

# Structure-Function Relationship in Glaucoma Using Spectral-Domain Optical Coherence Tomography

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**Objectives:** To determine the structure-function relationship in glaucoma using spectral-domain optical coherence tomography (SDOCT)-derived structural measurements and to evaluate this relationship using a linear model.

**Methods:** In a cross-sectional study, structure-function relationships were determined for all the participants in the DIGS (Diagnostic Innovations in Glaucoma Study) and the ADAGES (African Descent and Glaucoma Evaluation Study) who had undergone standard automated perimetry (SAP) and SDOCT within 6 months of each other. Strength of relationship was reported as coefficient of determination ( $R^2$ ). The relationship was also evaluated using a previously described linear model.

**Results:** The results of 579 SAP and SDOCT examinations from 80 eyes of 47 control subjects, 199 eyes of 130 patients with suspected glaucoma, and 213 eyes of 146 patients with glaucoma were analyzed. The  $R^2$  for the association between SAP total deviation and SDOCT variables ranged from 0.01 ( $P = .02$ ) for the nasal rim area to 0.30 ( $P < .001$ ) for inferior inner retinal thickness at the macula. The linear model fitted the data well.

**Conclusions:** The strongest structure-function associations using SDOCT were found for retinal nerve fiber layer measurements at arcuate areas and inner retinal thickness at the macula measurements. The linear model is useful in studying the structure-function relationship in glaucoma.

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**E**VALUATION OF THE RELATIONSHIP between anatomical structure (optic nerve and retinal nerve fiber layer [RNFL]) and function (visual sensitivity) in glaucoma can aid in assessing the relative efficacy of structural and functional tests in detecting glaucomatous damage and in their optimal use.<sup>1</sup> Although a significant relationship is expected between structure and function because both provide related information, studies<sup>2-7</sup> using the available measurement methods have shown that this relationship is modest at best. One reason for this imperfect relationship may be the variability associated with measurements obtained using currently available methods.

The introduction of spectral-domain optical coherence tomography (SDOCT) devices has enabled imaging of the anatomical structures at the posterior pole of the eye with better resolution and a much faster scan rate compared with earlier versions of this technology.<sup>8,9</sup> The greater scanning speed enables the acquisition of more

scans in a single imaging session, thereby reducing the need for data interpolation. The RTVue (Optovue, Inc, Fremont, California) is one such SDOCT device; it has a scan rate of 26 000 A-scans per second and an axial resolution of 5  $\mu\text{m}$  compared with its predecessor, the time-domain OCT (TDOCT) (Stratus OCT; Carl Zeiss Meditec, Dublin, California), which has a scan rate of 400 A-scans per second and an axial resolution of 8 to 10  $\mu\text{m}$ . Variability in the macular<sup>10,11</sup> and RNFL thickness measurements<sup>12-16</sup> using SDOCT has been shown to be less than that using TDOCT. Although it is expected that the structure-function relationship using SDOCT would be better than that using the previous methods used to evaluate anatomical structure, a recent study by Leung et al<sup>14</sup> showed that the structure-function relationship using SDOCT was similar to that using TDOCT. However, this study evaluated only the global structural measure (average RNFL thickness measurement) using the global visual field index (mean deviation) without evaluating the sectors sepa-

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rately. Because RNFL thickness varies around the optic disc and glaucoma preferentially affects the poles of the disc, comparing sectors of RNFL with corresponding sectors of visual field is likely to give better information.

Different investigators have used different methods to evaluate the structure-function relationship in glaucoma. Garway-Heath et al<sup>2</sup> found that visual sensitivities expressed in a linear scale defined the structure-function relationship better than did visual sensitivities expressed in a decibel (dB) scale. Bowd et al<sup>3</sup> showed that a linear fit between structure and function with visual sensitivity expressed in a dB scale was comparable with a logarithmic fit in describing the structure-function relationship. Hood and Kardon<sup>1</sup> showed that a simple linear model considering function in terms of visual sensitivity loss (total deviation plot on standard automated perimetry [SAP]) also can well describe the structure-function relationship. An advantage of this model is that it estimates visual loss and structural measurements by differentiating between RNFL thickness and supportive tissue (described in detail in the "Statistical Analysis" subsection of the "Methods" section).

The objective of this study was to determine the sectoral and global structure-function relationship between SDOCT-derived RNFL, optic nerve head (ONH), and macular measurements and visual sensitivity loss on SAP and to evaluate this relationship using the model proposed by Hood and Kardon.<sup>1</sup>

## METHODS

This was an observational study of participants included in the DIGS (Diagnostic Innovations in Glaucoma Study) and in the ADAGES (African Descent and Glaucoma Evaluation Study), which are prospective longitudinal studies designed to evaluate optic nerve structure and visual function in glaucoma conducted at the Hamilton Glaucoma Center, University of California at San Diego, La Jolla. Participants in both studies include control subjects, patients with glaucoma, and patients with suspected glaucoma, who are longitudinally evaluated clinically and using several functional and imaging tests. Informed consent was obtained from all the participants, and the University of California at San Diego human subjects committee approved all the methods. All the methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

The inclusion criteria were a best-corrected visual acuity of 20/40 or better, spherical refraction within  $\pm 5.0$  diopters (D) and cylinder correction within  $\pm 3.0$  D, and open angles on gonioscopy. Eyes with coexisting retinal disease, uveitis, or non-glaucomatous optic neuropathy were excluded. All the participants underwent a comprehensive ophthalmic examination, including review of medical history, visual acuity testing, slit-lamp biomicroscopy, intraocular pressure measurement using Goldmann applanation tonometry, gonioscopy, dilated fundoscopic examination with a 78-D lens, stereoscopic optic disc photography, and SAP using the 24-2 Swedish interactive threshold algorithm (Carl Zeiss Meditec).

