Time Lag Between Functional Change and Loss of Retinal Nerve Fiber Layer in Glaucoma

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PURPOSE. It is often suggested that structural change is detectable before functional change in glaucoma. However, this may be related to the lower variability and hence narrower normative limits of structural tests. In this study, we ask whether a time lag exists between the true rates of change in structure and function, regardless of clinical detectability of those changes.

METHODS. Structural equation models were used to determine whether the rate of change in function (mean linearized total deviation, AveTDLin) or structure (retinal nerve fiber layer thickness [RNFLT]) was predicted by the concurrent or previous rate for the other modality, after adjusting for its own rate in the previous time interval. Rates were calculated over 1135 pairs of consecutive visits from 318 eyes of 164 participants in the Portland Progression Project, with mean 207 days between visits.

RESULTS. The rate of change of AveTDLin was predicted by its own rate in the previous time interval, but not by rates of RNFLT change in either the concurrent or previous time interval (both $P > 0.05$). Similarly, the rate of RNFLT change was not predicted by concurrent AveTDLin change after adjusting for its own previous rate. However, the rate of AveTDLin change in the previous time interval did significantly improve prediction of the current rate for RNFLT, with $P = 0.005$, suggesting a time lag of around six months between changes in AveTDLin and RNFLT.

CONCLUSIONS. Although RNFL thinning may be detectable sooner, true functional change appears to predict and precede thinning of the RNFL in glaucoma.

Keywords: glaucoma, diagnostics, progression, structure-function relation, structural equation models

Several previous studies have suggested that structural changes may be detectable prior to functional changes in glaucoma. However, the focus of those studies was not on which modality shows true change first, but on which shows detectable change first. This is complicated by the issue of variability, which is higher for standard automated perimetry (SAP) than for retinal nerve fiber layer thickness (RNFLT).

Indeed, the World Glaucoma Association’s consensus document states the following:

With current technology, detection of structural defects generally precedes detectable functional defects in glaucoma patients while functional defects can precede structural defects in some patients... Structural tests based on the comparison to the normative data tend to show a statistically significant glaucomatous change earlier compared to the functional tests because of a greater variability in functional tests.

It is likely that the structure-function relation would be much tighter in the absence of this test-retest variability. As technology develops and variability is reduced, the temporal relation between being able to detect structural and functional changes could be altered, despite the course of underlying pathophysiology following the same sequence.

At the cellular level, there are strong reasons to hypothesize that functional change may actually precede structural changes in human glaucoma. Dead or terminally nonfunctional neurons may still occupy physical space and thus contribute to measurements of structure but not function; whereas functioning neurons must occupy some volume and thus contribute to measurements of both structure and function. Indeed, in experimental glaucoma, axon loss of around 12% was found in the optic nerves of eyes without any reduction in RNFLT compared with their contralateral control eye.

In this study, we ask whether there is evidence of a time lag between changes in structure (RNFLT in this case) and function (SAP) in human glaucoma. We aim to identify the temporal relation between true changes in these modalities, not just detectable changes; that is, without regard to whether those changes are outside the normal limits of test-retest variability. To achieve this, we use structural equation models (SEM), which allow us to examine the strength of the predictive relation between the two while accounting for unobservable latent variables, correlations between predictors, and autocorrelated repeated measures. By using biaxial testing, this technique requires that any time lag will not
to maximize the robustness of the results, for the primary analyses, data were not excluded on the basis of not meeting the standard reliability criteria. However, a secondary analysis was also performed, using only time points at which the OCT image quality score was ≥15 and there were fewer than 20% fixation losses and 15% false-positive results for SAP. For comparison with detectable change, we used linear regression to determine whether each eye ever demonstrated a significantly negative rate of change of AveTDLin and/or of age-corrected RNFLT based on the first n visits, for n ≥ 4.

SEM

SEMs are a Class of Statistical Models that are used to Analyze “Structural” Models, including latent growth models. The most relevant advantages of using SEMs for this study compared to more traditional approaches are that they allow modeling of unobservable latent variables such as the true rates of functional and structural change, they allow and adjust for correlations between predictors, and they allow the same data point to be both predicted by the status at a previous time point and be a predictor of the status at a future time point, that is, appearing on both left and right sides of different regression equations.

