Estimating Normative Limits of Heidelberg Retina Tomograph Optic Disc Rim Area with Quantile Regression

Paul H. Artes¹ and David P. Crabb²

PURPOSE. To investigate why the specificity of the Moorfields Regression Analysis (MRA) of the Heidelberg Retina Tomograph (HRT) varies with disc size, and to derive accurate normative limits for neuroretinal rim area to address this problem.

METHODS. Two datasets from healthy subjects (Manchester, UK, n = 88; Halifax, Nova Scotia, Canada, n = 75) were used to investigate the physiological relationship between the optic disc and neuroretinal rim area. Normative limits for rim area were derived by quantile regression (QR) and compared with those of the MRA (derived by linear regression). Logistic regression analyses were performed to quantify the association between disc size and positive classifications with the MRA, as well as with the QR-derived normative limits.

RESULTS. In both datasets, the specificity of the MRA depended on optic disc size. The odds of observing a borderline or outside-normal-limits classification increased by ~10% for each 0.1 mm² increase in disc area (P < 0.1). The lower specificity of the MRA with large optic discs could be explained by the failure of linear regression to model the extremes of the rim area distribution (observations far from the mean). In comparison, the normative limits predicted by QR were larger for smaller discs (less specific, more sensitive), and smaller for larger discs, such that false-positive rates became independent of optic disc size.

CONCLUSIONS. Normative limits derived by quantile regression appear to remove the size-dependence of specificity with the MRA. Because quantile regression does not rely on the restrictive assumptions of standard linear regression, it may be a more appropriate method for establishing normative limits in other clinical applications where the underlying distributions are nonnormal or have nonconstant variance. (Invest Ophtalmol Vis Sci. 2010;51:355–361) DOI:10.1167/iovs.08-3354

Confocal Scanning Laser Tomography with the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering GmbH, Heidelberg, Germany) is widely used in the management of patients with ocular hypertension and glaucoma. Although the greatest strength of this technology lies in its ability to measure progressive changes in optic nerve head surface topography over time,¹⁻³ it is also widely used to help detect optic discs that appear suspicious for glaucomatous damage (diagnosis).⁴⁻⁵ This application is particularly important in primary care or screening settings where expert optic disc assessment is not readily available.⁶⁻⁷ Owing to the large variation in optic disc appearance in healthy subjects and patients with glaucoma,⁸⁻¹⁰ recognition of early optic disc damage is not a trivial task.

One diagnostic tool incorporated into the software of the HRT is the Moorfields Regression Analysis (MRA).¹¹ This analysis is based on the well-established relationship between optic disc size and rim area: Large discs tend to have larger rim areas than small discs.⁹,¹²,¹³ By comparing the measured area of neuroretinal rim to normative limits established in a group of healthy subjects, globally as well as in six separate sectors, the MRA classifies discs as “within normal limits,” “borderline,” or “outside normal limits.” The principles of the MRA are intuitive and transparent, and its performance compares well to that of expert observers¹⁴,¹⁵ and other, more complex statistical analyses such as linear discriminant functions or machine-learning classifiers.¹⁶⁻¹⁸

However, several groups have reported that the diagnostic outcomes of the MRA are not independent of optic disc size.⁶,¹⁵,¹⁶,¹⁹⁻²³ In healthy eyes, large optic discs are more often classified as borderline or outside normal limits than are medium-sized or small optic discs.²⁰⁻²⁵ Conversely, in eyes with glaucoma, the MRA is less sensitive in small discs than in large ones.⁵,¹⁶,¹⁹,²² Since the loss of neuroretinal tissue may reveal itself less readily in small discs, the lower sensitivity of the MRA in such discs is understandable. However, as the analysis has been specifically designed to accommodate the variation of optic disc size in healthy subjects, its failure to provide uniform specificity is disappointing. This finding is particularly troubling because clinicians may show a similar bias in overcalling glaucomatous damage in large but healthy discs.¹⁰,²⁴

The normative limits of the MRA use the prediction intervals of ordinary least-squares (OLS) regression, which emphasize the central values of the distribution but fail to accurately model the extreme values. In particular, these intervals can give spurious results when the variance changes across the range of the independent variable, as is the case with rim area against increasing optic disc size.²⁵ Although a logarithmic transformation of rim area was performed, it did not completely equalize the variation of the data across the large spectrum of optic disc sizes.¹¹ It is likely, therefore, that the unequal specificity of the MRA is, at least in part, caused by a failure of OLS regression to accurately predict the lower limits of neuroretinal rim area in healthy subjects.²⁰

Quantile regression (QR) is a family of methods designed to model changes in the shape of a distribution across the spec-

From ¹Ophthalmology and Visual Sciences, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada; and the ²Department of Optometry and Visual Science, City University, London, United Kingdom.


