH, Heidelberg, Germany), along with IOP measurements and standard automated perimetry (SAP). Glaucoma progression was defined as a result of “Likely Progression” from the Guided Progression Analysis™ software for SAP. Linear mixed models were used to investigate the relationship between average IOP during follow-up and rates of RNFL thickness change, while taking into account potential confounding factors, such as age, race, corneal thickness, and baseline disease severity.

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Main Outcome Measures—The association between IOP and rates of global and sectorial RNFL thickness loss measured by SD OCT.

Results—Forty-six eyes (8.4%) showed progression on SAP during follow-up. Rates of global RNFL thickness change in eyes that progressed by SAP were faster than in those that did not progress (−1.02 μm/year versus −0.61 μm/year, respectively; $P = 0.002$). For progressing eyes, each 1 mmHg higher average IOP during follow-up was associated with an additional average loss of 0.20 μm/year [confidence interval (CI): 0.08 to 0.31 μm/year; $P < 0.001$] of global RNFL thickness versus only 0.04 μm/year (CI: 0.01 to 0.07 μm/year; $P = 0.015$) for non-progressing eyes. The largest associations between IOP and rates of RNFL change were seen for measurements from the temporal superior and temporal inferior sectors, whereas the smallest association was seen for measurements from the nasal sector.

Conclusions—Higher levels of IOP during follow-up were associated with faster rates of RNFL loss over time measured by SD OCT. These findings support the use of SD OCT RNFL thickness measurements as biomarkers for the evaluation of the efficacy of IOP-lowering therapies to slow down the rate of disease progression.

PRÉCIS

In a longitudinal study, higher levels of intraocular pressure during follow-up were associated with faster rates of glaucomatous retinal nerve fiber layer loss over time measured by spectral-domain optical coherence tomography.

INTRODUCTION

Glaucoma is a progressive optic neuropathy characterized by degeneration of retinal ganglion cells and their axons resulting in visual field loss and a characteristic appearance of the optic disc.[1] Intraocular pressure (IOP) is still considered the most important risk factor for the development and progression of primary open-angle glaucoma (POAG) and also remains the only known modifiable risk factor.[1]

Several clinical trials have provided evidence for the role of average IOP in the disease and the benefit of IOP-lowering treatment.[2–7] The Ocular Hypertension Treatment Study (OHTS) demonstrated that the cumulative incidence of POAG was 4.4% in the medication group and 9.5% in the observation group, after 5 years of follow-up.[3, 4] The Early Manifest Glaucoma Trial (EMGT) showed that progression was less frequent in treated patients with POAG than non-treated, thereby reducing visual field loss in the treated group.[5] Additionally, in the Advanced Glaucoma Intervention Study (AGIS), eyes that maintained IOP less than 18 mmHg during follow-up had less progression based on visual fields.[2] Most of the previous studies evaluating the role of IOP in glaucoma have used visual fields as the sole end point for estimating disease development and progression. However, there is evidence that many patients can progress by structural tests while not showing detectable change by functional measures.[4, 8, 9] In addition, these structural changes have been shown to be predictive of future functional losses and decrease in quality of life in glaucoma patients.[8–12]

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Optical coherence tomography (OCT) has become a widely used method for assessment of structural damage in glaucoma.[13–15] The technology can provide quantitative and reproducible measurements of the peripapillary retinal nerve fiber layer (RNFL), which have been shown to be helpful in the diagnosis and assessment of disease progression.[16, 17] The more recent introduction of spectral-domain (SD) OCT has enhanced the resolution, decreased scan acquisition time, and improved reproducibility compared to older versions of the technology.[18–21] However, despite the widespread use of SD OCT for assessment of glaucomatous change over time, no investigation has yet evaluated the impact of IOP on longitudinal SD OCT measurements in glaucoma. Evaluation and quantification of this relationship is important in order to validate this technology and also to provide a better understanding of the role of IOP as a risk factor for structural damage in the disease.

The purpose of the present study was to evaluate the relationship between IOP and longitudinal changes in the RNFL as assessed by SD OCT in a cohort of individuals with glaucoma and suspected of having the disease followed over time.

METHODS

This was a longitudinal observational cohort study consisting of participants from the African Descent and Glaucoma Evaluation Study (ADAGES) and the Diagnostic Innovations in Glaucoma Study (DIGS). The 3-site ADAGES collaboration includes the Hamilton Glaucoma Center at the Department of Ophthalmology, University of California San Diego, the New York Eye and Ear Infirmary, and the Department of Ophthalmology, University of Alabama at Birmingham. The DIGS includes participants recruited at the University of California San Diego. By design, the protocols of the two studies are identical. Methodological details have been described previously.[22] The institutional review boards at the University of California San Diego, New York Eye and Ear Infirmary, and University of Alabama at Birmingham approved the methods, and written informed consent was obtained from all participants. The study adhered to the laws of the Health Insurance Portability and Accountability Act, and all study methods complied with the Declaration of Helsinki guidelines for human subject research. The ADAGES and DIGS were registered at http://cilincaltrials.gov (NCT00221923 and NCT00221897, respectively).

All participants underwent a comprehensive ophthalmologic examination including review of medical history, visual acuity, slit-lamp biomicroscopy, IOP measurement, corneal pachymetry, gonioscopy, dilated fundoscopy examination using a 78-diopter lens, stereoscopic optic disc photography, and standard automated perimetry (SAP) using 24-2 Swedish Interactive Threshold Algorithm (SITA) Standard. Only subjects with open angles on gonioscopy were included. Subjects were excluded if they had undergone glaucoma filtering surgery or presented any other ocular or systemic disease that could affect the optic nerve or the visual field.

The study included patients diagnosed with glaucoma, as well as suspected of having the disease. Eyes were classified as glaucomatous if they had two or more repeatable glaucomatous visual field defects at baseline, defined as a pattern standard deviation (PSD) with $P < 0.05$, or a Glaucoma Hemifield Test result outside normal limits. Eyes were

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classified as glaucoma suspects if they had a history of elevated IOP (> 21 mmHg) and/or suspicious or glaucomatous appearance of the optic nerve, but normal and reliable visual field results at baseline. If both eyes from the same patient were eligible for the study, both eyes were included in the analysis and statistical procedures were used to take into account the correlation between measurements within the same patient.

