The Normative Database for the RTVue

Software version 4.0

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Glaucoma is a multi-factorial optic neuropathy with characteristic structural changes and subsequent functional impairment. Specifically, this optic neuropathy is marked by a loss of retinal ganglion cells, thinning of the retinal nerve fiber layer (RNFL), thinning of the neuro-retinal rim, and enlarged cupping. It is thought these structural changes occur before detectable visual field loss occurs, and detecting early structural damage can allow for earlier treatment which in turn may result in better outcomes. Early detection allows for early treatment which has been shown to slow or delay further damage. The RTVue OCT can be helpful to detect glaucomatous damage by quantifying the RNFL thickness, the layers associated with the ganglion cells (i.e., the ganglion cell complex, see below), and the morphology of the optic disc including the cup and neuro-retinal rim.

A normative database provides a benchmark against which a given eye can be compared in order to determine the relative standing in comparison to a group of known healthy eyes. The normative database provides the standard against which eyes are compared to determine whether the scanned eye falls within the normal range of the database or outside this range. The comparison is based on probability values taken from the distribution of the values of the healthy eyes. The normative database is used to set cut-offs based on the statistical distribution of normal eyes, a patient's result is then compared to this normal distribution and when their value falls outside the normal range the software flags this result. The cut-offs used by the normative database are typically the bottom 5% of the normal distribution for a classification of 'Borderline' and 1% for a classification of 'Outside Normal Limits'. There are several important aspects of a normative database that can affect how well it performs. First, it is important how a 'normal' or healthy eye is defined. Secondly, there are certain factors that can affect the measured values in normals that should be taken into account when establishing the normal range and cut-offs. For example, it is known that the normal aging process results in the death of approximately 5,000 ganglion cells per year. Thus the normal value for a 40 year old will be different than the normal values for an 80 year old because of the natural aging process.

The protocol used for the RTVue normative database was submitted and approved by an independent IRB agency, Western IRB. The protocol outlined a rigorous procedure for data collection including stringent inclusion and exclusion criteria. In brief, participants were eligible if they were over 18, free from known ocular pathology, had IOP below 22 mm Hg, and had a normal visual field test based on the Humphrey 24-2 white on white test. The appearance of the optic disc was not used as an exclusion criterion because it could introduce bias in the database (potentially creating a so called 'super-normal' database). The results were correlated with age and optic disc size for the RNFL measures and because of the significant associations found for both, all measurements were corrected for the normal age and optic disc size effects.

Data Collection Sites

Fifteen clinical sites worldwide participated in the data collection, all following the approved protocol. These sites were:

US sites

     University of Alabama Birmingham, Birmingham Alabama

     University of Pittsburgh Medical School, Pittsburgh Pennsylvania

     University of Southern California, Los Angeles California

     New York Eye and Ear Infirmary, New York City, New York

     New York VA Hospital, St. Alban's, St. Albans, New York

     Bascom Palmer Eye Institute, Palm Beach Gardens, Florida

International sites

     Moorfields Eye hospital, London England

     Zhongshan Ophthalmic Center, Guangzhou China

     Beijing University, Beijing China

     Eye and Ear Hospital of Fudan University, Shanghai, China

     Tokyo University, Tokyo Japan

     Osaka University, Osaka Japan

     Toho University, Tokyo Japan

     Grewal Eye Institute, Chandigarh India

   LV Prasad Eye Institute, Hyderabad India

Results

     A total of 861 eyes were collected from the 15 clinical sites. The average age was just over 50 years old with a range from 19-82 years of age. The table below summarizes these results and breaks them down into ethnic specific databases. The RTVue software version 4.0 allows the user to choose the ethnicity of a patient and uses the appropriate ethnic specific database for comparison. This is important because the statistical analysis found significant differences among the ethnicities even when factoring in the effects of age and optic disc size.