In this study, we are interested in whether there is a time lag between the true rates of change in AveTDLin from visit n to n + 1, denoted by $\Delta\text{AveTDLin}(n)$, and the corresponding rates of change in RNFLT, denoted by $\Delta\text{RNFLT}(n)$, regardless of whether that change is outside normal limits of variability (i.e., regardless of whether the change would be detectable in clinical care). We assume that for a given eye there are true underlying rates of functional and structural loss, represented by latent variables $F(n)$ and $S(n)$, respectively, and that these rates change linearly across the series with a fixed intercept and rate per eye. Thus the model allows the rate of progression to increase or decrease, but it does so consistently such that $\frac{dF}{dn}$ and $\frac{dS}{dn}$ remain constant; this assumption was believed to be reasonable for series of up to three years (seven visits). These underlying rates $F(n)$ and $S(n)$ are assumed to be positively correlated between eyes, but they are not constrained to be proportional because there is substantial interindividual variability in the relation between structure and function even in healthy eyes. The observed rate $\Delta\text{AveTDLin}(n)$ is treated as a random variable predicted by $F(n)$ but with variance $\sigma_F^2$. Similarly, the observed rate $\Delta\text{RNFLT}(n)$ is treated as a random variable predicted by $S(n)$ with variance $\sigma_S^2$. The variances $\sigma_F^2$ and $\sigma_S^2$ are assumed to be constant throughout the series, implicitly making the simplifying assumption that even though test-retest variability in perimetry is known to vary with severity, the rate of change is uncorrelated with both.

Four SEM models were constructed, differing only in their use of information from the other testing modality, and fit independently of each other:

Model A:
$$\Delta\text{AveTDLin}(n) = F(n) + \alpha_A \times \Delta\text{AveTDLin}(n - 1) + \beta_A \times \Delta\text{RNFLT}(n) + \epsilon_F$$
$$\Delta\text{RNFLT}(n) = S(n) + \gamma_A \times \Delta\text{RNFLT}(n - 1) + \epsilon_S$$

Model B:
$$\Delta\text{AveTDLin}(n) = F(n) + \alpha_B \times \Delta\text{AveTDLin}(n - 1) + \beta_B \times \Delta\text{RNFLT}(n - 1) + \epsilon_F$$
$$\Delta\text{RNFLT}(n) = S(n) + \gamma_B \times \Delta\text{RNFLT}(n - 1) + \epsilon_S$$
earlier than, and is predictive of, functional change over the next time interval. Conversely in Model D, there is a time lag whereby functional change occurs earlier than and is predictive of structural change over the next time interval. The coefficients $\alpha$, $\beta$, and $\gamma$ can differ between the four models. However, coefficients $\alpha$ and $\gamma$ are always expected to be negative; the change $\Delta\text{AveTDLin}(n-1)$ from visit $n-1$ to visit $n$ will be inversely correlated with the change $\Delta\text{AveTDLin}(n)$ from visit $n$ to visit $n+1$ since they both have the measurement $\text{AveTDLin}$ at visit $n$ in common. Coefficient $\beta$ is constrained to be nonnegative, for reasons of clinical plausibility. The primary hypothesis being tested is that more rapid change in one modality may predict more rapid change in the other modality, either in the same interval or the following interval; that is, whether $\beta$ is significantly greater than zero.

Analyses were performed using R statistical software, version 4.0.0, with the lavaan package.21 Models were fit using full information maximum likelihood estimation to ensure that the results are statistically consistent and unbiased despite the presence of missing data.35 Goodness of fit for each model was assessed using the root mean square error of approximation (RMSEA)22,23; the Tucker Lewis index (TLI, also known as the nonnormed fit index) representing the magnitude of the improvement in fit over a null model; and the adjusted goodness of fit (AGFI) representing the proportion of variance explained by the model, analogously to an adjusted $R^2$ value.24