We included 3 groups of participants: control subjects, patients with suspected glaucoma, and patients with glaucoma. Inclusion was based on eyes, and when both eyes of a participant satisfied the inclusion criteria, both were included. When an eye underwent more than 1 examination during follow-up, each examination was included separately. Appropriate statis-

tical methods were used to deal with the correlation of measurements from multiple examinations of the same eye and of both eyes of the same individual (see the "Statistical Analysis" subsection). Eyes were classified as glaucomatous if they had repeatable ( $\geq 2$  consecutive) abnormal SAP test results on the 24-2 program of the Humphrey visual field analyzer (Carl Zeiss Meditec). An abnormal SAP result was defined as having a pattern standard deviation outside the 95% confidence limits or a glaucoma hemifield test result outside the reference range, regardless of the appearance of the optic disc. Glaucoma suspects were defined as eyes with abnormal-appearing optic discs (presence of neuroretinal rim thinning or localized or diffuse RNFL defects indicative of glaucoma, ie, glaucomatous optic neuropathy) by masked stereophotograph assessment without repeatable abnormal SAP results. Glaucoma suspects also included eyes with intraocular pressure greater than 22 mm Hg but with healthy-appearing optic discs and without repeatable abnormal SAP results. Control subjects were recruited from the general population through advertisements and from the staff and employees of the University of California at San Diego. Control eyes had intraocular pressure of 21 mm Hg or less with no history of increased intraocular pressure and a normal SAP result. A normal SAP result was defined as a mean deviation and pattern standard deviation within the 95% confidence limits and a glaucoma hemifield test result within the reference range.

## INSTRUMENTATION

### RTVue

The SDOCT examination was performed using RTVue (software version 4.0.5.39). The principles and protocol used have been explained elsewhere.<sup>17</sup> The protocols used for imaging with RTVue in this study were ONH and ganglion cell complex (GCC). All the patients had both protocols performed on the same day.

### ONH Measurements

The ONH protocol was used to obtain ONH measurements. It consists of 12 radial scans 3.4 mm long (452 A-scans each) and 6 concentric ring scans ranging from 2.5 to 4.0 mm in diameter (587-775 A-scans each) all centered on the optic disc. The ONH variables considered in this study for the structure-function relationship analysis were the temporal ( $316^{\circ}$ - $45^{\circ}$ ), superior ( $46^{\circ}$ - $135^{\circ}$ ), nasal ( $136^{\circ}$ - $225^{\circ}$ ), inferior ( $226^{\circ}$ - $315^{\circ}$ ), and total neuroretinal rim areas.

### Peripapillary RNFL Measurements

The ONH protocol also generates a polar RNFL thickness map, which is the RNFL thickness measured along a circle 3.45 mm in diameter centered on the optic disc. It gives the average RNFL thickness in the temporal ( $316^{\circ}$ - $45^{\circ}$ ), superior ( $46^{\circ}$ - $135^{\circ}$ ), nasal ( $136^{\circ}$ - $225^{\circ}$ ), and inferior ( $226^{\circ}$ - $315^{\circ}$ ) quadrants and the overall average along the entire measurement circle. In addition, each quadrant is divided into 4 sectors, and the software provides the RNFL thicknesses in each of these 16 sectors. For this study, we divided the superior and inferior quadrants into superotemporal ( $46^{\circ}$ - $90^{\circ}$ ), superonasal ( $91^{\circ}$ - $135^{\circ}$ ), inferotemporal ( $271^{\circ}$ - $315^{\circ}$ ), and inferonasal ( $226^{\circ}$ - $270^{\circ}$ ) quadrants.

### Macular Measurements

The GCC protocol consists of 1 horizontal line scan 7 mm long (467 A-scans) followed by 15 vertical line scans 7 mm long (each

