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Retinal nerve fibre layer and visual function loss in glaucoma: the tipping point

Gadi Wollstein,¹ Larry Kagemann,^{1,2} Richard A Bilonick,¹ Hiroshi Ishikawa,^{1,2} Lindsey S Folio,¹ Michelle L Gabriele,^{1,2} Allison K Ungar,¹ Jay S Duker,³ James G Fujimoto,⁴ Joel S Schuman^{1,2,5}

¹Department of Ophthalmology, UPMC Eye Center, Eye and Ear Institute, Ophthalmology and Visual Science Research Center, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

²Department of Bioengineering, Swanson School of Engineering, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

³New England Eye Center, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts, USA

⁴Department of Electrical Engineering and Computer Science and Research Laboratory of Electronics, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA

⁵The McGowan Institute for Regenerative Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Correspondence to

Joel S Schuman, Department of Ophthalmology, UPMC Eye Center, University of Pittsburgh School of Medicine, 203 Lothrop Street, Eye and Ear Institute, Suite 816, Pittsburgh, PA 15213, USA; schumanjs@upmc.edu

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ABSTRACT

Aims To determine the retinal nerve fibre layer (RNFL) thickness at which visual field (VF) damage becomes detectable and associated with structural loss.

Methods In a prospective cross-sectional study, 72 healthy and 40 glaucoma subjects (one eye per subject) recruited from an academic institution had VF examinations and spectral domain optical coherence tomography (SD-OCT) optic disc cube scans (Humphrey field analyser and Cirrus HD-OCT, respectively).

Comparison of global mean and sectoral RNFL thicknesses with VF threshold values showed a plateau of threshold values at high RNFL thicknesses and a sharp decrease at lower RNFL thicknesses. A 'broken stick' statistical model was fitted to global and sectoral data to estimate the RNFL thickness 'tipping point' where the VF threshold values become associated with the structural measurements. The slope for the association between structure and function was computed for data above and below the tipping point.

Results The mean RNFL thickness threshold for VF loss was 75.3 μm (95% CI: 68.9 to 81.8), reflecting a 17.3% RNFL thickness loss from age-matched normative value. Above the tipping point, the slope for RNFL thickness and threshold value was 0.03 dB/ μm (CI: -0.02 to 0.08) and below the tipping point, it was 0.28 dB/ μm (CI: 0.18 to 0.38); the difference between the slopes was statistically significant ($p < 0.001$). A similar pattern was observed for quadrant and clock-hour analysis.

Conclusions Substantial structural loss (~17%) appears to be necessary for functional loss to be detectable using the current testing methods.

The structural and functional relationship in glaucoma has been extensively studied, but the point at which the clinical functional loss as measured by visual fields (VFs) becomes detectable and related to structural changes is unknown. Fundus photography demonstrated the occurrence of retinal nerve fibre layer (RNFL) defects before measurable VF defects.¹ Longitudinal observations revealed that RNFL thinning was associated with future VF damage.²⁻³ Detection of structural changes that precede the loss of visual function could be used to improve disease management and preserve vision.

Precise measurements of RNFL thickness are possible with optical coherence tomography (OCT).⁴⁻⁶ Previous studies proposed models to relate RNFL thickness and functional assessment, but none of them identified the threshold where functional changes can be expected to be detected clinically.^{7,8} Our hypothesis is that there is an RNFL

thickness threshold at which VF loss becomes clinically observable, where for values above the threshold there will be little correspondence between OCT measured structure and VF measured function, and in values below the threshold there will be a strong association between RNFL thickness and VF. The purpose of this study is to determine the RNFL thickness at which VF damage becomes detectable and associated with structural loss.

METHODS

Subjects were consecutively enrolled from the Pittsburgh Imaging Technology Trial, a prospective longitudinal study designed to assess ocular structure over time carried out at the University of Pittsburgh Eye Center. The study followed the principles of the Declaration of Helsinki and was performed in accordance with the Health Insurance Portability and Accountability Act. Institutional review board and ethics committee approval was obtained, and all participants gave their informed consent to be enrolled.

Subjects

Subjects were included if they were either healthy volunteers or open-angle glaucoma subjects of age 18 years or older. Subjects were excluded if any of the following was present: history of diabetes mellitus or any other systemic disease or medical treatment that might affect VF or retinal thickness, history of intraocular surgery except for uncomplicated cataract extraction at least a year prior to enrolment, best corrected visual acuity worse than 20/40, refractive error outside -12.00 to +8.00 dioptres and any ocular abnormality other than glaucoma. One eye of each subject was randomly selected. In unilateral glaucoma cases, the affected eye was selected.