Subjects were followed every 6 months. A minimum follow-up period of 2 years and a minimum of 5 separate visits were required for inclusion in this study. Figure 1 shows a flowchart depicting the selection of eyes and subjects for the study. The SD OCT images were obtained using the Spectralis® (Heidelberg Engineering GmbH, Heidelberg, Germany). The study included a total of 4068 visits, with an average of 7.4 ± 1.6 visits per eye (number of visits ranged from 5 to 13), and an average follow-up of 3.9 ± 0.9 years. Eligible subjects were required to have had IOP measurements and SD OCT scans at the same visit and a visual field examination taken close in time to this visit. During the follow-up period, each patient was treated at the discretion of the attending ophthalmologist.

Intraocular Pressure

IOP measurements were obtained with a Goldmann applanation tonometer model AT 900® (Haag-Streit International, Köniz, Switzerland). Only measurements taken on the same day of the SD OCT RNFL scans were included in the study. Average IOP during the follow-up period was calculated.

Spectral-Domain Optical Coherence Tomography

Spectralis® SD OCT (software version 5.4.7.0) was used to measure peripapillary RNFL thickness in the present study. Principles of operation of SD OCT have been described in detail previously.[19, 23] Peripapillary RNFL measurements were obtained in a circle scan centered on the optic disc. The circle scan contains 1536 A-scan points from a 12° circle, which equates to a retinal diameter of 3.5 mm in eyes with standard corneal curvature. The acquisition rate is 40000 A-scans per second at an axial resolution of approximately 4 μm and a lateral resolution of 6 μm. The temporal margin (9-o'clock position in the right eye and 3-o'clock position in the left eye) was designated 0°, and degrees were counted in a clockwise direction on right eye and in an anticlockwise direction on left eye. The RNFL assessment was also conducted by sectors provided by the software, divided as temporal (316°–45°), temporal superior (46°–90°), nasal superior (91°–135°), nasal (136°–225°), nasal inferior (226°–270°), and temporal inferior (271°–315°). The software also provides the quality score that indicates the signal strength. Quality scores range from 0 dB (poor) to 40 dB (excellent). Images with non-centered scans, inaccurate segmentation of the RNFL, or quality scores of 15 dB or less were excluded. As part of the protocol of the study, at least three scans were acquired at each visit and only the best quality one was chosen for inclusion in the analysis (Figure 1).

Standard Automated Perimetry

Standard automated perimetry visual fields were obtained using the Humphrey Field Analyzer II, model 750 (Carl Zeiss Meditec, Inc., Dublin, CA, USA). Only reliable tests (≤ 33% fixation losses and < 15% false positives) were included. Glaucomatous visual field

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progression was assessed using the Humphrey Field Analyzer Guided Progression Analysis™ (GPA™) software. Each eye had a minimum of 5 visual fields available to run the Humphrey Field Analyzer GPA™. For each individual point on the visual field, the GPA™ compares the sensitivity on a follow-up test with the sensitivity for the same location obtained from averaging 2 baseline tests. It flags points that show change greater than the expected variability (at the 95% significance level). If significant change is detected in ≥ 3 points, and repeated in the same points in 3 consecutive follow-up tests, the GPA™ software flags the last examination as *Likely Progression*. For the purpose of this study, the presence of a GPA™ classification *Likely Progression* during the follow-up period was considered as indicating visual field progression. The baseline tests were chosen as those closest to the baseline SD OCT date and the last visual field test date was also the one closest to the last available SD OCT examination. The GPA™ is not calculated for severely depressed visual fields; therefore those eyes were automatically excluded from the study.

Statistical Analysis

Values were presented as mean ± standard deviation for continuous variables and as percentage for categorical variables. Random coefficient models were used to evaluate the relationship between average IOP and RNFL thickness measurements over time. Details of the use of these models for assessment of longitudinal change in glaucoma have been previously described.[17, 24–26] In brief, these models are a type of linear mixed model that involve both random intercepts and random slopes and take into account the clustered structure of the data, allowing the residuals associated with the longitudinal measures on the same unit of analysis to be correlated.[27, 28]

A multivariable model was built to evaluate the relationship between average IOP during follow-up and SD OCT RNFL thickness measurements over time, considering potentially confounding variables that could affect this relationship, such as age at baseline, race, baseline SAP mean deviation (MD), central corneal thickness (CCT), and progression as assessed by visual fields. SD OCT RNFL thickness measurements were considered as the dependent variable and time was included as a continuous predictor. The 2-way interactions between time and the different predictors indicated whether these predictors were significantly associated with change in SD OCT RNFL thickness measurements over time. For example, the 2-way interaction between average IOP and time indicated whether average IOP was significantly associated with slopes of RNFL change over time. In addition, we included a 3-way interaction progression × average IOP × time in the model. This was necessary in order to investigate whether the association between IOP and RNFL thickness change over time was different between progressing and non-progressing eyes. Significance of the predictors was evaluated using Wald tests and deviance statistics to reach the most parsimonious final model. After the final model was built, estimates of rates of change for individual eyes were obtained by best linear unbiased prediction.[24, 25]

All statistical analyses were performed using commercially available software Stata, version 13 (StataCorp LP, College Station, TX). The alpha level (type I error) was set at 0.05.

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RESULTS

The present study included 547 eyes of 339 patients with a mean age of 65.8 ± 10.5 years at baseline. One hundred eighty-one patients were female (53.4%) and 158 (46.6%) were male. One hundred ninety-three patients were white (56.9%), 131 were African American (38.6%), and 10 were Asian American (2.9%). From the 547 eyes included in the study, 308 (56.3%) had a diagnosis of glaucoma and 239 (43.7%) were considered as glaucoma suspects at baseline. Forty-six of the 547 eyes (8.4%) showed progression over time on SAP GPA™ during the follow-up period. Table 1 summarizes baseline demographic and clinical characteristics for progressing and non-progressing eyes. Progressing eyes had thinner RNFL measurements than those of non-progressing eyes at baseline for global average thickness and all sectorial parameters, except for the temporal average.