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Corresponding author: Paul H. Artes, Ophthalmology and Visual Sciences, Dalhousie University, Room 2035, West Victoria, 1276 South Park Street, Halifax, Nova Scotia, B3H 2Y9; Canada; paul@dal.ca.

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trum of an independent variable. These methods have been designed for situations where the extremes of a distribution change at different rates from that of the average. Since these methods can directly estimate the extremes (quantiles) of a distribution, they may be particularly appropriate for deriving normative reference limits (e.g., the fifth percentile) with diagnostic tests. In this article, we show that quantile regression provides a somewhat simpler yet more accurate approach (compared to OLS regression) for modeling the relationship of optic disc size and the lower limits of rim area in healthy subjects. We demonstrate that normative limits for rim area derived by quantile regression remove the size-dependent variation in specificity reported with the MRA. Finally, we briefly discuss other potential applications of quantile regression techniques in ophthalmology.

METHODS

Datasets

The data for this project were obtained from two independent prospective studies, one at the Royal Eye Hospital in Manchester (UK), the other at the QEI1 Eye Centre of Queen Elizabeth II Health Sciences Centre in Halifax (Nova Scotia, Canada). The two datasets are briefly described in the next sections, and the demographics are shown in Table 1. In both studies, optic disc images from healthy subjects and patients with glaucoma were obtained with the HRT 1 and subsequently converted to HRT 3 format. Contour lines had been drawn by experienced clinicians and were all reviewed by one of the authors (PHA) at the outset of the study.

The emphasis of this study was primarily on the specificity in healthy eyes. Patients with glaucoma were included only to investigate how the altered normative limits affect the sensitivity of the analysis in eyes with glaucomatous damage. The studies from which both datasets were drawn followed the tenets of the Declaration of Helsinki and were approved by the Institutional Review Boards of both centers. All participants had provided written informed consent.

Manchester Dataset. Healthy subjects had been recruited from patients’ spouses and through advertisements in public areas. They had a normal eye examination, intraocular pressure <22 mm Hg, and normal results in a visual field examination with a Humphrey Field Analyzer (HFA) 24-2 full-threshold test (Glaucoma Hemifield test result within normal limits, corrected pattern standard deviation $P > 0.10$).

Patients with glaucoma were recruited consecutively from the clinics at the Manchester Royal Eye Hospital. Inclusion criteria were a diagnosis of open-angle glaucoma and a repeatable visual field defect (either Glaucoma Hemifield test result outside normal limits, or corrected pattern standard deviation $P < 0.05$). If both eyes were eligible, one eye was randomly selected as the study eye.

For both groups of participants, the inclusion criteria stipulated a refractive error within $\pm 5.00$ D sphere and $\pm 5.00$ D astigmatism and a best-corrected visual acuity better than $6/18$ (+0.5 logMAR). If participants were enrolled in the longitudinal arm of the study, we selected the image in which the mean pixel height standard deviation (MPHSD, a HRT-specific measure of image quality), was closest to the median value observed during the entire follow-up; thus, we analyzed the most representative image of the available series.

Halifax Dataset. Healthy subjects had been recruited from seniors’ groups, local church organizations, and employees of a local telephone company. They had a normal ocular examination, intraocular pressure $<21$ mm Hg, and a negative family history of glaucoma. Patients with glaucoma had a visual field MD between $-2$ and $-10$ dB, open anterior chamber angles by gonioscopy, and no concomitant ocular or systemic disease known to affect the visual field.

In both groups of subjects, the inclusion criteria stipulated best corrected VA better than 6/12 (+0.3 logMAR) and refractive error within $\pm 5.00$ D sphere and $\pm 3.00$ D astigmatism. One eye of each participant was selected as the study eye, and since both groups of participants were observed longitudinally, we selected the most representative image of the available series based on the median MPHSD.