In order to prevent selection bias in a study that evaluates the relationship between structure and function, the diagnostic definition of all subjects was based solely on VF findings without consideration of structural appearance. Healthy subjects had a normal VF examination in both eyes. Glaucoma subjects had typical and reproducible glaucomatous scotomas. Subjects who were clinically suspected of having glaucoma due to optic nerve head or RNFL appearance or because of elevated intraocular pressure but with normal VFs were included in the healthy group to ensure representation of the full spectrum of disease.

VF testing

Swedish Interactive Thresholding Algorithm standard 24-2 perimetry (Carl Zeiss Meditec, Dublin,

California (CZM)) was performed in all subjects. Qualified tests had a false positive of <15% and fixation loss and false negative of <30%. Healthy subjects had a glaucoma hemifield test (GHT) within normal limits and their mean deviation (MD) and pattern SD within 95% of healthy population. Glaucomatous VFs were defined as those with at least one of the following confirmed on two consecutive visits: GHT outside normal limits or pattern standard deviation probability outside the 95% of the healthy population.

VF total deviation values were recorded in all 52 testing points. The individual values were grouped in correspondence with the distribution of the sectors as given by spectral domain optical coherence tomography (SD-OCT). The allocation of the individual threshold points to their group was determined according to Garway-Heath *et al* distribution map.⁹ Total deviation values were unlogged, and the average of all values in each group was log transformed back to the decibel scale.⁷ A secondary analysis was performed using the mean of the unlogged total deviation values. MD was also recorded.

SD-OCT

SD-OCT was acquired at the same visit as the clinical examination and VF. Detailed descriptions of the principles of SD-OCT have been published previously.¹⁰ All OCT scans were performed using the Cirrus HD-OCT (CZM). Optic disc 200×200 cube scans were obtained, quantifying a 6×6×2 mm volume. Scan quality scores >7 were acceptable, with no overt eye movement as detected by observing blood vessel discontinuity or distortion in the OCT *enface* image. Mean, quadrant and clock hour peripapillary RNFL thicknesses were used in the statistical analysis. SD-OCT sectors corresponding to a single VF threshold value (clock hours 2-4 and 10) were removed from the analysis because the reliability of the data might be limited.

Statistical analysis

VF values and OCT data were registered at the right eye orientation. Scatter plot of RNFL thicknesses with threshold values shows a plateau of VF at high RNFL thicknesses and a steep decrease at lower RNFL thicknesses. A 'broken stick' nonlinear statistical model was fit to the data to calculate the 'tipping point'.¹¹ The estimation is considered to be nonlinear because the tipping point is simultaneously estimated along with the slopes. An initial estimate of the tipping point was determined using Davies' test,¹² then a segmented regression model with unknown breakpoint was fit to the data using the estimated threshold from Davies' test as the initial value:

$$Y_i = \alpha + \beta_1 X + \beta_2 (X_i - \psi)_+ + \epsilon_i$$

where Y_i denotes the threshold for subject i , X denotes the RNFL thickness for subject i , α is the intercept, β_1 is the slope for the segment below the threshold Ψ , $\beta_1 + \beta_2$ is the slope for the segment above the threshold Ψ and ϵ is a random error which is assumed to be statistically independent and normally distributed with mean 0 and SD σ . Note that if there is no breakpoint, β_2 will equal zero. Similar analysis was performed in the secondary analysis using the 1/L values.

All analyses were conducted using R Language and Environment for Statistical Computing program (<http://www.R-project.org>)¹³ and the *segmented* R library.¹⁴ $P < 0.05$ was considered statistically significant.

RESULTS

One hundred twelve subjects were recruited: 72 healthy and 40 glaucoma subjects; 44 men and 68 women. Demographics are summarised in table 1.

Table 1 Demographic characteristics of the healthy and glaucomatous subjects

	Healthy n=72	Glaucoma n=40	p
Age (yrs)	50.0±16.4	65.5±10.9	<0.001†
Female/Male	39/33	29/11	0.06*
VF MD (dB)	-0.21±0.80	-5.04±4.64	<0.001‡
VF PSD (dB)	1.46±0.25	5.98±3.97	<0.001‡
OCT mean RNFL (µm)	90.8±8.6	69.8±12.1	<0.001†

*χ².