Localized Analysis

The analyses described above used global indexes for both function ($\text{AveTDLin}$) and structure (RNFLT). These are less sensitive to the smaller localized defects that are typically seen in early glaucoma. Additionally, there is not a perfect mapping between the two. Due to the layout of test locations in the 24-2 grid, AveTDLin will better detect changes in the superior and inferior mid-peripheral regions where there are several test locations, versus in the central or temporal regions where there are very few test locations. By contrast, RNFLT is a simple mean value around the circumpapillary scan, and so gives equal weight to defects occurring at all angles around the optic nerve head. Therefore two localized analyses were also performed. RNFLT(Sup) was defined as the average RNFLT within the combined superior nasal and superior temporal 40°-wide sectors that are output by the Spectralis OCT software. This was compared against $\text{AveTDLin(Inf)}$, defined as the average of the sensitivities (on the linear scale as before) of the corresponding 21 visual field locations, based on the map of Garway-Heath et al.35; namely all locations in the inferior hemifield, except for the three locations closest to the blind spot at 3° below the horizontal midline and the two locations temporal of the blind spot. Similarly, RNFLT(Inf) was defined as the average RNFLT within the combined inferior nasal and inferior temporal 40°-wide sectors, and was compared against $\text{AveTDLin(Sup)}$ defined as the average of the corresponding 21 locations in the superior hemifield of the visual field.

RESULTS

Table 1 summarizes the cohort. An available interval was defined as two visits occurring in consecutive six-month time periods; for example, one visit occurring nine to 15 months after their first visit, and another visit occurring.
Model A: \[ \Delta \text{AveTDLin}(n) = F(n) - 0.550 \times \Delta \text{AveTDLin}(n - 1) + 0 \times \Delta \text{RNFLT}(n) + \epsilon_F \]
\[ \Delta \text{RNFLT}(n) = S(n) - 0.313 \times \Delta \text{RNFLT}(n - 1) + \epsilon_S \]

Model B: \[ \Delta \text{AveTDLin}(n) = F(n) - 0.550 \times \Delta \text{AveTDLin}(n - 1) + 0 \times \Delta \text{RNFLT}(n - 1) + \epsilon_F \]
\[ \Delta \text{RNFLT}(n) = S(n) - 0.313 \times \Delta \text{RNFLT}(n - 1) + \epsilon_S \]

Model C: \[ \Delta \text{RNFLT}(n) = S(n) - 0.313 \times \Delta \text{RNFLT}(n - 1) + 0 \times \Delta \text{AveTDLin}(n) + \epsilon_S \]
\[ \Delta \text{AveTDLin}(n) = F(n) - 0.550 \times \Delta \text{AveTDLin}(n - 1) + \epsilon_F \]

That is, after adjusting for the rate of functional change during the previous interval, neither the rates of structural change \( \Delta \text{RNFLT} \) in the same interval (Model A) nor the previous interval (Model B) were significant predictors of the rate of functional change. Similarly, after adjusting for the rate of functional change during the previous interval, the rate of functional change \( \Delta \text{AveTDLin} \) in the same interval (Model C) was not a significant predictor of the rate of structural change.

The latent variable \( F(n) \) had an intercept of \(-0.043 \text{ L}^{-1}\text{y}^{-1} \) in Models A-C, indicating the predicted rate of change in AveTDLin within an interval if the rate in the previous interval had been zero. Similarly, the latent variable \( S(n) \) had intercept \(-0.717 \mu\text{m/y} \) indicating the rate of change in RNFLT if the rate in the previous interval had been zero. It should be noted at this point that AveTDLin is age-corrected whereas RNFLT is not; the only effect of this inconsistency is to alter these constant intercepts for \( S(n) \) and \( F(n) \), and age correction would not alter the magnitude or statistical significance of any of the other coefficients. As predicted, the fitted values of coefficients \( \alpha \) and \( \gamma \) were both negative, because of the effect of variability in the measurement at time \( n \) on the rates \( \Delta \text{AveTDLin}(n - 1) \) and \( \Delta \text{AveTDLin}(n) \) and similarly for RNFLT. If there were no true changes in AveTDLin or RNFLT, we would expect both \( \alpha \) and \( \gamma \) to be \(-1 \); that is, the average rate of change in interval \( n \) would be the exact opposite of the rate in interval \( n - 1 \). The fact that both \( \alpha \) and \( \gamma \) are greater than \(-1 \) indicates that the true rates of change in intervals \( n - 1 \) and \( n \) would be correlated in the absence of measurement variability. It should also be noted that the coefficient \( \beta \) was constrained to be nonnegative to maintain physiological plausibility; hence, the best fit estimate is \( \beta = 0 \) for all three of the above models. Removing that constraint gave slightly negative but nonsignificant values for \( \beta_S \) (\( P = 0.520 \)) and \( \beta_F \) (\( P = 0.062 \)). The unconstrained fitted value of \( \beta_C \) was \(-0.999 \) with \( P = 0.017 \).