Average IOP during follow-up was 15.6 ± 3.5 mmHg for all eyes included in the study. However, there was a large variation in the levels of average IOP, as shown in Figure 2 (available online at http://www.aaojournal.org). Table 2 shows the results of the random coefficients model for investigating the relationship between IOP and RNFL loss for the global average thickness parameter. The overall rate of global average RNFL thickness change was −0.63 μm/year [confidence interval (CI): −0.75 to −0.52 μm/year; $P < 0.001$]. However, rates of global average RNFL thickness change were faster in eyes that progressed by SAP versus eyes that did not progress by SAP (−1.02 μm/year versus −0.61 μm/year; $P = 0.002$). Overall, each 1 mmHg higher average IOP during follow-up was associated with an additional average loss of 0.05 μm/year (CI: 0.02 to 0.08 μm/year; $P = 0.002$) of global RNFL thickness. Nevertheless, the association between average IOP and rates of RNFL thickness loss was different for progressing and non-progressing eyes ($P < 0.001$). For progressing eyes, each 1 mmHg higher average IOP during follow-up was associated with an additional average loss of 0.20 μm/year (CI: 0.08 to 0.31 μm/year; $P < 0.001$) of global RNFL thickness; whereas for non-progressing eyes, each 1 mmHg higher average IOP during follow-up was associated with an additional average loss of only 0.04 μm/year (CI: 0.01 to 0.07 μm/year; $P = 0.015$). Figure 3 illustrates the relationship between IOP and slopes of RNFL loss over time for the global average RNFL thickness parameter for progressing and non-progressing eyes.

Similar models were constructed using sectorial RNFL thickness measurements. The results are summarized on Table 3. The largest associations between IOP and rates of RNFL change were seen for measurements from the temporal superior (Figure 4, available online at http://www.aaojournal.org) and temporal inferior sectors, whereas the smallest association was seen for the measurements from the nasal sector (Figure 5, available online at http://www.aaojournal.org). For progressing eyes, each 1 mmHg higher IOP was associated with additional losses of 0.35 and 0.31 μm/year for the temporal superior and temporal inferior sectors, respectively.

DISCUSSION

In the present study, higher levels of IOP during follow-up were associated with progressive RNFL loss as measured by SD OCT. As IOP is a well-established risk factor for the

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development and progression of glaucoma, this finding contributes to support the use of SD OCT as a method for assessing structural damage in glaucoma and as a potential biomarker to monitor the efficacy of IOP-lowering treatments in the disease.[29]

Average IOP during follow-up was associated with RNFL thickness change over time. The association was statistically significant for both progressing as well as non-progressing eyes, but there was a major difference in the magnitude of this association for the two groups, as demonstrated in Figure 3. For progressing eyes, each 1 mmHg higher average IOP during follow-up was associated with 0.20 μm/year faster rate of global RNFL loss versus only 0.04 μm/year for non-progressing eyes. In general, for progressing eyes, higher IOP during follow-up was associated with faster RNFL loss over time. In contrast, some non-progressing eyes had relatively slower rates of RNFL change over time despite high average IOP levels during follow-up. This finding seems to indicate a heterogeneous susceptibility to IOP in leading to structural damage in glaucoma. In fact, one would expect that eyes that show greater susceptibility to IOP would be those prone to have faster rates of RNFL loss over time, which would lead to visual field progression and a positive classification based on the SAP GPA™ algorithm.

The magnitude of the association between IOP and RNFL thickness over time may have important implications for understanding neural losses in glaucoma. For example, an eye that is showing progression with an average IOP of 25 mmHg had an estimated rate of RNFL loss of 2.82 μm/year, or a predicted loss of approximately 14 μm in 5 years. On the other hand, an eye that is showing progression but with an average IOP of 15 mmHg had an estimated rate of RNFL loss of 0.82 μm/year, or a predicted loss of approximately 4 μm in 5 years. Therefore, these two rates of change would translate into a difference of 10 μm of RNFL thickness in 5 years. It is known that global average RNFL thickness values in the Spectralis® range from approximately 98 μm (average value in normal subjects)[30] to 48 μm (residual measurement that persists even in end stage damage), resulting in a dynamic range of approximately 50 μm.[31] Therefore, a difference of 10 μm in RNFL thickness represents about 20% of the range of SD OCT measurements. These findings show that rates of structural loss can be largely different even in progressing eyes and may better reflect IOP-related damage than assessment of progression based only on an event-based method such as the SAP GPA™.

Previous investigations have suggested that structural imaging measurements might be suitable surrogate endpoints in clinical trials investigating new treatments for glaucoma.[29, 32] To qualify as surrogate endpoint, a biomarker needs to be able to predict a clinically relevant endpoint, such as functional loss. In addition, the biomarker should be responsive to the effects of treatment and predict the effect of treatment on the clinically relevant endpoint.[29] Previous studies have shown that rates of RNFL thickness change measured by SD OCT are predictive of future development of visual field loss. In a study performed by Miki et al,[33] glaucoma suspects who developed visual field loss over time had an average rate of change of −2.02 μm/year versus only −0.82 μm/year in those who did not develop visual field damage. Although we did not evaluate the predictive ability of SD OCT in our study, the significant difference found in rates of change between eyes that progressed by visual fields versus those who did not (−1.02 μm/year and −0.61 μm/year, respectively; $P = 0.002$) seems

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to support this finding. More importantly, the main contribution of our investigation is to show that SD OCT RNFL thickness changes over time are associated to levels of average IOP, which suggests that they could be used as potential endpoints in clinical trials evaluating the effect of IOP-lowering medications in slowing down the rate of neural loss in glaucoma. It should be noted, however, that qualification of a biomarker to serve as a surrogate endpoint requires the fulfillment of rigorous conditions and may be conditional to a particular form of treatment.[29, 34] Further studies are necessary to investigate the potential role of SD OCT measurements as surrogate endpoints in glaucoma.