†Student t test.

‡Wilcoxon test.

VF MD, visual field mean deviation; VF PSD, visual field pattern SD; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer.

Scatter plots of RNFL thickness and VF threshold values showed a region where the OCT measured RNFL thickness was unrelated to VF measured visual function followed by a region where the relationship between these parameters was strong (figure 1). Estimates of the statistically optimal tipping points between these regions for average and quadrant RNFL thicknesses are listed in table 2. The global mean and the superior, temporal and inferior quadrants showed tight CI around the deflection point and the location of the tipping point was statistically significant (all $p < 0.05$, Davies' test). The nasal quadrant showed a wide CI and the tipping point location was not significant ($p = 0.82$). Using population-based normative data of RNFL thickness values at the mean age of the participants in this study (personal communication with Michael V Patella, OD, Carl Zeiss Meditec), the percentage of RNFL loss necessary to reach the tipping point was also calculated for the mean and quadrants (table 2). The tipping point for the mean RNFL measurement occurred after a loss of 17.3% from the expected aged-matched value and approximately 25% loss in the superior and inferior quadrants. The RNFL thickness at the tipping point for the global mean and the inferior quadrant was considered as a borderline measurement based on the comparison with the normative data set criteria set by the manufacturer and outside normal limits for the superior quadrant.

Tipping points for clock hours with percent loss from the mean normative values are summarised in table 2. The percentage of RNFL loss from the mean of age-matched normative thickness was highest for 1:00 (39.9%), while for all other sectors the range was 18.5–29.5%, with the lowest loss in the 9:00 location. The tipping point was located in the borderline zone for 1:00 when compared with the normative values, and for all other locations the tipping point occurred within the normal range.

The slopes for VF threshold as a function of RNFL thickness above and below the tipping points are listed in table 3. The models for the slope estimate did not converge for clock hours 1, 5 and 8, and therefore the slope could not be determined with confidence in these particular locations. The slopes above the tipping point in all tested locations were not different than a zero slope (CI included zero), except for the inferior quadrant and 1:00. The slopes below the tipping point were statistically significantly different than a zero slope except for the nasal quadrant. The slopes below the tipping points were statistically significantly steeper than the slopes above the tipping point for all locations except for the nasal quadrant.

A similar segmented relationship was noted in the secondary analysis using 1/L values (figure 2). The estimated tipping point was 77.0 µm (95% CI: 67.5 to 86.5), with a slope above the tipping point of 0.01 1/(L×µm) (CI: -0.01 to 0.01) and a slope below the tipping point of 0.03 1/(L×µm) (CI: 0.02 to 0.04). The