However, for the fourth SEM model:

\[ \Delta \text{RNFLT}(n) = S(n) - 0.293 \times \Delta \text{RNFLT}(n - 1) + 1.130 \times \Delta \text{AveTDLin}(n - 1) + \epsilon_S \]
\[ \Delta \text{AveTDLin}(n) = F(n) - 0.545 \times \Delta \text{AveTDLin}(n - 1) + \epsilon_F \]

The rate of functional change in the previous interval was a significant predictor of the rate of structural change in the current interval, with \( P = 0.007 \), and 95% confidence interval (CI) for the coefficient (0.308, 1.953). That is, more rapid structural change in interval \( n - 1 \) did not predict more rapid functional change in interval \( n \) (Model B); but more rapid functional change in interval \( n - 1 \) did predict more rapid structural change in interval \( n \) (Model D). Overall, this suggests that functional change as measured by AveTDLin predicts and precedes structural change as measured by RNFLT.
When using localized analyses, results were similar. In Models A, B, and C, coefficients $\beta_a$, $\beta_b$, and $\beta_c$ were zero when using RNFLT(Sup) against $\Delta$AveTDLin(Inf) and when using RNFLT(Inf) against $\Delta$AveTDLin(Sup), regardless of whether only reliable visits were used. However in Model D, coefficient $\beta_D$ was consistently greater than zero. Using data from all visits:

Inferior hemifield:

$$\Delta$$RNFLT(Inf)$(n) = S(n) - 0.392 *$$AveTDLin (Inf)(n - 1) + 0.450 *$$AveTDLin $$(Sup)(n) - \varepsilon_S$$

$$\Delta$$AveTDLin(Inf)(n) = F(n) - 0.529 *$$AveTDLin $$(Inf)(n - 1) + \varepsilon_F$$

Superior hemifield:

$$\Delta$$RNFLT(Sup)$(n) = S(n) - 0.431 *$$AveTDLin (Sup)(n - 1) + 2.545 *$$AveTDLin (Inf)(n) - \varepsilon_S$$

$$\Delta$$AveTDLin(Sup)$(n) = F(n) - 0.655 *$$AveTDLin (Inf)(n - 1) + \varepsilon_F$$

The coefficients $\beta_D$ had $P = 0.022$ for $\Delta$AveTDLin(Inf), and $P = 0.356$ for $\Delta$AveTDLin(Sup). Although those coefficients appear quite different from one another, the 95% CIs were wide; 0.236 to 3.066 for $\Delta$AveTDLin(Inf), and −0.51 to 1.405 for $\Delta$AveTDLin(Sup).

Using data from reliable visits only:

Inferior hemifield:

$$\Delta$$RNFLT(Inf)$(n) = S(n) - 0.428 *$$AveTDLin (Inf)(n - 1) + 1.316 *$$AveTDLin $$(Sup)(n) - \varepsilon_S$$

$$\Delta$$AveTDLin(Inf)(n) = F(n) - 0.567 *$$AveTDLin (Sup)(n - 1) + \varepsilon_F$$

In this case, the coefficients $\beta_D$ had $P = 0.006$ for $\Delta$AveTDLin(Inf), and $P = 0.032$ for $\Delta$AveTDLin(Sup).