Table 1. Demographic Details of the Two Datasets

<table>
<thead>
<tr>
<th></th>
<th>Manchester</th>
<th>Halifax</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>$n$</td>
<td>88</td>
<td>146</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>59.3 ± 11.1</td>
<td>70.2 ± 9.7</td>
</tr>
<tr>
<td>Optic disc size, mm$^2$, mean ± SD</td>
<td>1.85 ± 0.46</td>
<td>2.04 ± 0.43</td>
</tr>
<tr>
<td>(min, max)</td>
<td>(1.05, 3.24)</td>
<td>(1.19, 3.37)</td>
</tr>
<tr>
<td>Visual field MD, dB</td>
<td>$-0.4 ± 1.1$</td>
<td>$-6.1 ± 6.1$</td>
</tr>
</tbody>
</table>

Analyses

Quantile Regression: A Brief Description. The term quantile is synonymous with percentile; the median is the best-known example of a quantile, being the 50th in a ranked distribution of numbers. If we say that an infant’s height is at the 95th quantile, then they are taller than the proportion $r$ of the reference group of infants and shorter than the proportion $1 - r$. The median (50th), lower (25th) and upper (75th) quartiles are specific quantiles. The 95% reference interval commonly used for measurements in medicine captures the data between the 2.5 and 97.5 quantiles. Often a measurement varies with age, such as in infant growth, and the challenge is to estimate the 95% reference intervals at different specific ages. The problem then becomes one of regression where limits around the average (mean) relationship between, say, the infant’s height and age are captured. However, just as a mean often gives an incomplete picture of a single distribution of numbers (it only indicates the center of the distribution), so the single OLS regression line gives only an incomplete picture of the relationship between two variables. The alternative is quantile regression. Just as classic linear regression methods based on minimizing sums of squared residuals enables one to estimate models for conditional mean functions, regression quantile methods offer a mechanism for estimating models for the conditional median function, and the full range of conditional quantile functions. Estimation here is based on a weighted sum (with weights depending on the order of the quantiles) of absolute values of residuals. In short, we can generate a regression line at any point in the distribution of values, and this is what we sought to do with rim area against optic disc size in this work. There are variants on how to fit the lines but we have adopted the standard method used in a package quantreg from the open-source statistical programming environment R. For more technical detail, the statistically minded reader is directed toward. For more accessible descriptor of the methods are referred to a well-written paper by Cade and Noon.

Application of Quantile Regression to the Datasets. To investigate the association between optic disc size and MRA outcome, proportional odds logistic regression analyses were performed separately in healthy subjects and patients with glaucoma. These analyses
established how the odds \( \frac{p}{1 - p} \) of observing a positive test (MRA classification of borderline or outside normal limits) vary with a change in the predictor variables (disc area, in units of 0.1 mm², and age).

The relationships between neuroretinal rim area and disc size in healthy subjects were examined globally as well as in six separate sectors of the optic disc. OLS regression, as used in the MRA, was performed with log-transformed rim area as the dependent variable and disc area as the independent variable, and compared to the results from quantile regression, with quantile limits of 10%, 5%, 2%, and 1%. Quantile regression was also performed on untransformed (linear) rim area and disc area.

Our hypothesis was that normative limits for rim area derived by quantile regression would remove the dependency of specificity on optic disc size. We therefore performed an MRA-type analysis using normative limits derived by quantile regression (Quantile Regression Analysis, QRA). A range of QRA quantiles was investigated to find those that matched, approximately, the classification criteria of the MRA (false-positive rate in healthy subjects; true-positive rate in patients with glaucoma). The logistic regression analyses were then repeated with the QRA and compared with the results of the MRA.

The quantile regression analyses were performed with the open-source statistical programming environment R.35,34

**RESULTS**

In both datasets, the specificity of the MRA appeared dependent on the size of the optic disc. The magnitude of the effect was similar in the Manchester and Halifax datasets: The odds of a borderline or outside-normal-limits classification increased by 10% and 15% for each 0.1-mm² increase in disc size, respectively (Table 2). Healthy discs classified as borderline or outside normal limits were significantly larger than those classified as within normal limits (Mann-Whitney, \( P < 0.05 \)).

To determine the cause of the size-dependent loss in specificity with the MRA, we reexamined the relationship of log-transformed rim area with optic disc area in the two datasets (Fig. 1). In both datasets, the relationship between log rim area and disc area was similar to that previously reported.11 However, Figure 1 also shows that the log transform of rim area did not equalize the scatter around the regression line. The increase in variance was statistically significant in both datasets (\( P < 0.05 \), Levene’s test).