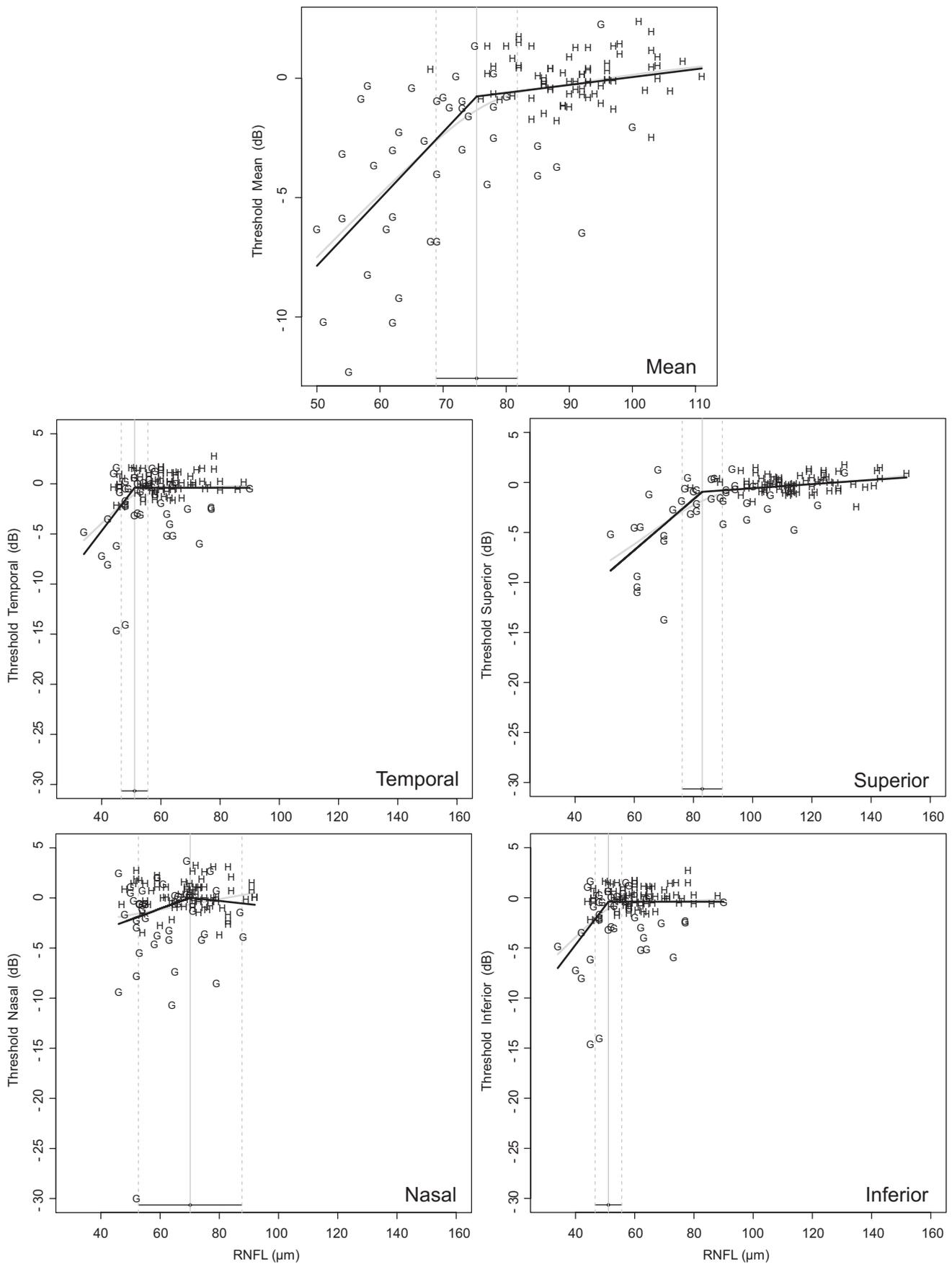


Figure 1 Healthy (H) and glaucoma (G) retinal nerve fibre layer (RNFL) thickness in the mean and in quadrants with corresponding visual field threshold values. Spline fit is the grey line; 'broken stick' model is the black line.

Table 2 Retinal nerve fibre layer thickness tipping point with corresponding optical coherence tomography normative values.

	Tipping point		Normative values				Davies' test p value
	Mean	95% CI	Mean	BDL cut-off	Outside normal limit cut-off	% Loss for tipping point from mean normative	
Mean	75.3	68.9 to 81.8	91.1	77.5	69.9	17.3	0.003
Temporal	51.1	46.6 to 55.6	63.1	46.4	42.2	19.0	0.002
Superior	83.0	76.3 to 89.7	115.0	92.1	85.6	27.8	<0.001
Nasal	70.2	52.7 to 87.7	68.2	51.3	43.0	NA	0.82
Inferior	87.5	73.6 to 101.4	117.9	93.4	85.8	25.8	0.002
1:00	62.7	53.1 to 72.2	104.4	76.2	61.9	39.9	0.003
5:00	73.4	66.7 to 80.1	95.5	65.7	56.8	23.1	<0.001
6:00	103.8	83.3 to 124.3	129.8	90.1	81.2	20.0	0.010
7:00	97.2	77.2 to 117.3	128.5	88.9	74.0	24.4	0.004
8:00	46.0	41.2 to 50.7	63.4	43.4	36.2	27.4	<0.001
9:00	41.3	36.7 to 45.9	50.7	37.0	31.9	18.5	0.012
11:00	94.4	82.3 to 106.5	124.2	89.9	71.1	24.0	<0.001
12:00	82.1	69.2 to 95.0	116.5	74.1	63.2	29.5	0.002

All measurements are reported in micrometers.
BDL, borderline; NA, non-applicable.

difference between the slopes was 0.02 1/(L×μm) (CI: 0.01 to 0.03) and statistically significant (p=0.003).