Age

	Hispanic	Caucasian	African Desc.	Japanese	Chinese	Indian	All
n	96	158	81	160	247	119	861
avg age	39.4	54.6	49	55.3	50	51.4	50.7
sd age	14.7	16.9	11.8	14.9	14.8	13.7	15.5

range	19-71	22-82	22-70	22-78	23-75	20-76	19-82

Optic Disc Size
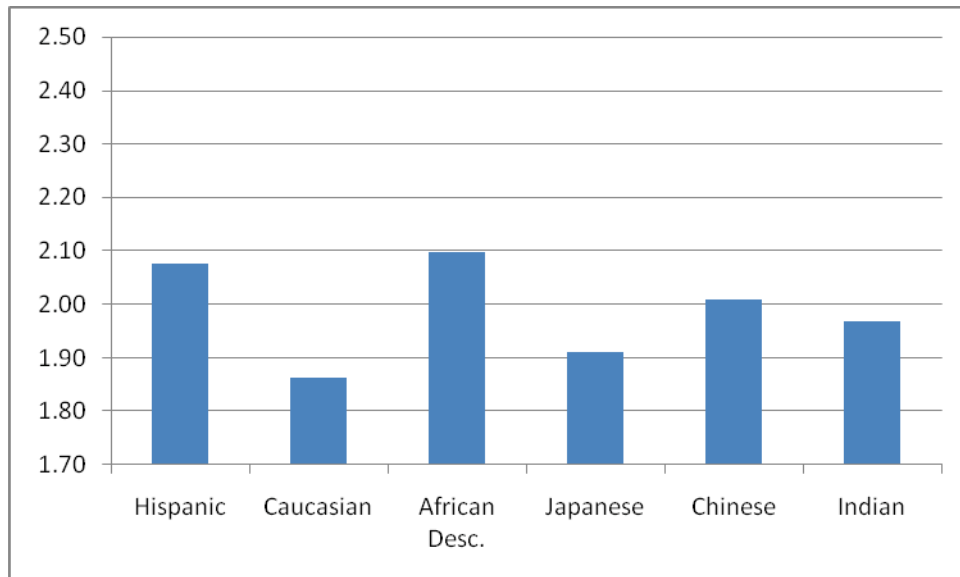
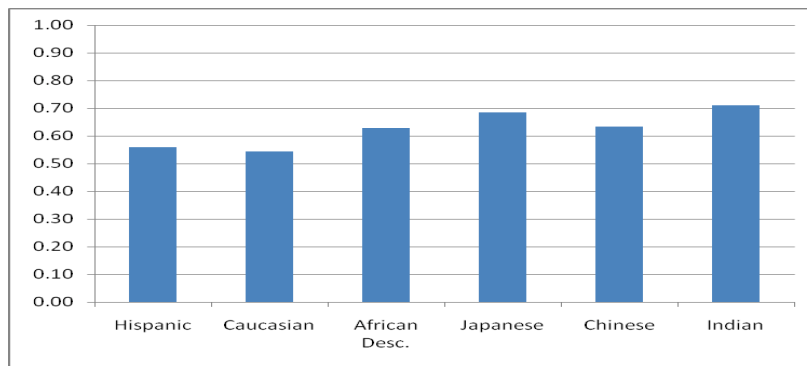| Disc Size	Hispanic	Caucasian	African Desc.	Japanese	Chinese	Indian	All
mean	2.08	1.86	2.10	1.91	2.01	1.97	1.97
sd	0.36	0.39	0.35	0.36	0.38	0.34	0.37
range	1.2-3.0	1.2-3.4	1.5-3.0	1.3-2.7	1.1-3.0	1.2-2.7	0.9-3.7