It is interesting to note that several eyes that did not show progression on visual fields had rates of RNFL loss (left column of Figure 3) that were faster than those expected from normal aging (approximately −0.50 μm/year).[35, 36] These eyes were generally those with relatively higher IOP during follow-up. For example, even among eyes that were declared as non-progressing by SAP GPA™, those with average IOP of approximately 25 mmHg had a mean rate of change of −0.97 μm/year during follow-up, which is almost two times faster than the expected age-related loss. This finding suggests that SD OCT might be detecting glaucomatous change in some eyes that were not detected by conventional SAP GPA™ analysis. This is in agreement with a previous study by Liu et al[37] showing that SD OCT detects progression in a large number of the contralateral eyes of glaucoma patients that show unilateral progression by SAP GPA™. However, it should be noted that it is not possible to exclude the possibility that RNFL loss was age-related in some of these eyes. Conversely, it is also interesting that some eyes that showed progression on SAP GPA™ had rates of RNFL loss that were slower than the age-expected rate of RNFL loss. Although some of these may indeed be true progressing eyes, it is noteworthy that their average IOP during follow-up was only 12 mmHg, suggesting that some of them might actually represent false-positive classifications by the SAP GPA™ algorithm.[38]

When sectorial RNFL analyses were conducted, the largest differences in rates of change between progressing and non-progressing eyes were seen for the temporal superior and temporal inferior sectors. In addition, the largest IOP associations were also seen for these sectors. For progressing eyes, each 1 mmHg higher IOP was associated with an additional loss of 0.35 μm/year for the temporal superior sector and 0.31 μm/year for the temporal inferior sector. In contrast, the associations between IOP and rates of RNFL thickness loss were smaller for the temporal and nasal sectors. It is known that these sectors are affected relatively late in glaucomatous damage,[39] which might be related to differential susceptibility to IOP caused by the structure of the lamina cribrosa. Previous studies have shown that the ratio of pore to interpore connective tissue is higher in the superior and inferior sectors,[40, 41] which might predispose the lamina to greater deformation in these sectors as a result of higher IOP. This would lead to greater neural losses in the superior and inferior regions as compared to the temporal and nasal regions of the optic disc. However, it is important to note that our findings may also reflect a better ability of SD OCT in detecting RNFL thickness change in the superior and inferior regions, as a result of the greater dynamic range of RNFL thickness measurements in these areas.

Our study has limitations. We only investigated the association between average IOP and rates of RNFL change. Although average IOP has been consistently established as a risk

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factor for development and progression of glaucoma, other IOP parameters, such as 24-hour peaks and fluctuations have been proposed as potentially related to glaucomatous damage.[42, 43] However, the design of our study did not include 24-hour IOP measurements, which precluded us from being able to evaluate their relationship with RNFL loss. Another potential limitation was the fact that patients were treated at the discretion of the attending ophthalmologist. This may have caused variations in the slopes of RNFL change over time. Ideally, one would assess potential variations in the slopes of RNFL change and their relationship with preceding (historical) IOP levels over a certain period. However, the relatively limited follow-up time and number of images in our study did not allow such investigation. It is also possible that IOP-lowering treatment may have been intensified if visual field changes or RNFL loss were detected before the GPA™ was flagged as *Likely Progression*. This may have resulted in a lower average IOP in some of the progressing eyes during follow-up and an underestimation of the relationship between IOP and rates of RNFL change.

In conclusion, higher IOP was associated with faster rates of progressive RNFL loss over time, as measured by SD OCT. Our findings support the use of RNFL thickness measurements obtained by SD OCT in evaluating the efficacy of IOP-lowering therapies to slow down the rate of disease progression. In addition, they may lead to a better understanding of the relationship between IOP and neural losses in glaucoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

ADAGES	African Descent and Glaucoma Evaluation Study
AGIS	Advanced Glaucoma Intervention Study
CCT	central corneal thickness

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CI	confidence interval
dB	decibels
DIGS	Diagnostic Innovations in Glaucoma Study
EMGT	Early Manifest Glaucoma Trial
GPA™	Guided Progression Analysis™
IOP	intraocular pressure
MD	mean deviation
μm	micrometers
OCT	optical coherence tomography
OHTS	Ocular Hypertension Treatment Study
POAG	primary open-angle glaucoma
PSD	pattern standard deviation
RNFL	retinal nerve fiber layer
SAP	standard automated perimetry
SD	spectral-domain