Employing the same approach using VF MD instead of the threshold values identified the tipping point at 76.7 μm (CI: 71.3 to 86.5), with slopes above the tipping point of 0.03 dB/μm (CI: -0.03 to 0.10) and below the tipping point of 0.39 dB/μm (CI: 0.28 to 0.51), with a statistically significant difference between the slopes.

DISCUSSION

In the present study, analysis of ocular structural and functional data by a 'broken stick' statistics identifies a tipping point at which the relationship between RNFL thickness and VF threshold values are clearly different. The tipping point allows us to define the RNFL threshold where strong association with VF abnormalities can be expected. This study reveals that substantial structural loss (approximately 17%) appears to be necessary for functional loss to be detectable, using the current testing methods.

Similar to numerous previous studies, we demonstrate that thicker RNFL values are not associated with abnormalities in the VF threshold.^{7 8 15-18} Moreover, our analysis indicates that in this region (above the tipping point) the slope of VF threshold versus RNFL is not statistically significantly different than zero for global and most sectoral analysis. This can be mostly

attributed to the higher variability in VF outcomes than structural outcome in the early stage of glaucoma.^{7 8} From the clinical perspective, this can be interpreted as an indication that structural evaluation is a more sensitive measure of health at the early stage of glaucoma, as it was suggested previously by histology and disc photography assessment.¹⁻³ Below the tipping point, there is a strong association between structure and function with a rate of change that varies substantially by RNFL location.

The tipping point could be detected in all tested locations except for the nasal quadrant. The estimate for the tipping point in the nasal quadrant presented with a wider CI than the other quadrants, reflecting the lack of prominent deflection point between the subpopulation of data. The wide CI in the nasal quadrant may be the result of undersampling (relative to the other quadrants) of the corresponding tissues in the VF. In addition, OCT measurements in the nasal quadrant have the lowest test-retest reproducibility.¹⁹ The combined influences of fewer nasal VF data points and lower nasal OCT reproducibility may have masked a tipping point in the nasal quadrant. Additionally, the statistical model did not converge in clock hours 1, 5 and 8; although a tipping point was detected, the accuracy of the actual value is questionable. Because the analysis is based on detection of the optimal deflection point in multi-dimensional plane, it is difficult to discern the reason for the non-convergence.

Table 3 Fitted slopes of retinal nerve fibre layer thickness and visual field threshold above and below the tipping point. All slopes are in decibels per micrometre

	Slope below tipping point (95% CI)	Slope above tipping point (95% CI)	Difference between slopes (95% CI)	p Value
Mean	0.28 (0.18 to 0.38)	0.03 (-0.02 to 0.08)	0.25 (0.13 to 0.36)	<0.001
Temporal	0.39 (0.14 to 0.63)	-0.01 (-0.06 to 0.06)	0.39 (0.13 to 0.64)	0.003
Superior	0.25 (0.16 to 0.34)	0.02 (-0.01 to 0.05)	0.23 (0.14 to 0.33)	<0.001
Nasal	0.11 (-0.02 to 0.24)	-0.03 (-0.20 to 0.14)	0.14 (-0.07 to 0.36)	0.20
Inferior	0.16 (0.09 to 0.23)	0.03 (0.01 to 0.06)	0.13 (0.05 to 0.20)	<0.001
1:00	0.55 (0.07 to 1.03)	0.04 (0.13 to 0.77)	0.51 (0.02 to 0.99)	<0.001
5:00	0.35 (0.20 to 0.49)	0.01 (-0.03 to 0.05)	0.33 (0.18 to 0.48)	<0.001
6:00	0.11 (0.06 to 0.15)	0.02 (-0.01 to 0.05)	0.09 (0.03 to 0.14)	0.001
7:00	0.17 (0.09 to 0.25)	0.01 (-0.04 to 0.06)	0.16 (0.06 to 0.26)	<0.001
8:00	0.98 (0.39 to 1.57)	-0.09 (-0.19 to 0.01)	0.95 (0.35 to 1.54)	0.002
9:00	0.52 (0.02 to 1.01)	-0.09 (-0.19 to 0.01)	0.61 (0.10 to 1.12)	0.018
11:00	0.17 (0.10 to 0.24)	0.01 (-0.02 to 0.04)	0.16 (0.09 to 0.24)	<0.001
12:00	0.15 (0.06 to 0.23)	0.01 (-0.02 to 0.03)	0.14 (0.05 to 0.22)	0.002