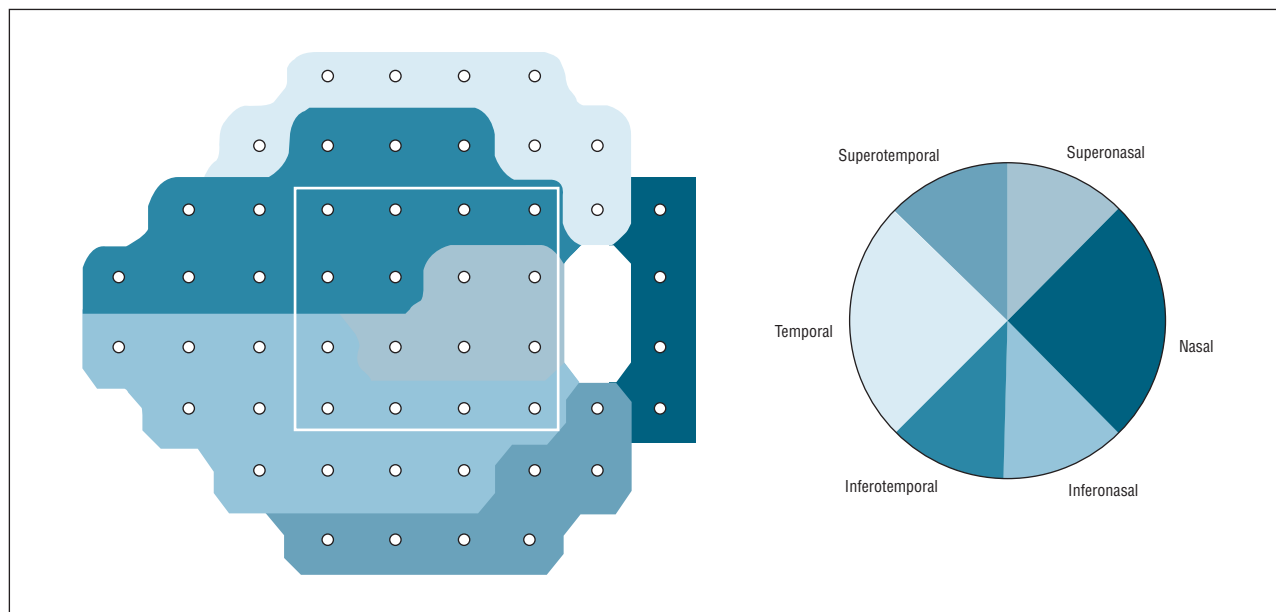


**Figure 1.** The relationship between visual field sectors and optic disc regions/retinal nerve fiber layer quadrants based on the map by Garway-Heath et al.<sup>2</sup> The square centered on the fovea shows the area used to assess the relationship between central visual field sectors and macular regions.

400 A-scans) and at 0.5-mm intervals centered 1 mm temporal to the fovea. The GCC protocol is designed to measure inner retinal thickness, which includes the nerve fiber layer, ganglion cell layer, and inner plexiform layer, collectively called the GCC. The variables generated by the GCC analysis and considered for analysis in this study were average inner retinal thickness, superior inner retinal thickness (0°-180°), and inferior inner retinal thickness (181°-360°).

In addition to the inner retinal thickness variables, the GCC protocol also measures full retinal thickness at the macula. The full retinal thickness variables obtained by the GCC protocol were full retina thickness average and superior and inferior retinal thickness average.

### Standard Automated Perimetry

Visual field data were divided into sectors based on the map proposed by Garway-Heath et al<sup>2</sup> (**Figure 1**). This map relates sectors of ONH with their corresponding visual field sectors. For example, the inferotemporal optic disc sector relates to the superonasal visual field sector, and the superotemporal optic disc sector relates to the inferonasal visual field sector. The same relationship as with ONH sectors was used for RNFL sectors. The square in the center of the visual field in Figure 1 shows the area that relates to the macular region. The SAP-measured visual sensitivity loss was calculated by first converting the dB scale values at each test location on the total deviation numerical plot to a linear scale (reciprocal of the Lambert scale) using the following formula:

$$1/\text{Lambert} = (10)^{0.1 \times \text{dB}}$$

Then, values from all test points in the visual field sectors corresponding to the anatomical sectors described previously herein with each scanning protocol were averaged. The average visual sensitivity loss per sector was used as such in the linear scale and also was converted back to the dB scale for the analysis.

Only good-quality RTVue images, as defined by a signal strength index of 30 or greater, were used for analysis. Only images and visual field testing pairs acquired within 6 months of each other were included in the analysis.

### STATISTICAL ANALYSIS

Descriptive statistics included mean (SD) values for normally distributed variables and median, first quartile, and third quartile values for nonnormally distributed variables. Analysis of variance or Kruskal-Wallis tests were used to evaluate visual field variable and clinical differences among controls, patients with suspected glaucoma, and patients with glaucoma. Because measurements from both eyes of a participant and from different examinations of a participant are correlated, a nested model was used for comparisons among the groups. Eye and visit were nested within the participant, and participant as a variable was nested within the group.

Structure-function associations were investigated by using linear ( $y = ax + b$ ) regression between rim area, RNFL and macular thickness, and visual sensitivity loss expressed in the linear and dB scales. The results are reported as  $R^2$ . Locally weighted scatterplot smoothing (LOWESS) curves were also used to fit the relationship graphically; LOWESS is a modeling method that combines the linear least squares regression with the non-linear regression.<sup>18</sup> It does this by fitting simple models to localized subsets of the data to build a function that describes the deterministic part of the variation in the data, point by point. The LOWESS curve has the advantage in describing the structure-function relationship because it does not need the specification of a function (linear, quadratic, etc) to fit a model to all the data in a given sample.

Details of the model proposed by Hood and Kardon<sup>1</sup> are explained elsewhere. This model makes some basic assumptions to evaluate the structure-function relationship. It proposes that RNFL thickness,  $R$ , measured using OCT is composed of 2 components: thickness due to retinal ganglion cell axons, called signal or  $s_0$ , and residual thickness due to glial cells and blood vessels, called base level or  $b$ , so that the measured RNFL thickness is given by the following equation:  $R = s_0 + b$ .