**DISCUSSION**

In this study, we used SEMs to investigate whether there is a time lag between the true changes in structural and functional measures (RNFLT and SAP, respectively). Because of their ability to incorporate latent variables in time series for which the same observed value is both dependent on previous values and predictive of future values, SEMs allow us to test the relative utility of time-lagged variables and, hence, to identify time lags between the true rates of change even when those changes do not exceed normal variability (i.e., they are not “detectable” clinically). We found that the rate of functional change in a given time interval was predictive of the rate of structural change in the following time interval, but the converse was not true. This is despite the fact that more eyes demonstrated detectable change for RNFLT than for SAP, when defined as a significantly negative rate of change over ≥4 visits. This time lag implies that although detectable change may occur sooner for RNFLT than for SAP, true change for SAP occurs sooner than and is predictive of subsequent change in RNFLT.

**Table 2. Goodness-of-Fit Measures for the Models**

| Model | RMSEA | TLI | AGFI |
|-------|-------|-----|------|
| All visits | 0.107 (0.094–0.120) | 0.563 | 68.0% |
| Model A | 0.107 (0.094–0.120) | 0.563 | 68.0% |
| Model B | 0.107 (0.094–0.120) | 0.563 | 68.0% |
| Model C | 0.105 (0.093–0.118) | 0.577 | 68.3% |
| Reliable visits only | 0.114 (0.101–0.129) | 0.487 | 64.5% |
| Model A | 0.114 (0.101–0.129) | 0.487 | 64.5% |
| Model B | 0.114 (0.101–0.129) | 0.487 | 64.5% |
| Model C | 0.114 (0.101–0.129) | 0.487 | 64.5% |
| Model D | 0.112 (0.098–0.126) | 0.508 | 65.3% |

In all, 88% of individual visits were considered reliable; that is, there were ≤20% fixation losses and ≤15% false-positive results for SAP, and an OCT scan quality of ≥15. The regression equations in the SEM models require that data be available for two consecutive intervals, that is, for test dates falling within three consecutive six-month time periods. There were 743 pairs of consecutive intervals but just 538 pairs of consecutive reliable intervals. Thus, even though 88% of individual visits were considered reliable, only 72% of the available consecutive intervals could be used for the secondary analysis restricted to reliable data only. The best fit coefficients using only reliable data were as follow:

Model A: $\Delta$AveTDLin(n) = F(n) - 0.616 * $\Delta$AveTDLin(n - 1) + 0 * $\Delta$RNFLT(n) + $\varepsilon_F$

$\Delta$RNFLT(n) = S(n) - 0.346 * $\Delta$RNFLT(n - 1) + $\varepsilon_S$

Model B: $\Delta$AveTDLin(n) = F(n) - 0.616 * $\Delta$AveTDLin(n - 1) + 0.001 * $\Delta$RNFLT(n - 1) + $\varepsilon_F$

$\Delta$RNFLT(n) = S(n) - 0.346 * $\Delta$RNFLT(n - 1) + $\varepsilon_S$

Model C: $\Delta$RNFLT(n) = S(n) - 0.346 * $\Delta$RNFLT(n - 1) + 0 * $\Delta$AveTDLin(n) + $\varepsilon_S$

$\Delta$AveTDLin(n) = F(n) - 0.616 * $\Delta$AveTDLin(n - 1) + $\varepsilon_F$

Model D: $\Delta$RNFLT(n) = S(n) - 0.315 * $\Delta$RNFLT(n - 1) + 1.634 * $\Delta$AveTDLin(n - 1) + $\varepsilon_S$

$\Delta$AveTDLin(n) = F(n) - 0.608 * $\Delta$AveTDLin(n - 1) + $\varepsilon_F$

All four models are qualitatively similar to those derived including unreliable test visits. In Model D, the coefficient $\beta_D$ for $\Delta$AveTDLin(n - 1) now has $P = 0.003$ and 95% CI for the coefficient (0.541, 2.727), supporting the robustness of the model.