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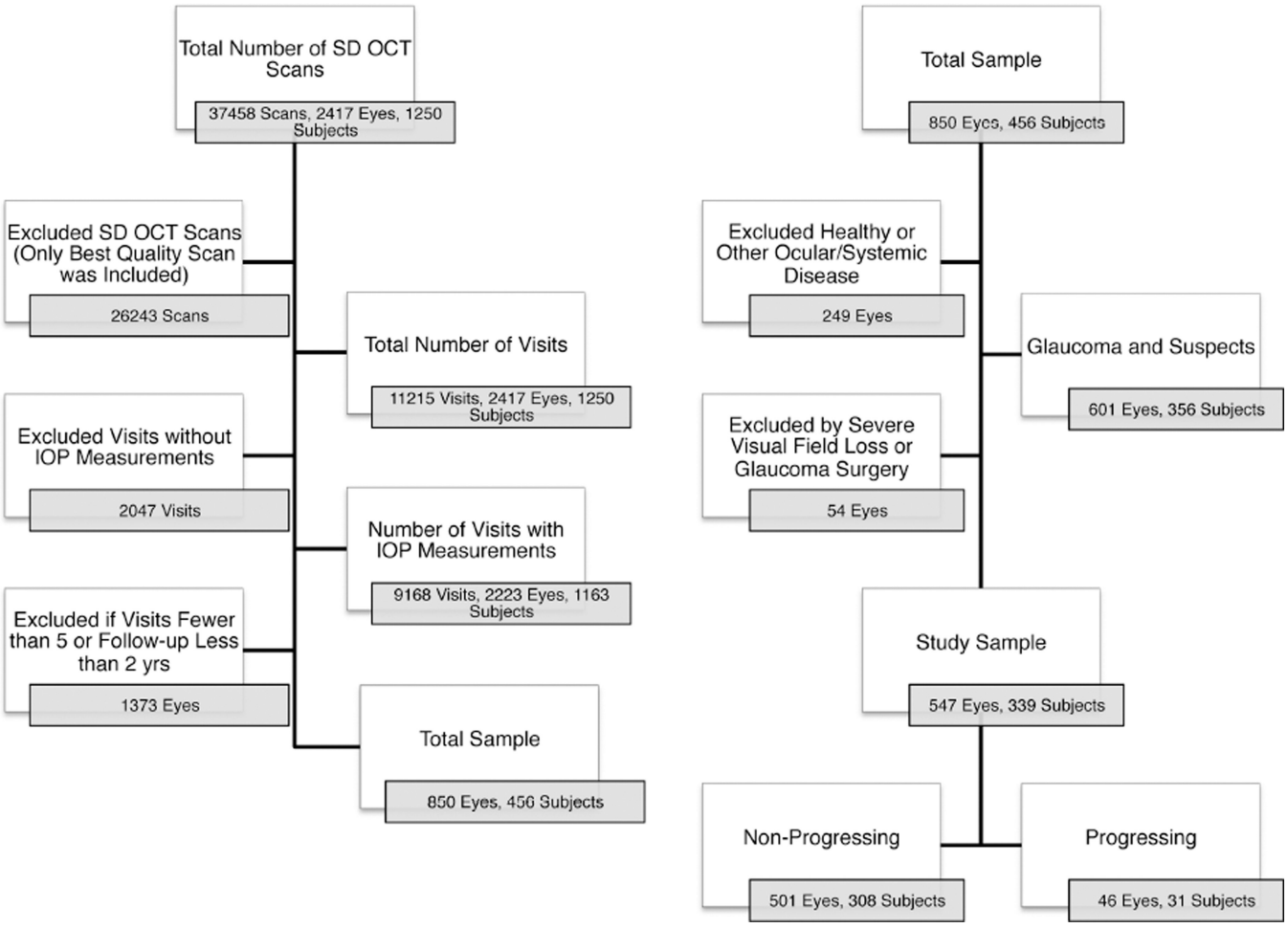

Figure 1.

Flowchart depicting the selection of eyes and subjects for the study. SD OCT = spectral-domain optical coherence tomography; IOP = intraocular pressure.

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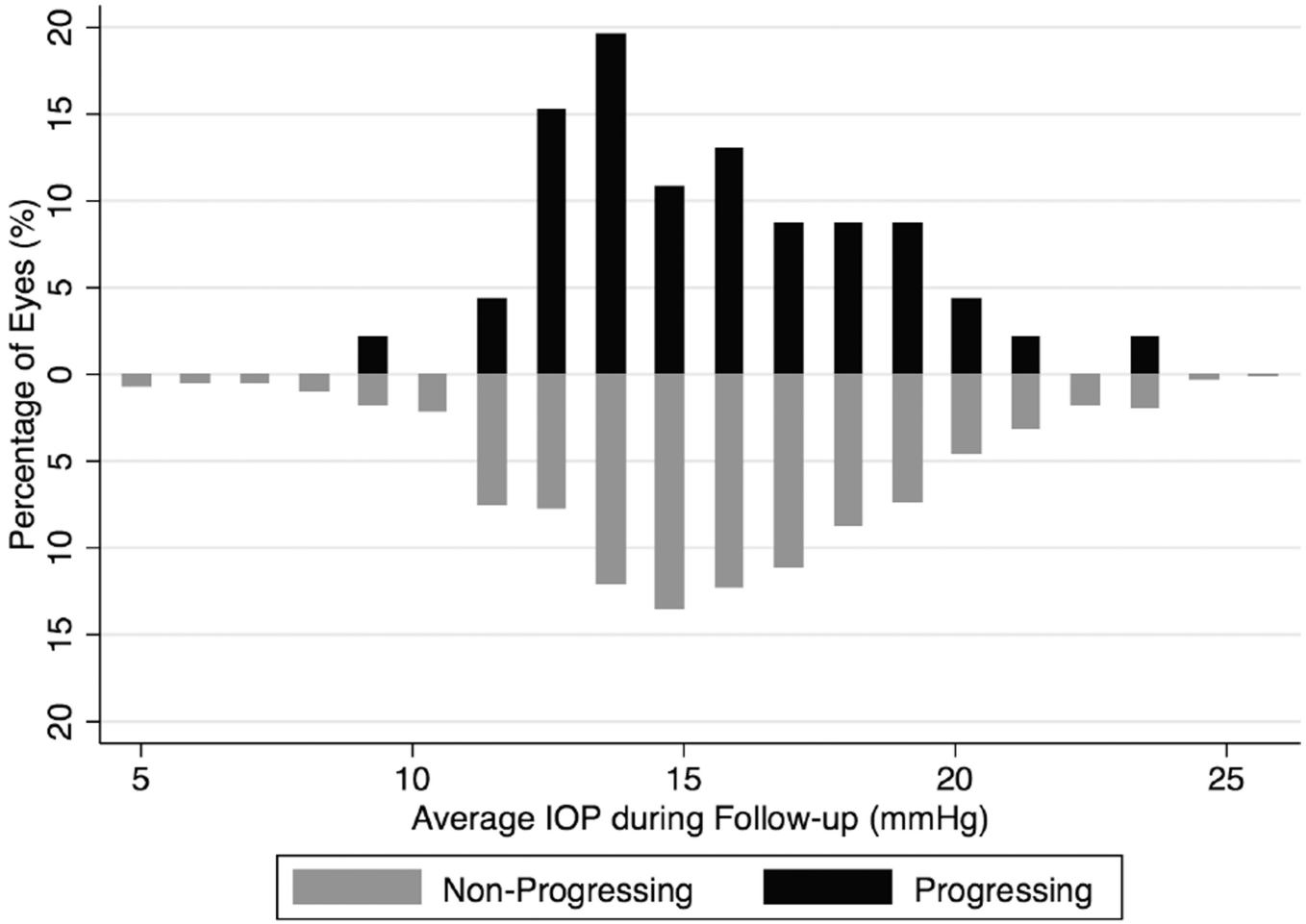

Figure 2.
Distribution of average intraocular pressure (IOP) measurements during follow-up for all 547 eyes included in the study.