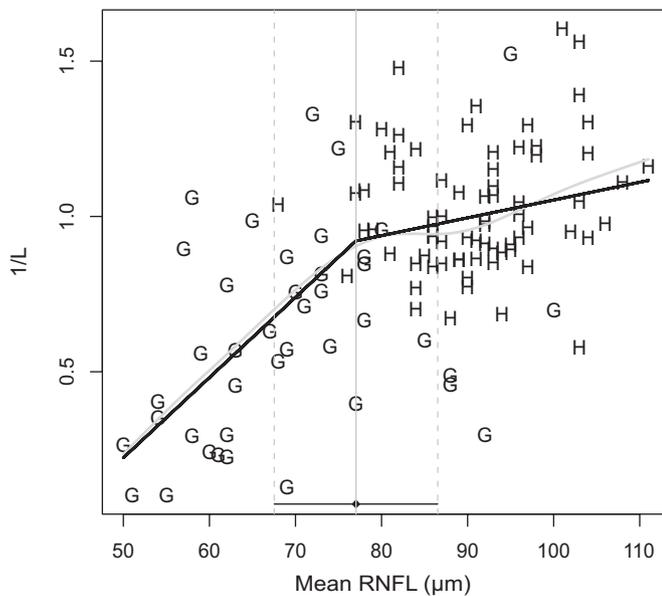


Figure 2 Scatter plot of healthy (H) and glaucoma (G) values using unlogged (1/L) visual field threshold values. The grey line is a spline fit, and the black line is the two-segment 'broken stick' model. RNFL—retinal nerve fiber layer, L—Lambert.

Eye movements have a greater impact on sectoral measurement variability than global variability, resulting in lower sectoral reproducibility¹⁹ and wider range of the sectoral CIs (table 2). This may have contributed to the tipping point being outside the normal range for mean, while inferior and superior quadrants being within the normal range in the corresponding clock hours.

Ageing has been shown to cause gradual thinning of the RNFL²⁰ and reduction in visual sensitivity.²¹ In order to account for this effect, we use VF total deviation threshold values that are age corrected. For RNFL measurements, we use the mean age-adjusted normative value, allowing us to identify the percentage tissue loss while accounting for the ageing effect. The tipping point occurs with a mean RNFL thickness 17% below the level that would be expected in the age-matched healthy population. In the superior and inferior quadrants and clock hours, the tipping point occurs after ~25% loss. The highest loss (40%) occurs at the 1:00 location, but as stated above the reliability of the analysis in this location is questionable. The lowest sectoral percentage loss is at 8:00 and the temporal quadrant. This finding might be explained by the high concentration of thinner axons in the papillomacular bundle passing through this location.²² Therefore, in the same RNFL thickness as in other locations, the number of axons passing through the temporal quadrant is larger, leading to the appearance of VF abnormality after a smaller RNFL thickness loss. A 'floor effect', where no further structural damage can be detected while functional changes can still occur, was not identified in this study, but this could be expected in situations where very advanced stages of structural damage exist.

Numerous studies evaluate the relationship between structure and function in glaucomatous eyes. Most of the studies employ a single model throughout the data, either linear or curvilinear.^{7 8 15–17} Ajtony *et al* have speculated that a mean RNFL thickness of approximately 70 μm might represent a profound threshold value in glaucomatous structure changes.¹⁸ In the present study, we utilise a statistical method to accurately

determine this location that is found to be at 75.3 μm. Identifying the actual location where VF abnormality is expected to occur is of utmost importance in clinical management especially for individuals suspected of having glaucoma.

Our secondary analysis shows that with both decibel and 1/L units, the tipping point appears approximately at the same RNFL thickness, thus confirming the true basis of this range for distinguishing between phases of structure and function relationship. We also performed an analysis using VF MD because this parameter is commonly used in clinical practice. The tipping point for MD occurs at an RNFL thickness of 77 μm.

The limitations of the study include its cross-sectional nature and the population data used. Caution should be used when applying these results to individual subjects. A person might start with a thicker or thinner RNFL and their actual tipping point RNFL thickness value might vary from the one reported herein. The study design, however, is appropriate for initial testing of the hypothesis.

In conclusion, the 'broken-stick' analysis allows the identification of a structural and functional tipping point. It appears that 'pre-perimetric' glaucoma (using current standard automated perimetry) can be identified by OCT RNFL thickness, with the detectable VF loss first appearing with RNFL approximately 17% below that expected for healthy eyes.

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Ethics approval This study was conducted with the approval of the University of Pittsburgh.