The average optic disc size is dependent on ethnicity. In our large sample of healthy eyes, indivisuals of African descent were found to have the largest optic discs, followed by Hispanics, Chinese, Indians, Japanese and then Caucasians. Although there is a wide range of overlap among all groups, the size differences were significant.
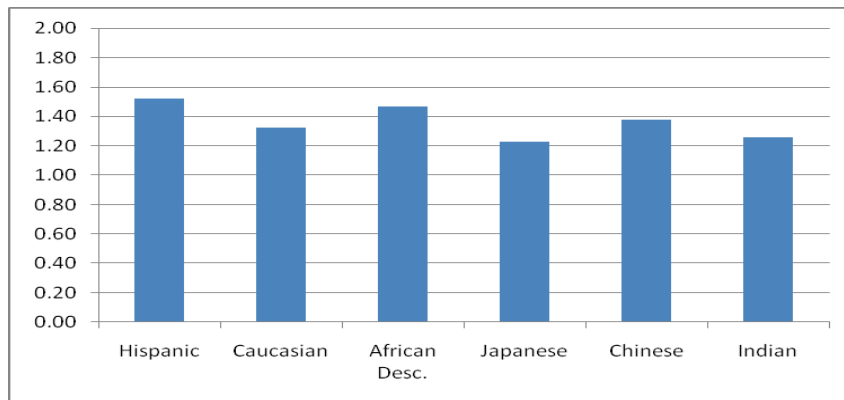
Vertical Cup to Disc Ratio
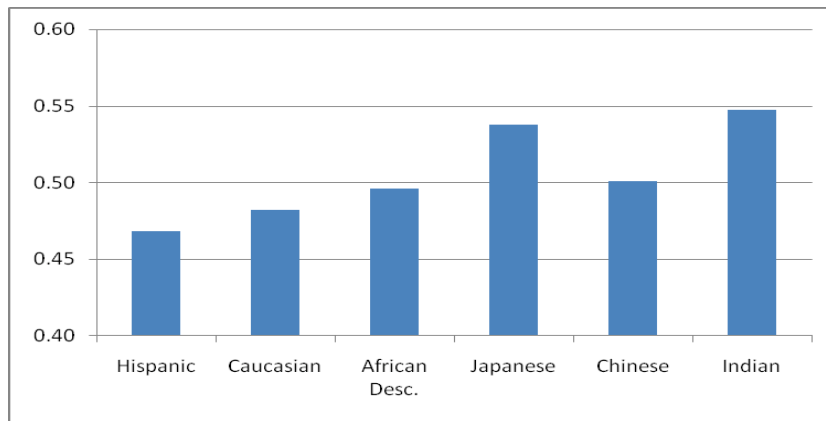
V. C/D	Hispanic	Caucasian	African Desc.	Japanese	Chinese	Indian	All
mean	0.47	0.48	0.50	0.54	0.50	0.55	0.51
sd	0.21	0.22	0.20	0.20	0.22	0.23	0.22

Cup Area

Cup Area	Hispanic	Caucasian	African Desc.	Japanese	Chinese	Indian	All
mean	0.56	0.54	0.63	0.69	0.63	0.71	0.63
sd	0.43	0.43	0.40	0.47	0.44	0.47	0.45

Rim Area

Rim Area	Hispanic	Caucasian	African Desc.	Japanese	Chinese	Indian	All
mean	1.52	1.32	1.47	1.23	1.37	1.26	1.35
sd	0.35	0.36	0.30	0.32	0.34	0.33	0.35

Average RNFL Thickness
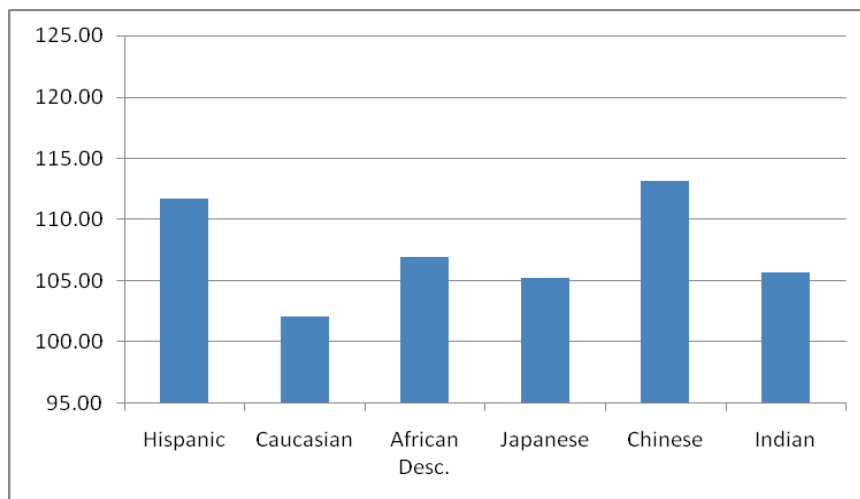
| Avg. RNFL	Hispanic	Caucasian	African Desc.	Japanese	Chinese	Indian	All
mean	111.71	102.14	106.96	105.28	113.18	105.71	107.90
sd	9.66	8.99	9.65	8.92	10.35	9.16	10.40