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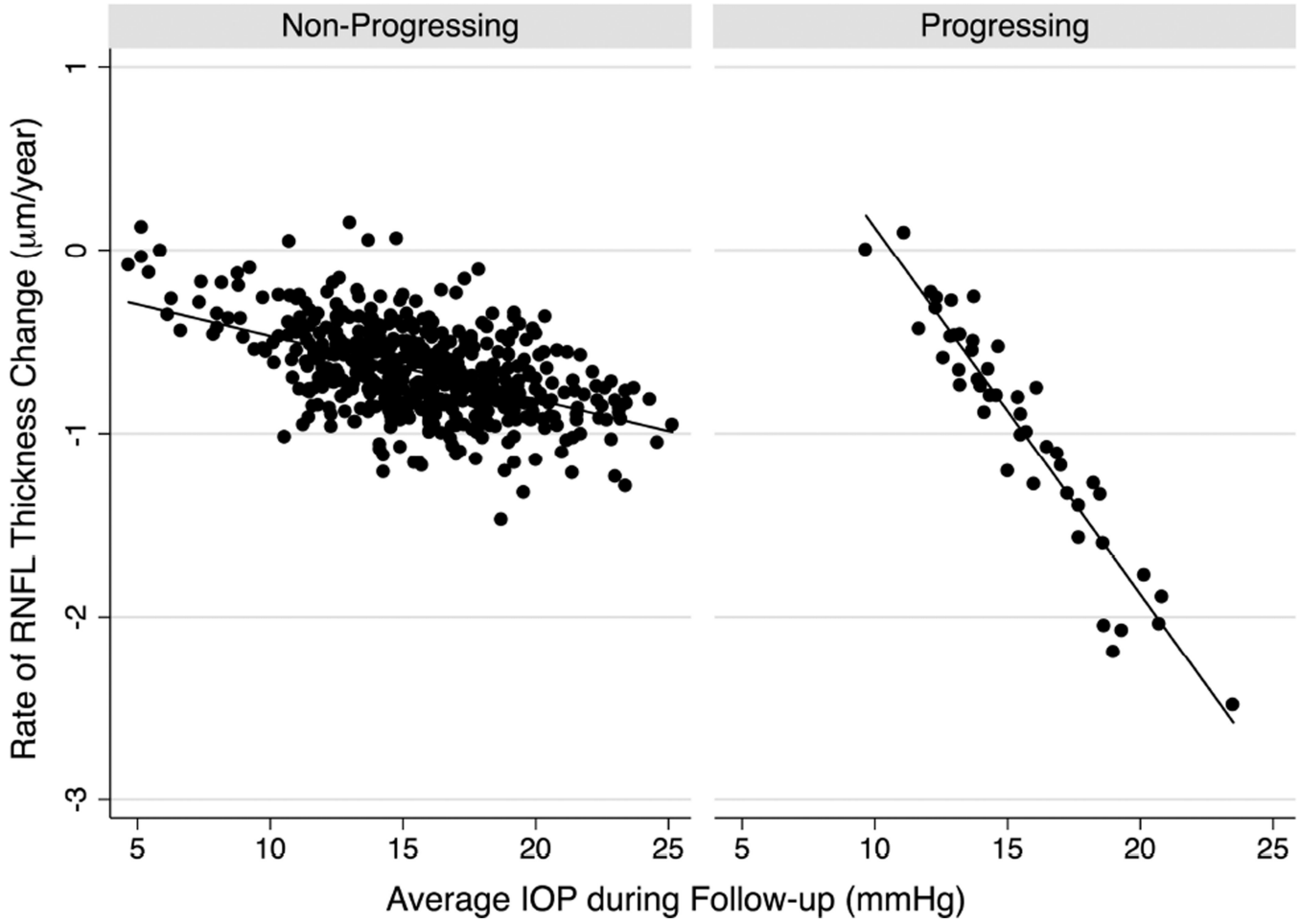

Figure 3.

Scatterplot illustrating the relationship between rates of change in global average retinal nerve fiber layer (RNFL) thickness and average intraocular pressure (IOP) during follow-up. Relationships are shown separately for eyes that progressed (progressing) as well as for eyes that did not progress (non-progressing) by visual fields.