It also proposes that visual sensitivity decreases as signal ( $s_0$ ) decreases but residual  $b$  does not change. So, the previous equation is written as follows:  $R = s_0 \times 10^{0.1 \times D} + b$ , where  $D$  is the loss of visual sensitivity on the dB scale, represented on the total deviation numeric map. Base level, or  $b$ , is taken as the RNFL

**Table 1. Structural and Functional Characteristics of the Participants<sup>a</sup>**

| Characteristic                                                 | Control Group<br>(84 Examinations<br>From 80 Eyes<br>of 47 Participants) <sup>b</sup> | Glaucoma Suspect Group<br>(235 Examinations<br>From 199 Eyes<br>of 130 Participants) <sup>b</sup> | Glaucoma Group<br>(260 Examinations From<br>213 Eyes of 146<br>Participants) <sup>b</sup> |
|----------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Age, median (quartile), y                                      | 63 (54.5, 67)                                                                         | 66 (55, 72)                                                                                       | 72 (62, 77)                                                                               |
| African American race, No. (%)                                 | 5 (11)                                                                                | 22 (17)                                                                                           | 43 (29)                                                                                   |
| Visual field variables, median (quartile)                      |                                                                                       |                                                                                                   |                                                                                           |
| Mean deviation, dB                                             | 0.15 (−0.55, 0.76)                                                                    | −0.17 (−1.04, 0.53)                                                                               | −2.76 (−5.61, −1.43)                                                                      |
| Pattern standard deviation, dB                                 | 1.49 (1.34, 1.67)                                                                     | 1.55 (1.35, 1.74)                                                                                 | 3.07 (2.15, 6.67)                                                                         |
| Visual field index, %                                          | 100 (99 to 100)                                                                       | 99 (99 to 100)                                                                                    | 95 (87 to 98)                                                                             |
| Optic nerve head variables, median (quartile), mm <sup>2</sup> |                                                                                       |                                                                                                   |                                                                                           |
| Total rim area                                                 | 1.20 (1.03, 1.52)                                                                     | 0.93 (0.73, 1.23)                                                                                 | 0.76 (0.48, 1.16)                                                                         |
| Temporal rim area                                              | 0.17 (0.10, 0.27)                                                                     | 0.09 (0.04, 0.17)                                                                                 | 0.07 (0.02, 0.17)                                                                         |
| Superior rim area                                              | 0.34 (0.28, 0.41)                                                                     | 0.29 (0.22, 0.37)                                                                                 | 0.23 (0.14, 0.35)                                                                         |
| Nasal rim area                                                 | 0.35 (0.30, 0.41)                                                                     | 0.31 (0.22, 0.38)                                                                                 | 0.27 (0.15, 0.38)                                                                         |
| Inferior rim area                                              | 0.35 (0.30, 0.43)                                                                     | 0.24 (0.17, 0.34)                                                                                 | 0.17 (0.09, 0.30)                                                                         |
| RNFL variables, median (quartile), μm                          |                                                                                       |                                                                                                   |                                                                                           |
| Temporal                                                       | 78.47 (66.22, 86.55)                                                                  | 70.00 (64.02, 78.37)                                                                              | 64.45 (56.03, 73.65)                                                                      |
| Superotemporal                                                 | 132.63 (119.53, 146.46)                                                               | 121.12 (106.54, 134.34)                                                                           | 100.96 (88.34, 117.56)                                                                    |
| Superonasal                                                    | 114.58 (100.11, 128.97)                                                               | 107.02 (94.26, 120.02)                                                                            | 92.07 (82.97, 108.67)                                                                     |
| Nasal                                                          | 77.78 (68.62, 87.56)                                                                  | 71.95 (66.21, 81.00)                                                                              | 64.44 (58.21, 75.69)                                                                      |
| Inferonasal                                                    | 125.01 (111.83, 137.06)                                                               | 113.63 (101.87, 127.84)                                                                           | 99.66 (89.23, 116.43)                                                                     |
| Inferotemporal                                                 | 137.79 (126.98, 155.21)                                                               | 130.09 (117.27, 143.58)                                                                           | 100.62 (85.74, 124.68)                                                                    |
| Average                                                        | 102.75 (95.12, 111.02)                                                                | 96.09 (88.10, 102.65)                                                                             | 81.45 (74.40, 93.56)                                                                      |
| Inner retina variables, median (quartile), μm                  |                                                                                       |                                                                                                   |                                                                                           |
| Average                                                        | 94.84 (89.00, 99.87)                                                                  | 89.82 (84.34, 94.49)                                                                              | 82.74 (75.52, 89.85)                                                                      |
| Superior                                                       | 95.28 (87.88, 100.82)                                                                 | 89.66 (83.44, 95.24)                                                                              | 83.93 (77.34, 91.67)                                                                      |
| Inferior                                                       | 94.69 (89.99, 100.13)                                                                 | 90.01 (84.06, 94.41)                                                                              | 81.23 (72.81, 89.67)                                                                      |
| Full retina thickness, median (quartile), μm                   |                                                                                       |                                                                                                   |                                                                                           |
| Average                                                        | 267.84 (252.86, 279.21)                                                               | 259.55 (251.75, 268.45)                                                                           | 252.95 (242.34, 263.84)                                                                   |
| Superior                                                       | 268.67 (252.96, 282.13)                                                               | 261.02 (251.94, 270.07)                                                                           | 255.94 (245.18, 266.96)                                                                   |
| Inferior                                                       | 266.37 (252.20, 276.16)                                                               | 257.11 (250.79, 267.42)                                                                           | 250.51 (239.10, 261.64)                                                                   |

Abbreviation: RNFL, retinal nerve fiber layer.