A multi-variate analysis using a linear model found significant differences between the various ethnic groups even when adjusting for effects due to age and optic disc size.
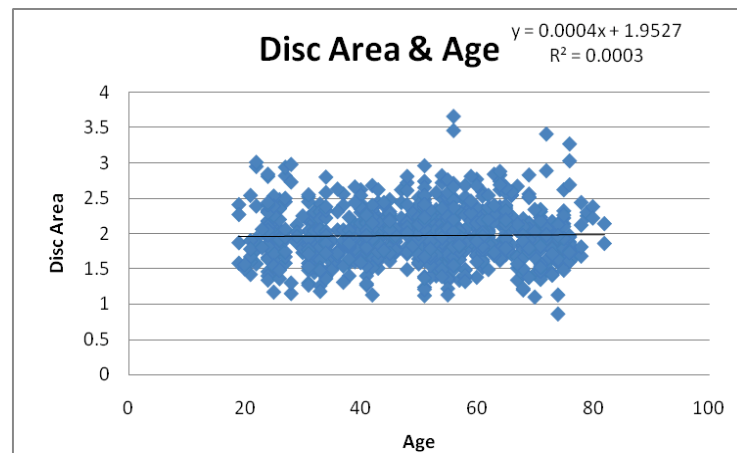
Correlations

The relationship between parameters and factors such as age, optic disc size, and signal strength was performed using a Pearson product correlation coefficient. These results are