The increase in variance of log rim area with increasing disc size was more clearly apparent when the residuals (observed values minus values predicted by linear regression) were plotted against disc area (Fig. 2).

OLS regression requires that the “errors” in the independent variable come from a Gaussian distribution with uniform variance. The nonuniformity of variance (heteroscedasticity) in the logarithmically transformed rim area values violates this assumption. Although this has little effect on the actual regression line, it does affect the prediction limits on which the MRA is based. Under the assumption of equal variance, the prediction limits are too small (overly specific) for small discs, and too large for large discs.

An alternative technique to investigate the suitability of the OLS regression is the coefficient plot (Fig. 3). Simply put, this is a plot of the individual slopes of all the regression lines that might exist across the distribution of disc area size. Under the assumptions made by OLS regression, the relationship between the dependent and independent variables should be equal for different quantiles of the data. If the line was flat, running

**TABLE 2. ORs for the Effect of Optic Disc Size and Age on Outcomes of the MRA in Healthy Subjects, Determined by Proportional-Odds Logistic Regression**

<table>
<thead>
<tr>
<th>MRA Control Subjects</th>
<th>Optic Disc Area (0.1 mm²)</th>
<th>Age (y)</th>
</tr>
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<tbody>
<tr>
<td>Manchester, ( n = 88 )</td>
<td>1.10 (0.99–1.22)</td>
<td>1.06 (1.02–1.11)</td>
</tr>
<tr>
<td>( P = 0.07 )</td>
<td>( P = 0.006 )</td>
<td></td>
</tr>
<tr>
<td>Halifax, ( n = 76 )</td>
<td>1.15 (1.02–1.29)</td>
<td>1.00 (0.96–1.04)</td>
</tr>
<tr>
<td>( P = 0.02 )</td>
<td>( P = 0.89 )</td>
<td></td>
</tr>
<tr>
<td>Combined, ( n = 164 )</td>
<td>1.10 (1.02–1.18)</td>
<td>1.03 (1.00–1.06)</td>
</tr>
<tr>
<td>( P = 0.01 )</td>
<td>( P = 0.04 )</td>
<td></td>
</tr>
</tbody>
</table>

Data are OR (95% confidence interval [CI]).

**FIGURE 1.** Relationship between the logarithmically transformed global rim area and disc area in the healthy subjects from Manchester and Halifax. The OLS regression line (heavy line) provides a reasonable fit to the average. The prediction limits (5%, 0.5%) are parallel to the regression line, displaced by multiple standard deviations of the residuals. Because the scatter around the regression line increases with optic disc size, the prediction limits do not describe the extremes of the rim area distribution well.

**FIGURE 2.** The relationship between the residuals (observed values minus predicted values) in logarithmically transformed global rim area and disc area in the healthy subjects from Manchester and Halifax clearly shows an increase in the variance with increasing rim area. The 5% and 0.5% prediction limits, derived under the assumption of equal variance, are therefore overly conservative in small discs and not sufficiently conservative in large discs.
against disc size in the combined dataset. The 10% and 2% limits derived by quantile regression of rim area were larger (more sensitive, less specific) for small discs and smaller (more specific, less sensitive) for large discs. In the two datasets we evaluated in this study, quantile regression classified healthy optic discs independently of their size, removing the size-related bias of the MRA.

Our hypothesis was that normative limits for rim area derived by quantile regression should remove the dependency of specificity on optic disc size. We therefore created an MRA-type analysis based on the rim area limits derived by quantile regression globally as well as in the six disc sectors (QRA). Quantiles of 10% and 2% were found to match, approximately, the median. The QRA coefficients (intercepts and slopes) derived from the combined dataset for the global and sectoral rim area limits of 10%, 5%, 2%, and 1% are available online as Supplementary Material at http://www.iovs.org/cgi/content/full/51/1/355/DC1.

**DISCUSSION**

Our analyses confirmed that the low specificity of the MRA in large healthy optic discs is most likely due to a bias in the normative limits, caused at least in part by the failure of linear regression to accurately model the extremes of the rim area distribution. Compared to the MRA, the normative limits derived by quantile regression were larger (more sensitive, less specific) for small discs and smaller (more specific, less sensitive) for large discs. In the two datasets we evaluated in this study, quantile regression classified healthy optic discs independently of their size, removing the size-related bias of the MRA.