<sup>a</sup>  $P \leq .001$  for all.<sup>b</sup> Numbers in parentheses indicate the first and third quartile values.

thickness corresponding to a decrease in visual sensitivity of more than 10 dB (compared with age-matched controls) on the total deviation numeric plot.

Converting visual sensitivity loss to the linear scale, the previous equation can be represented as follows:  $R = s_0 \times T + b$ , where  $T$  is the visual sensitivity loss in a linear scale.

Statistical analyses were performed using a commercially available software program (STATA, version 10.0; StataCorp LP, College Station, Texas).  $P \leq .05$  was considered statically significant.

## RESULTS

Structural and functional measurements in the healthy, suspect, and glaucoma cohorts are given in **Table 1**. Age and visual field variables were significantly different between the glaucoma and control groups and between the glaucoma and suspect groups but were not significantly different between the control and suspect groups. Temporal and nasal ONH rim areas were significantly different between the control and suspect groups and between the control and glaucoma groups but were not significantly different between the suspect and glaucoma groups. All the other structural variables were significantly different among the control, suspect, and glaucoma groups.

**Table 2** lists the structure-function associations between ONH rim area (expressed in the linear scale) and

visual sensitivity loss (expressed in the dB and linear scales) in the corresponding visual field sectors. **Table 3** gives the structure-function associations between RNFL thickness (expressed in the linear scale) and visual sensitivity loss (expressed in the dB and linear scales) in the corresponding visual field sectors. **Table 4** provides the structure-function associations between inner retinal thickness at the macula and full macular thickness (expressed in the linear scale) and visual sensitivity loss (expressed in the dB and linear scales) in the corresponding visual field sectors. The strongest associations were found between RNFL thickness at the arcuate regions and visual field total deviation in their corresponding sectors and between inner retinal thickness at the macula and visual field total deviation in the corresponding sector. Associations between visual field total deviation and ONH measurements were weakest. Because  $R^2$  measures the strength of linear relationships, it is not an appropriate measure for evaluation of the strength of non-linear relationships, such as that observed when SAP sensitivity is expressed in a dB scale. Also,  $R^2$  values should not be used to directly compare the linear and log-linear models.

The strength of the association varied by diagnostic group. The association between structure and function in control subjects in this study was not statistically sig-

**Table 2. Structure-Function Associations With Optic Nerve Head Rim Area**

| Sector            | Loss of Visual Sensitivity |                |                       |                |
|-------------------|----------------------------|----------------|-----------------------|----------------|
|                   | Linear Scale               |                | Decibel Scale         |                |
|                   | <i>R</i> <sup>2</sup>      | <i>P</i> Value | <i>R</i> <sup>2</sup> | <i>P</i> Value |
| Temporal rim area | 0.02                       | .006           | 0.02                  | <.001          |
| Superior rim area | 0.06                       | <.001          | 0.07                  | <.001          |
| Nasal rim area    | 0.01                       | .02            | 0.02                  | .02            |
| Inferior rim area | 0.08                       | <.001          | 0.08                  | <.001          |
| Total rim area    | 0.05                       | .001           | 0.07                  | <.001          |

**Table 3. Structure-Function Associations With RNFL Thickness Measurements**

| Sector         | Loss of Visual Sensitivity |                |                       |                |
|----------------|----------------------------|----------------|-----------------------|----------------|
|                | Linear Scale               |                | Decibel Scale         |                |
|                | <i>R</i> <sup>2</sup>      | <i>P</i> Value | <i>R</i> <sup>2</sup> | <i>P</i> Value |
| Temporal       | 0.10                       | <.001          | 0.12                  | <.001          |
| Superotemporal | 0.22                       | <.001          | 0.19                  | <.001          |
| Superonasal    | 0.09                       | <.001          | 0.09                  | <.001          |
| Nasal          | 0.06                       | <.001          | 0.08                  | <.001          |
| Inferonasal    | 0.08                       | <.001          | 0.08                  | <.001          |
| Inferotemporal | 0.26                       | <.001          | 0.22                  | <.001          |
| Average RNFL   | 0.17                       | <.001          | 0.19                  | <.001          |

Abbreviation: RNFL, retinal nerve fiber layer.

**Table 4. Structure-Function Associations With Inner Retinal and Full Macular Thickness Measurements**

| Sector        | Loss of Visual Sensitivity |                |                       |                |
|---------------|----------------------------|----------------|-----------------------|----------------|
|               | Linear Scale               |                | Decibel Scale         |                |
|               | <i>R</i> <sup>2</sup>      | <i>P</i> Value | <i>R</i> <sup>2</sup> | <i>P</i> Value |
| Inner retinal |                            |                |                       |                |
| Superior      | 0.19                       | <.001          | 0.22                  | <.001          |
| Inferior      | 0.30                       | <.001          | 0.27                  | <.001          |
| Average       | 0.25                       | <.001          | 0.28                  | <.001          |
| Full macula   |                            |                |                       |                |
| Superior      | 0.09                       | <.001          | 0.10                  | <.001          |
| Inferior      | 0.14                       | <.001          | 0.13                  | <.001          |
| Average       | 0.12                       | <.001          | 0.13                  | <.001          |