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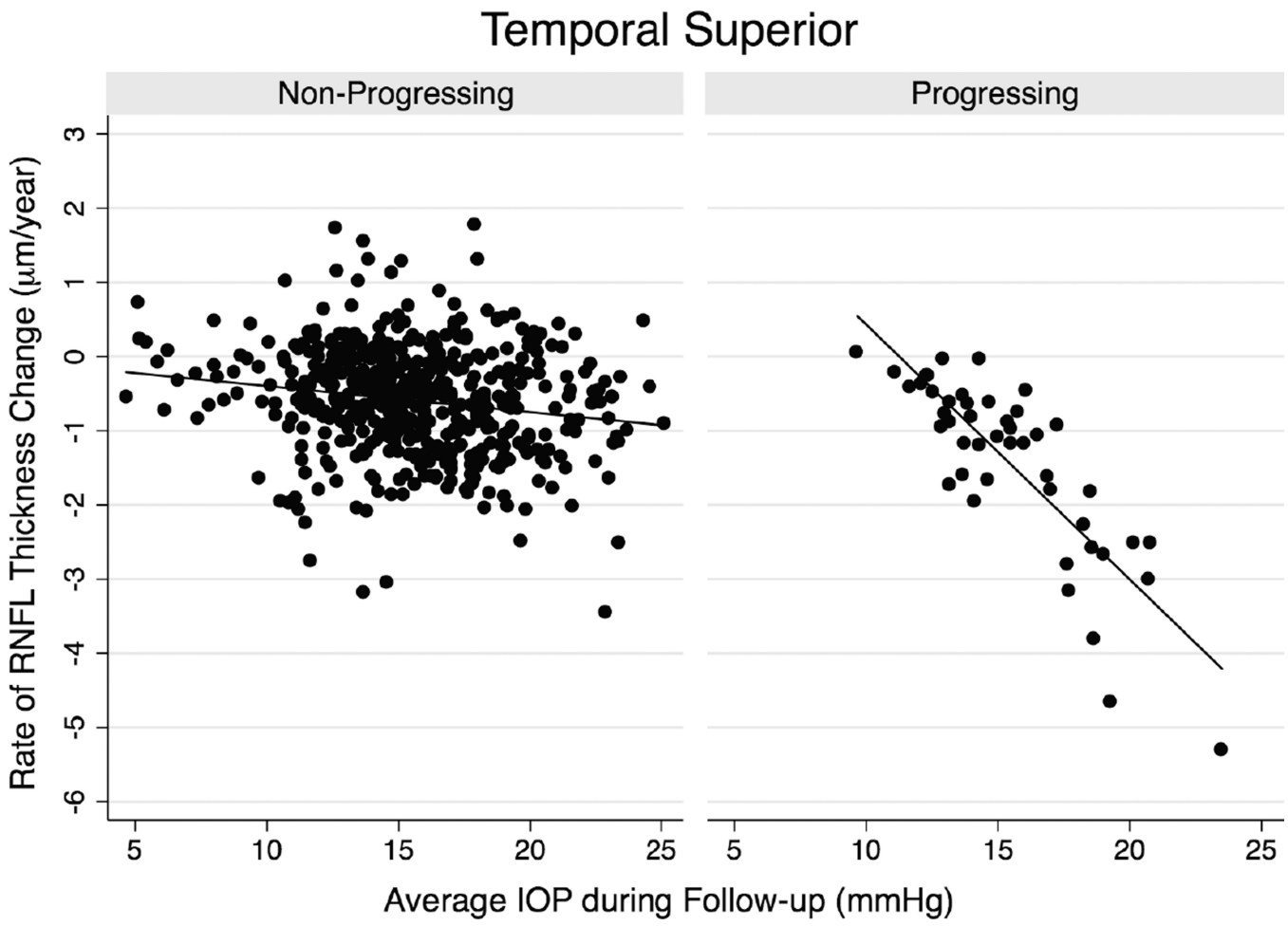

Figure 4.

Scatterplot illustrating the relationship between rates of change in retinal nerve fiber layer (RNFL) thickness for the temporal superior sector and average intraocular pressure (IOP) during follow-up. Relationships are shown separately for eyes that progressed (progressing) as well as for eyes that did not progress (non-progressing) by visual fields.

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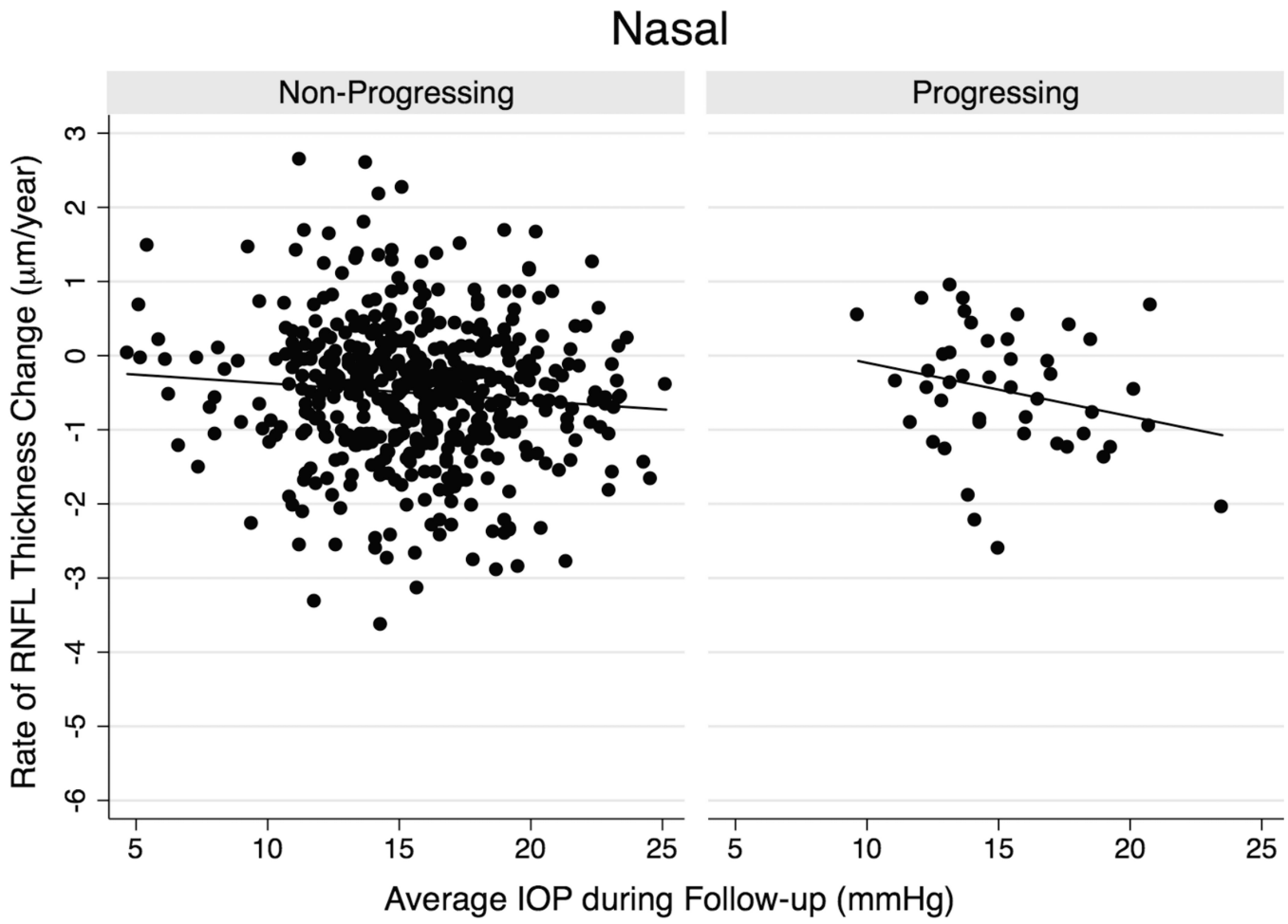

Figure 5.