Table 2 shows a selection of goodness-of-fit measures for each model.24 Model D fit the data slightly better than Models A to C, as indicated by lower RMSEA (lower prediction error), higher TLI (greater improvement in fit over a null model), and higher AGFI (greater proportion of variance explained). Although direct comparisons should be treated with caution, the models using only reliable data appeared to have slightly worse fits to the data, presumably because of reduced sample size.
Several previous studies have suggested that glaucomatous damage may be able to be detected sooner using structural testing than functional testing. A classic study by Kerrigan-Baumrind et al.\(^1\) is often cited as evidence that 25% to 35% of retinal ganglion cells (RGCs) are lost before functional abnormalities develop that are measurable using SAP; although that interpretation of their results has been questioned\(^2\) because their results actually showed a 6-decibel (dB) functional loss in eyes without RGC loss.\(^25\)

A more recent study by Wollstein et al.\(^3\) suggested that \(\sim17\%\) of RNFLT, as measured by optical coherence tomography (OCT), must be lost before functional abnormalities were detected; although it should be noted that due to the specific purpose of their study that conclusion was based on a segmented linear regression fit on decibel-scaled sensitivity values rather than the more commonly-used linear fit on linear-transformed sensitivities. A study by Kuang et al.\(^4\) also found evidence of RNFL defects before confirmed functional loss, suggesting higher sensitivity, although they did not look for functional loss being detected before RNFL thinning. Progression was more commonly detected using optic disc photos before perimetry in the OHTS (3.0% of eyes, vs. 1.7% of eyes for which progression was detected the other way round);\(^1\) but this in part reflects conformational changes to the optic nerve head connective tissues that do not affect peripapillary RNFL measurements.\(^29\) These comparisons are also heavily influenced by the greater test-retest variability of SAP,\(^5,7\) which means that even if both structure and function change concurrently by the same amount, that change would exceed normal limits sooner for structural change.\(^5\)

It is not surprising that true functional change could occur earlier than RNFL thinning. The largest proportion of the RNFL consists of axons. These axons likely stop being fully functional some time before their soma undergo apoptosis and efferocytosis. This unknown time gap may be short, but it must be present, because vision function cannot persist after an RGC or its axon are gone. The only way RNFL thinning could precede, and be predictive of, subsequent functional loss would be if individual axons or non-neural tissue became thinner because of compression, stretching, or both. This transverse compression has been reported in rim tissue in experimental glaucoma, but it was not detected at the 6° distance from the centroid of the optic nerve head at which the circle scan used to measure RNFLT is conducted.\(^30\) On the contrary, evidence suggests that RNFL thinning is actually significantly delayed after axon loss.\(^6,9\) postulated to be due to a combination of axon enlargement\(^11\) and mechanical resistance to layer collapse,\(^12\) causing a decreased density of axons within the layer but little or no change in the layer thickness, something that has also been suggested in human glaucoma based on results from adaptive optics scanning laser ophthalmoscopy.\(^35\) Furthermore, there is evidence of RGC functional deficits preceding loss of RGCs in experimental models of glaucoma, such as impaired axonal transport\(^34\) and altered neural responsiveness to stimuli.\(^33-39\) Thus results from animal models suggest functional loss preceding RGC loss preceding RNFL thinning.

Our results extend that principle to human glaucoma, showing not only that RNFL thinning lags behind functional loss, but also that the time lag is substantial enough to be meaningful. Longitudinal testing in this study was performed once every six months. This precludes providing a highly precise estimate of the time lag, which might vary substantially between eyes anyway. In further analyses (not shown), there was no evidence supporting a time lag of one year (i.e., two time intervals), but the sample size was much smaller for those analyses, and so we cannot definitively conclude that the duration of the time lag is only one time interval. However, we can reasonably conclude that the average time lag is on average closer to six months than it is to zero.

Use of the SEM framework in this study reveals a time lag that may not be detected using simpler statistical techniques, but also comes with inherent disadvantages. One is that the models require use of data collected at discrete time intervals. Thus a major advantage of our study population in this context is the regularity of the testing interval; 72% of intervisit intervals were within \(\pm30\) days of six months, and 85% were within \(\pm60\) days. Additionally, the shortest actual time interval was 161 days, and so there are none of the unrealistically large rates of change of structure or function that could occur if tests happened only a few days apart.