One important limitation of our study is that we applied normative limits to the same group of healthy subjects from which we derived them. Ideally, we would have derived and

The overall agreement between MRA and QRA was high, in healthy subjects as well as in patients (κ > 0.75). There were no cases in which the analyses disagreed by more than one category (i.e., between within normal limits and outside normal limits; Table 4).

The 12 healthy subjects (7%) in which the QRA indicated a less positive result than the MRA (a shift from borderline to within normal limits, or a shift from outside normal limits to borderline) had larger discs (mean 2.39 mm², SD 0.40; P < 0.001, Wilcoxon) than those whose classification did not change (mean, 1.85; SD 0.44 mm²). The six healthy subjects (4%) in whom the QRA gave a more positive result than the MRA had smaller discs (mean differences, 0.23 and 0.28 mm², NS).

In the glaucomatous eyes, the size differences between discs in which the QRA gave a different classification from the MRA were smaller and not statistically significant. Similarly, the odds ratios for disc size in the glaucoma eyes were slightly smaller with the QRA than the MRA, but a comparison of the relatively large confidence intervals indicated that these changes were not statistically significant (Table 5).

The QRA coefficients (intercepts and slopes) derived from the combined dataset for the global and sectoral rim area limits of 10%, 5%, 2%, and 1% are available online as Supplementary Material at http://www.iovs.org/cgi/content/full/51/1/355/DC1.

**Figure 4.** The relationship between disc size and rim area (untransformed) described by quantile regression. *Heavy line:* the median; *light lines:* 10% and 2% limits. Since the variance increases with disc size, the 10% and 2% limits have a shallower slope than the median.
tested the performance of the limits in separate, independent samples. Quantile regression relies on fewer assumptions than OLS regression, but it requires a larger number of data points to provide meaningful estimates for the more extreme quantiles (e.g., 2%). Because both groups of healthy subjects used in this research were relatively small (n = 88 and 76), we were unable to estimate robust normative limits without pooling the samples. However, the increased variance of log-transformed neuroretinal rim area in larger optic discs was similarly evident in both independent datasets (Figs. 1, 2) and has also been reported by other groups,20 and we therefore believe that quantile regression is the correct approach. However, the true specificity of the quantile regression limits, for any given nominal value, should be estimated from a larger population-based dataset, independent of those used in the present study, but such data are available.6

The quantile regression limits reduced the size-related differences in sensitivity with glaucomatous disc, but in the sample of data considered in this study this effect was small and not statistically significant (Table 4). Because the quantile limits systematically predict a slightly larger rim area in small discs compared with OLS regression, a minor increase in sensitivity to damage in small optic discs is likely to be a true effect. However, quantile regression may not eliminate the principal problem of the HRT in detecting cupping in small optic discs, and as such the small gain in sensitivity may not be clinically meaningful. A similar problem has been shown with other diagnostic analyses of the HRT, for example the GPS,22 and with expert classification by clinicians.10,24

**FIGURE 5.** Comparison of normative limits of optic disc rim area derived by quantile regression (QR, heavy line) and OLS regression, for 10% (top) and 2% (bottom). To facilitate comparison, the plots on the left show untransformed rim area whereas those on the right are shown with the logarithmic transform of rim area; both sides show the same data and the same fits. One data point in the extreme top right has been omitted in the plots but not in the fits.

**TABLE 3.** ORs Determined by Proportional-Odds Logistic Regression Relating Optic Disc Size and Age to Outcomes of QRA in Healthy Subjects

<table>
<thead>
<tr>
<th>QRA Healthy Subjects</th>
<th>Optic Disc Area (0.1 mm²)</th>
<th>Age (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manchester, n = 88</td>
<td>1.00 (0.99–1.01)</td>
<td>1.07 (1.02–1.11)</td>
</tr>
<tr>
<td></td>
<td>P = 0.39</td>
<td>P = 0.005</td>
</tr>
<tr>
<td>Halifax, n = 76</td>
<td>1.00 (0.99–1.01)</td>
<td>1.01 (0.97–1.06)</td>
</tr>
<tr>
<td></td>
<td>P = 0.97</td>
<td>P = 0.51</td>
</tr>
<tr>
<td>Combined, n = 164</td>
<td>1.00 (0.99–1.01)</td>
<td>1.04 (1.01–1.07)</td>
</tr>
<tr>
<td></td>
<td>P = 0.81</td>
<td>P = 0.01</td>
</tr>
</tbody>
</table>

Data are OR (95% CI). Quantiles of 10% and 2% were selected for borderline and outside-normal-limits classifications to match, approximately, the criteria of the MRA.