nificant for any structural variable, with *R*<sup>2</sup> values between 0.00 (for all ONH and most macular inner retinal thickness measurements) and 0.02 (for the average RNFL thickness measurement). The *R*<sup>2</sup> in glaucoma suspects ranged from 0.00 for the nasal rim area (*P* = .99) to 0.03 for macular full-thickness superior average (*P* = .04) on the dB scale and from 0.00 for the nasal rim area (*P* = .91) to 0.03 for macular full-thickness superior average (*P* = .03) on the linear scale. The *R*<sup>2</sup> in patients with glaucoma ranged from 0.01 for the nasal rim area (*P* = .29) to 0.29 for macular inner retinal average (*P* < .001) on the dB scale and from 0.00 for the nasal rim area (*P* = .49) to 0.32 for macular inner retinal inferior average (*P* < .001) on the linear scale.

**Figures 2, 3, 4, and 5** show the model proposed by Hood and Kardon<sup>1</sup> fit to the inferotemporal and supero-

temporal RNFL sectors in the present data. The base level, *b*, was calculated as the RNFL thickness corresponding to a mean loss of sensitivity of 10 dB or less in the inferotemporal (19 eyes) and superotemporal (19 eyes) RNFL sectors. The mean base level value was 83.26 μm for the inferotemporal RNFL sector, and 80.74 μm for the superotemporal RNFL sector. The 3 theoretical curves (dashed lines) in the figures, representing the mean and 95% prediction interval, were plotted according to the method proposed by Hood and Kardon.<sup>1</sup> The base level in the inferotemporal quadrant was 60% of the mean inferotemporal RNFL thickness in control subjects (137.79 μm), and the base level in the superotemporal quadrant was 61% of the mean superotemporal RNFL thickness in controls (132.63 μm). The central dashed lines in the figures were derived by joining the mean RNFL

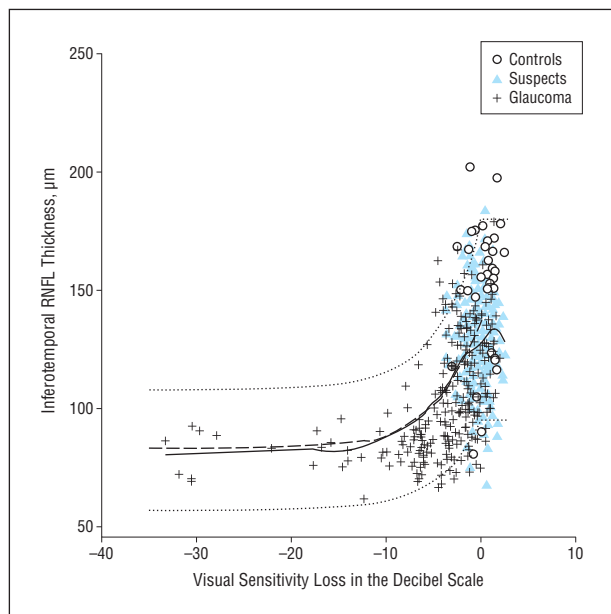


**Figure 2.** Linear model showing the relationship between inferotemporal retinal nerve fiber layer (RNFL) thickness and superonasal sector visual sensitivity loss in decibel scale. Solid black line indicates the locally weighted scatterplot smoothing curve fitting the data; dashed line and the 2 short dashed lines above and below the dashed line indicate the 50th, 95th, and 5th percentiles, respectively, of the model.

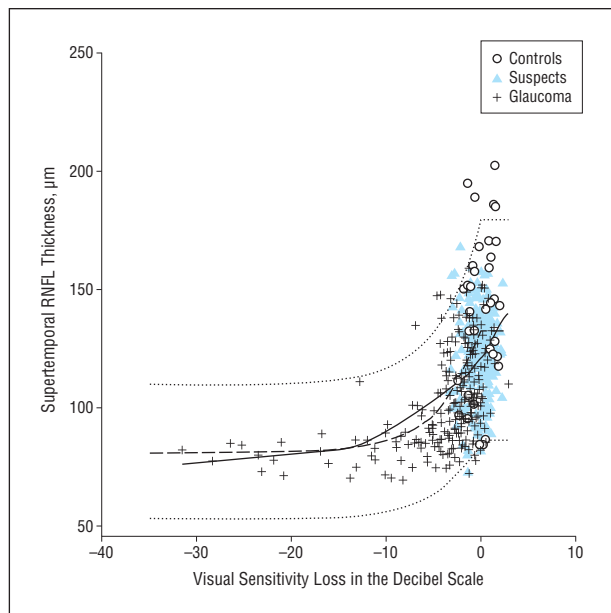


**Figure 3.** Linear model showing the relationship between superotemporal retinal nerve fiber layer (RNFL) thickness and inferonasal sector visual sensitivity loss in decibel scale. Solid black line indicates the locally weighted scatterplot smoothing curve fitting the data; dashed line and the 2 short dashed lines above and below the dashed line indicate the 50th, 95th, and 5th percentiles, respectively, of the model.

thicknesses in the inferotemporal and superotemporal sectors of controls with 60% and 61% of this thickness, respectively. The short dashed lines above and below the dashed line were derived by connecting the value 2 SD above and below the mean RNFL thickness in the inferotemporal and superotemporal sectors of controls with 60% and 61% of these values (2 SD above and below the