Scatterplot illustrating the relationship between rates of change in retinal nerve fiber layer (RNFL) thickness for the nasal sector and average intraocular pressure (IOP) during follow-up. Relationships are shown separately for eyes that progressed (progressing) as well as for eyes that did not progress (non-progressing) by visual fields.

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Table 1

Baseline Demographic and Clinical Characteristics of Eyes Included in the Study

Parameter	Non-Progressing (n = 501 Eyes, 308 Patients)	Progressing (n = 46 Eyes, 31 Patients)	*P* Value
Age, years	65.0 ± 10.4	73.1 ± 8.2	<0.001
Gender, n (%) female	168 (54.6)	13 (41.9)	0.191
Race, n (%) African American	122 (39.6)	9 (29.0)	0.503
SAP 24-2 MD, dB	−1.8 ± 3.4	−2.7 ± 3.3	0.070
SAP 24-2 PSD, dB	2.9 ± 2.8	3.6 ± 2.6	0.084
CCT, μm	546.0 ± 40.2	536.9 ± 35.7	0.139
RNFL global thickness, μm	84.3 ± 15.5	74.2 ± 15.4	<0.001
RNFL temporal thickness, μm	64.1 ± 13.5	61.3 ± 16.8	0.183
RNFL temporal superior thickness, μm	110.8 ± 25.7	95.7 ± 25. 0	<0.001
RNFL nasal superior thickness, μm	90.3 ± 24.5	77.8 ± 21.5	<0.001
RNFL nasal thickness, μm	66.0 ± 15.4	58.8 ± 14.0	0.003
RNFL nasal inferior thickness, μm	97.7 ± 28.1	83.6 ± 26.4	0.001
RNFL temporal inferior thickness, μm	115.5 ± 32.7	96.7 ± 30.0	<0.001

SAP = standard automated perimetry; MD = mean deviation; dB = decibels; PSD = pattern standard deviation; CCT = central corneal thickness; μm = micrometers; RNFL = retinal nerve fiber layer.

Values are presented as mean ± standard deviation, unless otherwise noted.

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Table 2

Results of the Random Coefficients Model Investigating the Relationship between Intraocular Pressure and Changes in Retinal Nerve Fiber Layer Global Average Thickness Over Time

Parameter	Coefficient	95% Confidence Interval	*P* Value
Time	−0.61 *	−0.73 to −0.50	<0.001
Average IOP, per 1 mmHg higher	−0.01 §	−0.40 to 0.38	0.958
Average IOP × Time	−0.04 *	−0.07 to −0.01	0.015
Progression, yes	−3.25 §	−6.16 to −0.34	0.029
Progression × Time	−0.41 *	−0.67 to −0.15	0.002
Progression × Average IOP × Time	−0.16 *	−0.24 to −0.07	<0.001
Age at baseline, per decade older	−1.15 §	−2.45 to 0.15	0.082
Age at baseline × Time	0.01 *	−0.08 to 0.10	0.819
Race, African American	3.24 §	0.40 to 6.08	0.026
Race × Time	−0.15 *	−0.34 to 0.04	0.121
Baseline SAP 24-2 MD, per 1 dB lower	−2.24 §	−2.55 to −1.94	<0.001
Baseline SAP 24-2 MD × Time	0.02 *	−0.01 to 0.05	0.144
CCT, per 100 μm thinner	−4.14 §	−7.70 to −0.57	0.023
CCT × Time	−0.15 *	−0.40 to 0.09	0.216
Intercept	82.06 §	80.31 to 83.80	<0.001

* Coefficients refer to longitudinal rates of retinal nerve fiber layer thickness change per year.

§ Coefficients refer to baseline retinal nerve fiber layer thickness.

IOP = intraocular pressure; SAP = standard automated perimetry; MD = mean deviation; dB = decibel; CCT = central corneal thickness; μm = micrometers.

Parameters were centered on the mean for all eyes (average IOP = 16 mmHg; age at baseline = 65 years; baseline SAP 24-2 MD = −2 dB; CCT = 550 μm).

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Table 3

Results of the Random Coefficients Models* Investigating the Relationship between Intraocular Pressure and Changes in Retinal Nerve Fiber Layer Global and Sectorial Average Thicknesses Over Time

Parameter	Average Rate of RNFL Change, μm/year			Association between IOP (per 1 mmHg higher) and Rate of RNFL Change, μm/year		
	Non-Progressing	Progressing	*P* Value	Non-Progressing	Progressing	*P* Value
Global	−0.61	−1.02	0.002	−0.04	−0.20	<0.001
Temporal	−0.72	−1.05	0.090	−0.04	−0.16	0.006
Temporal superior	−0.49	−1.43	0.001	−0.06	−0.35	<0.001
Nasal superior	−0.11	−0.85	0.009	−0.02	−0.23	0.035
Nasal	−0.39	−0.57	0.473	−0.01	−0.09	0.463
Nasal inferior	−0.90	−1.10	0.547	−0.02	−0.25	0.043
Temporal inferior	−1.11	−1.84	0.027	−0.10	−0.31	<0.001

*Multivariable models adjusted for progression as assessed by visual fields, age at baseline, race, baseline SAP 24-2 MD, and CCT.

RNFL: retinal nerve fiber layer; μm = micrometer(s); IOP: intraocular pressure.

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