**TABLE 4.** Agreement between QRA and MRA in Healthy Subjects and Patients with Glaucoma

<table>
<thead>
<tr>
<th></th>
<th>QRA</th>
<th>MRA</th>
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<tbody>
<tr>
<td></td>
<td>Within</td>
<td>Borderline</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>103</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>4</td>
</tr>
<tr>
<td>Patients with glaucoma</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>109</td>
<td>39</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>45</td>
</tr>
</tbody>
</table>

Healthy subjects (n = 164; data in bold); patients with glaucoma (n = 252). Quantile regression limits had been set at 10% and 2% to match the positive rates of the MRA (nominally 5%, 0.1%). The κ values were 0.77 (healthy subjects) and 0.86 (patients).
An overall comparison between the classifications derived from quantile regression (QRA) and those of the MRA indicates close agreement. This is not surprising, given that disagreements are expected only in particularly large and small discs. However, even small differences in specificity may have important implications for clinical practice—a difference between 90% and 98%, for example, means a fivefold reduction in the rate of false-positive decisions. Clinical anecdote abounds on the problems of false-positive decisions with large discs, and differences of this magnitude are certainly very important in screening situations where the prevalence of the disease is low.

Decision support systems such as the MRA can provide useful guidance and do not claim to provide statistically sound estimates of the likelihood of disease. Nevertheless, they should be based on the most appropriate statistical methods to make it easier to interpret the findings. With the MRA, the false-positive rates reported in empiric studies have often been much larger than expected from the nominal designations (5% and 0.1% for borderline or outside normal limits). As the comparison to normal limits is performed seven times (globally, as well as in six optic disc sectors), it is clear that the overall false-positive rate must be somewhat higher than the nominal value. However, in our study, the positive rates of the MRA were matched, approximately, by the 10% and 2% limits of quantile regression. In part, this discrepancy may be due to systematic differences between the datasets in our study and those used by the manufacturers of the instrument, but it is also not unlikely that the distribution of rim area (or log rim area) has longer tails than a normal distribution.84 If this were the case, one would expect that the quantile regression normative limits would provide false-positive rates closer to their nominal designations. In the absence of a large independent dataset we were unable to confirm this hypothesis, this remains an objective of future research.

Methods to estimate empiric normative limits for diagnostic decision-making have been the subject of much research.87 The classic application for quantile regression in medicine, for example, is the relationship between age and height or weight in children as modeled by growth curves.88 This is one example of an application where the extremes of a distribution change at rates different from the average, leading to changes in the shape and/or the variance. In vision science, similar phenomena are likely to occur with psychophysical tests that exhibit ageing effects (for example in perimetry).39–41 If ageing changes were to vary between subjects, as seems likely, this would lead to a greater spread with increasing age. Quantile regression techniques may prove advantageous over other techniques for estimating limits of normality in these situations. We present this article to encourage the use of these methods, especially since the software to implement them is freely available and easy to use.

### Table 5

<table>
<thead>
<tr>
<th>MRA</th>
<th>QRA</th>
</tr>
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<tbody>
<tr>
<td>Manchester, n = 146</td>
<td>1.16 (1.06–1.26)</td>
</tr>
<tr>
<td></td>
<td>P = 0.002</td>
</tr>
<tr>
<td>Halifax, n = 106</td>
<td>1.20 (1.08–1.34)</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Combined, n = 252</td>
<td>1.16 (1.08–1.24)</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Data are OR (95% CI). Both analyses remain more sensitive to damage in larger optic discs.

### References


### Conclusions

The low specificity of the MRA with large optic discs is caused by systematically biased normative limits for rim area. Quantile regression, a method specifically designed to model the extremes of a distribution, appears to provide more accurate normative limits and remove the disc-size-related variation in specificity. These findings should be validated in a larger dataset of healthy subjects obtained from an epidemiologic survey.

### Acknowledgments

The authors thank Balwantray C. Chauhan, Marcelo T. Nicolecia, and Raymond P. LeBlanc (Dalhousie University, Halifax, Nova Scotia), and David B. Henson and Anna Kwartz (University of Manchester), for allowing us the use of their HRT datasets.