summarized below in the following scatter plots. The linear regression line, equation, and R square value is shown for each figure.
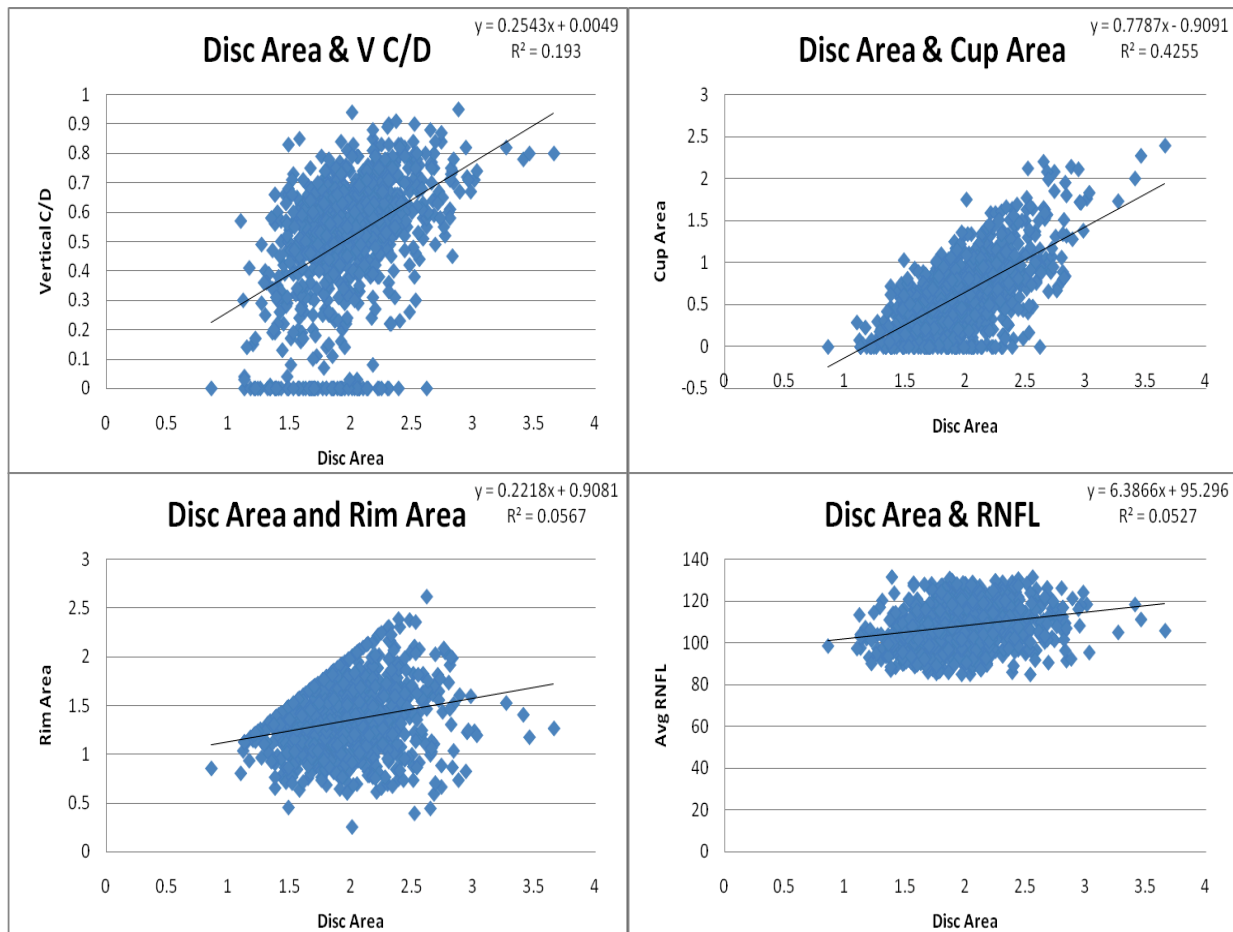
Signal Strength
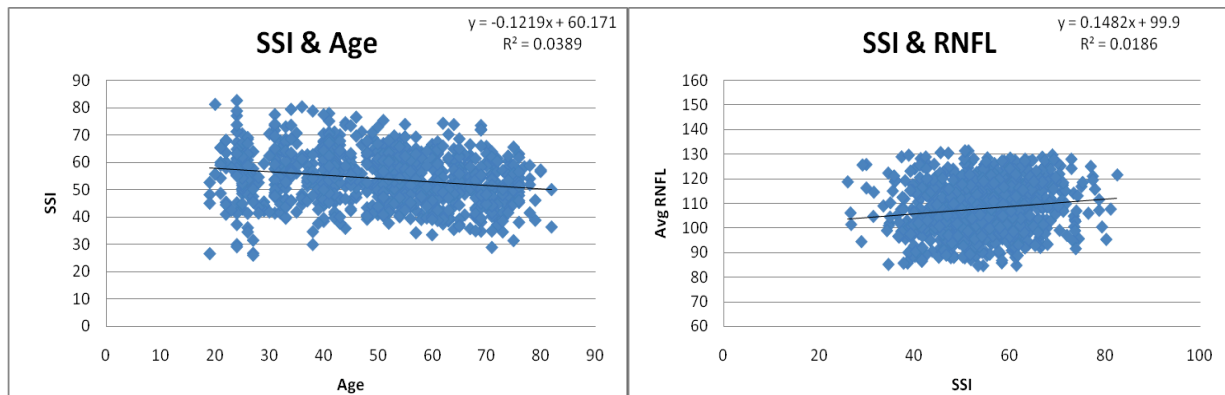
The signal strength of the scans was found to be correlated with age, where older individuals tended to have weaker signal strengths. This is likely du to the effect of media clarity within the eye and the formation of early cataracts. However the graph on the right shows that signal strength has only a weak effect on measured RNFL thickness. This means that while the scan strength tends to be weaker in older individuals, these weaker signal does not affect the RNFL thickness.
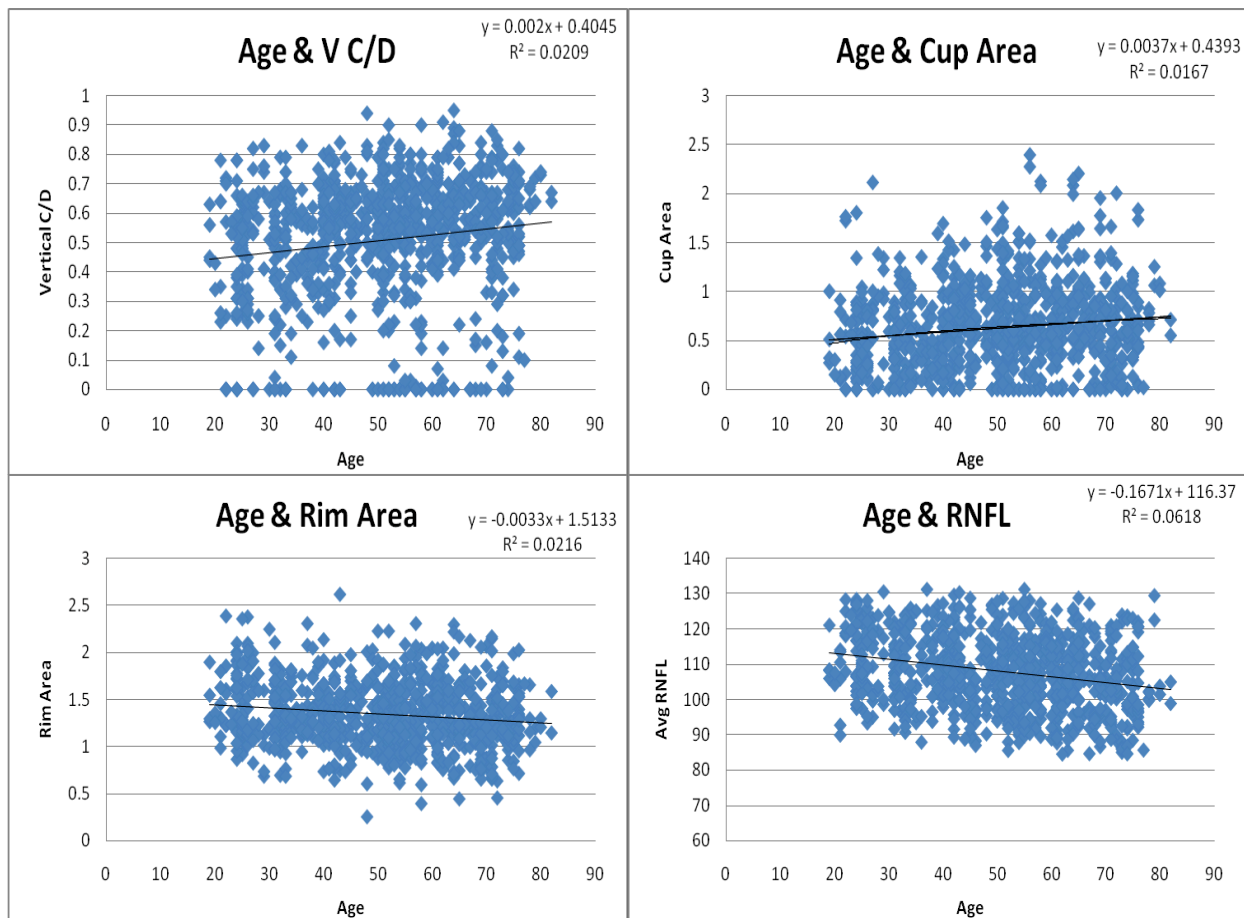