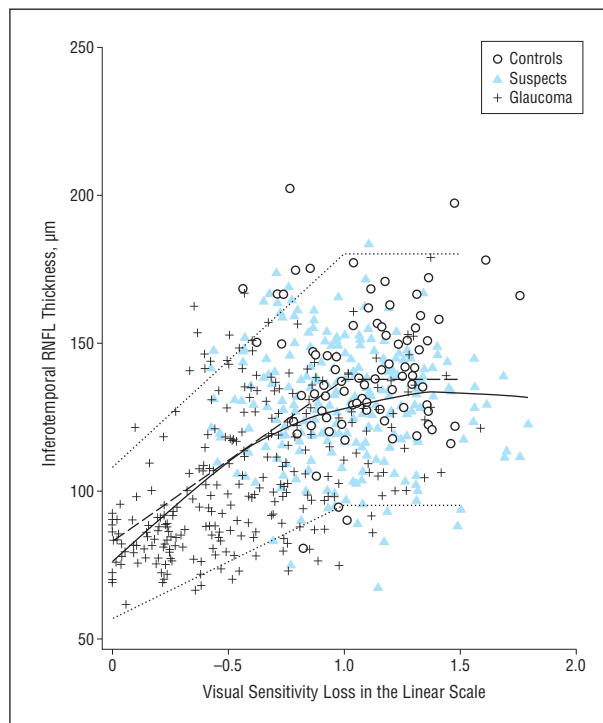


**Figure 4.** Linear model showing the relationship between inferotemporal retinal nerve fiber layer (RNFL) thickness and superonasal sector visual sensitivity loss in linear scale. Solid black line indicates the locally weighted scatterplot smoothing curve fitting the data; dashed line and the 2 short dashed lines above and below the dashed line indicate the 50th, 95th, and 5th percentiles, respectively, of the model.

mean), respectively. Figures 2 and 3 show the model with the visual sensitivity loss in the dB scale, and Figures 4 and 5 show the visual sensitivity loss in the linear scale. To check the goodness of fit, we calculated the number of points falling outside the short dashed lines. For the inferotemporal RNFL sector–superonasal visual field association (dB scale), 24 glaucoma, 13 suspect, and 5 control eyes (total of 7.3%) fell outside the short dashed lines. For the superotemporal RNFL sector–inferonasal visual field association (dB scale), 10 glaucoma, 3 suspect, and 5 control eyes (total of 3.1%) fell outside.

## COMMENT

We evaluated the structure-function relationship in glaucoma using the SDOCT-derived ONH, RNFL, and macular thickness variables and found that the strongest associations were for the RNFL measurements at the arcuate areas and for the inner retinal thickness measurements at the macula. To our knowledge, this is the first study to evaluate the structure-function relationship to the RNFL, macula, and ONH measurements of SDOCT.

The RNFL sectors with the strongest association with visual sensitivity loss in this study were the inferotemporal, superotemporal, and average measurements. This is similar to the results reported by Horn et al,<sup>19</sup> who evaluated the structure-function relationship using SDOCT-derived RNFL thickness measurements. This is also similar to the results reported by previous studies using TDOCT.<sup>3-6</sup> The reported  $R^2$  in different studies have

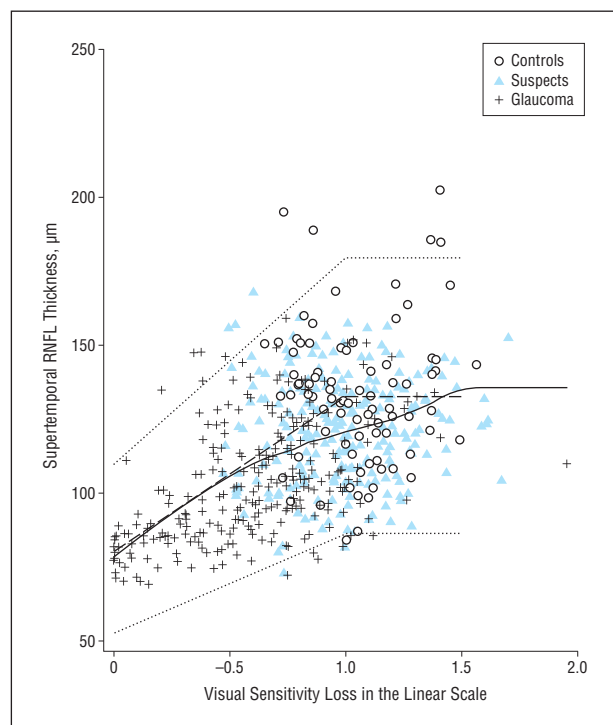


**Figure 5.** Linear model showing the relationship between superotemporal retinal nerve fiber layer (RNFL) thickness and inferonasal sector visual sensitivity loss in linear scale. Solid black line indicates the locally weighted scatterplot smoothing curve fitting the data; dashed line and the 2 short dashed lines above and below the dashed line indicate the 50th, 95th, and 5th percentiles, respectively, of the model.

been variable, ranging from 0.33 in the study by Bowd et al<sup>3</sup> to 0.56 in the study by Miglior et al.<sup>5</sup> Differences in the  $R^2$  between studies are likely to occur because of differences in the populations and severity of glaucoma of included patients. It has been shown that the strength of association between structure and function is weak in controls and suspected and early glaucoma because the range of visual sensitivity loss is too narrow in these populations.<sup>20</sup> The glaucoma cohort in the present study had milder visual field loss (median mean deviation of  $-2.52$  dB) compared with the study by Miglior et al<sup>5</sup> (median mean deviation of  $-7.8$  dB).