A bigger caveat with the results is the unusual decision to include study visits with unreliable test results to minimize the proportion of missing data. Only 0.9% of OCT images had quality score <15, the manufacturer’s recommended cutoff. Of the visual fields, 0.9% had >15% false-positive results. A far higher proportion of visual fields, 16.0%, had >20% fixation losses; most of those tests did in fact have subjectively acceptable fixation as viewed by the technician on the instrument’s monitor, with the recorded level of fixation losses reflecting inaccurate mapping of the blind spot in the initial phase of the test. Moreover, the effect of these unreliable results can safely be assumed to just be an increase in test-retest variability, rather than imparting any bias on the results, because they are distributed randomly through a patient’s test series. Indeed, the goodness-of-fit measures reported in Table 2 were consistently slightly worse when restricting the data to reliable tests only, possibly because of the reduced sample size. Excluding data from a single visit could reduce the number of available pairs of consecutive intervals by three. Given the reduction in power of SEMs caused by missing data,\(^15\) even in a case such as this where the data can be considered as missing completely at random, it was felt preferable to include all data for the primary analysis. Reassuringly, the secondary analysis restricted to only reliable test results gave very similar model fits. The coefficients were of slightly larger magnitude, indicating that the data from the previous time period or other modality were slightly more predictive due to being more reliable, but differences were small.

The primary analysis used global measures of both function and structure, which have lower variability due to averaging out much of the measurement noise. Results were very similar when using localized analyses, which compared the average sensitivities at 21 visual field locations against the RNFLT within the corresponding 80° sector, strengthening our confidence in the conclusions. With our current data, the higher variability precludes performing more localized or pointwise analyses, but these would be of interest once more data is available.

Even with global measures, the goodness-of-fit indexes reported in Table 2 are weaker than those typically recommended when using SEMs. Commonly-used definitions of a “good fit” would be TLI > 0.90, or AGFI > 0.90; various cutoffs for RMSEA have been suggested from <0.05 to <0.10.\(^24\) However, use of these kinds of fixed cutoffs has been criticized, because it does not take into account the nature of the data or of the research question.\(^22\) In particular, AGFI reflects the percentage of variance explained, adjusted for the number of free parameters, analogous to...
the more familiar adjusted $R^2$ for regression models. Given the well-known variability of perimeter measures in particular, a method that can explain 60% to 70% of the variance in the rate of change between two visits should probably be considered as an impressively good fit to the data; the standard SEM cutoff of explaining 90% of the variance is unrealistic given the level of measurement variability.

The conclusions drawn are specific to the test modalities used. In particular, minimum rim width (MRW) may show changes sooner than RNFLT. It could be hypothesized that the observed time lag may not be present or may even be reversed, when considering MRW versus SAP instead of RNFLT versus SAP.

SAP sensitivities were transformed onto a linear 1/Lambert scale before averaging, because this has been reported as resulting in a more linear structure-function relation. However, the true relation may be better represented by a nonlinear or segmented linear fit. The Size III stimulus is larger than Ricco’s area in early glaucoma, potentially causing SAP to underestimate RGC loss and hence RNFL thickness; whereas at more damaged locations Ricco’s area expands and exceeds this stimulus size. For this study, information was averaged across multiple locations, often including some locations with sensitivities above this break point and others below, and so the impact of this caveat is hard to predict; but it seems unlikely that it would cause functional changes to artefactually appear to precede structural changes as seen in our results.

A final caveat is that the cohort consists mostly of patients with early glaucoma or glaucoma suspects. Furthermore, both eyes are tested even if only one eye has developed glaucomatous damage, on the basis that the fellow eye is at increased risk of developing glaucoma. Indeed, only 19% of eyes had MD worse than −3 dB at the start of their series, and 8% worse than −6 dB. The presence and magnitude of the time lag between changes in function and in RNFLT may vary through the course of the disease process.

In summary, we present evidence of a time lag of several months, whereby loss of visual function precedes and is predictive of thinning of the RNFL in human glaucoma. This does not negate previous findings suggesting that change in RNFLT may be detectable sooner using current testing techniques, because of lower variability, meaning that less change is needed to be outside normal limits. However, the presence of a time lag should be taken into account when considering the pathophysiologic mechanisms that cause glaucomatous damage. It also encourages the development of improved and less variable functional testing, and use of alternative structural measures, which may allow earlier detection of damage and provide better prognostic information about disease progression.

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