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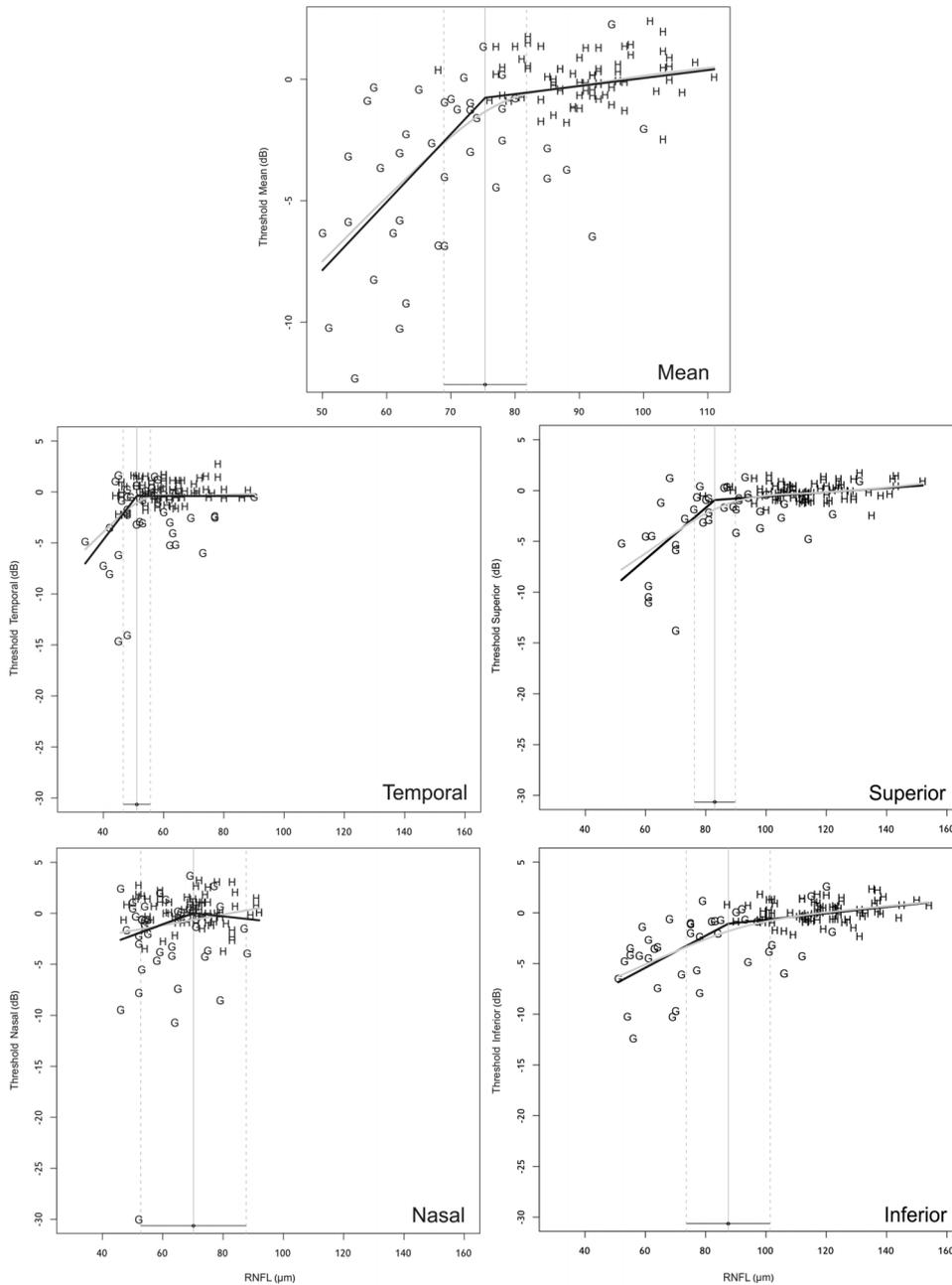


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Corrections

Wollstein G, Kagemann L, Bilonick RA, *et al.* Retinal nerve fibre layer and visual function loss in glaucoma: the tipping point. *Br J Ophthalmol.* 2012;96:47–52. In Figure 1, the authors erroneously included the same plot for the temporal and inferior sectors. The correct figure is shown below.



Br J Ophthalmol 2013;97:1088. doi:10.1136/bjo.2010.196907corr1