The structure-function associations for the inner retinal thickness variables were similar to those found with the inferotemporal and superotemporal RNFL sectors. This finding could be related to the improvement in software analysis of SDOCT compared with TDOCT macular thickness data, which now concentrates on the inner retinal layers instead of on all the retinal layers at the macula. Such improvement has been made possible by the higher resolution of SDOCT compared with TDOCT, enabling better identification of the different retinal layers.

The association between ONH sectors and visual field loss was weak. To our knowledge, there are no studies of the structure-function relationship using SDOCT-derived ONH variables. Previous studies<sup>2,3,7</sup> have used Heidelberg retina tomography-derived ONH sectors to determine this relationship. Garway-Heath et al<sup>2</sup> reported an  $R^2$  of 0.38 between the temporal neuroretinal rim area and central visual field mean visual sensitivity in the dB scale on quadratic regression and an  $R^2$  of 0.30 on linear

regression using the reciprocal of the Lambert scale. Bowd et al<sup>3</sup> reported an  $R^2$  of 0.16 between the inferotemporal ONH rim area and superonasal visual field sector sensitivity on linear regression. One possible reason for a weak structure-function association may be greater variability in the rim area measurement compared with the RNFL measurement as measured by SDOCT.<sup>21,22</sup> In addition, this may also be because of the weaker performance of the RTVue software for topographic assessment of the ONH compared with its macular and RNFL thickness evaluation algorithms.

We used visual sensitivity loss as determined on the total deviation numeric plot as the functional measure, as described by Hood and Kardon,<sup>1</sup> and not the visual threshold, as has been used in most other studies. The total deviation numeric plot adjusts visual sensitivity loss according to the age of the individual. In this way, age-related variability in the functional measurement is minimized. For the structural measurements, although there are no age-corrected values, the change with age has been reported to be small.<sup>23-25</sup> We used LOWESS curves to estimate the structure-function relationship. The advantage of the LOWESS curve is that it does not need the specification of a function to model the relationship in a given sample. The shape of the LOWESS curves shows the lag between structural and functional components in glaucoma. In the early stages of glaucoma, the decline in RNFL thickness is rapid, and there is a lag in visual sensitivity loss. But as the glaucoma damage becomes severe, RNFL thickness reaches a base level beyond which only visual sensitivity declines.

We also evaluated the structure-function relationship using the model proposed by Hood and Kardon<sup>1</sup> and demonstrated that their linear model fits the structure-function data well. The LOWESS curve fitting the present data was similar to the predicted curve according to the model by Hood and Kardon (central dashed line in Figures 2-5). The number of points lying outside the proposed 95% prediction lines (the 2 short dashed lines in the figures) was smaller in the superotemporal sector than in the inferotemporal sector. Hood and Kardon<sup>1</sup> demonstrated that the RNFL thickness in the arcuate regions reached a floor level (b) at a mean sensitivity loss of 10 dB, beyond which there was no significant decline in RNFL thickness. They estimated that the floor level was close to 33% of normal RNFL thickness in the arcuate sectors measured using TDOCT. We found that the floor level with SDOCT was significantly higher (close to 80  $\mu$ m). It was 60% of normal RNFL thickness in the arcuate sectors. A possible limitation in the estimation of base level from these data is that the number of eyes with mean visual sensitivity loss greater than 10 dB in the inferotemporal and superotemporal RNFL sectors was only 19. As shown in Figures 2 and 3, there were a substantial number of glaucomatous eyes with average visual sensitivity loss per sector of 5 to 10 dB, with RNFL thickness less than 80  $\mu$ m. Also, more points fell below the predicted curve than above, especially in Figures 2 and 3. This may be because of the higher floor level estimated using SDOCT. When we considered base level as 33% of normal RNFL thickness at the arcuate areas, as found by Hood and Kardon<sup>1</sup> using TDOCT, and plot-

ted the graphs as in Figures 2 and 3, close to 25% of glaucomatous eyes were above the 95th percentile line. Determination of the base level, b, using SDOCT needs more work with a good number of eyes with severe visual sensitivity loss. Note that recently a nonlinear model to evaluate the structure-function relationship in glaucoma has been proposed by Harwerth et al.<sup>26</sup> We, however, did not evaluate the model proposed by Harwerth et al<sup>26</sup> separately because both of these models have been shown to have similar accuracy for grouped data.

Overall, the relationship between structure and function in the present study was weak to moderate. Different factors have been proposed to explain the imperfect relationship between structure and function; important among them are eyes that show a lag in either the structural or the functional test during the disease course. Similarly, there may be eyes wherein the structure to function correspondence map proposed by Garway-Heath et al<sup>2</sup> might fail, leading to a weak association between structure and function.

In conclusion, we found that the strongest associations between structure and function using SDOCT were found for RNFL measurements at arcuate areas and inner retinal thickness measurements at the macula. The linear model proposed by Hood and Kardon<sup>1</sup> is useful in studying the structure-function relationship in glaucoma.

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