No effect of age on the size of the optic disc was found, as expected.

Disc Area

Disc Area & V C/D
$y = 0.2543x + 0.0049$
$R^2 = 0.193$

Disc Area & Cup Area
$y = 0.7787x - 0.9091$
$R^2 = 0.4255$

Disc Area and Rim Area
$y = 0.2218x + 0.9081$
$R^2 = 0.0567$

Disc Area & RNFL
$y = 6.3866x + 95.296$
$R^2 = 0.0527$

Strong correlations were found for the size of the optic disc and various optic disc structures such as the vertical cup to disc ratio (top left), cup area (top right), and rim area (bottom left). There was also a correlation with the average RNFL thickness, although not as strong. These correlations demonstrate the need to adjust cut-off values based on the size of the optic disc. For example, a vertical C/D of 0.8 may be within the normal range for an individual with a large optic disc, but would be abnormal for an individaul with a small optic disc.

Age

Age & V C/D — $y = 0.002x + 0.4045$, $R^2 = 0.0209$

Age & Cup Area — $y = 0.0037x + 0.4393$, $R^2 = 0.0167$

Age & Rim Area — $y = -0.0033x + 1.5133$, $R^2 = 0.0216$

Age & RNFL — $y = -0.1671x + 116.37$, $R^2 = 0.0618$

Strong correlations were found for age and all parameters, as expected. The strongest correlation with age was average RNFL thickness, however there was also a tendency to have increased cupping and larger C/D ratios with increased age as well as decreased rim area. Age is also an important consideration when establishing the normal range and appropriate cut-offs.

Age by Ethnicity for RNFL
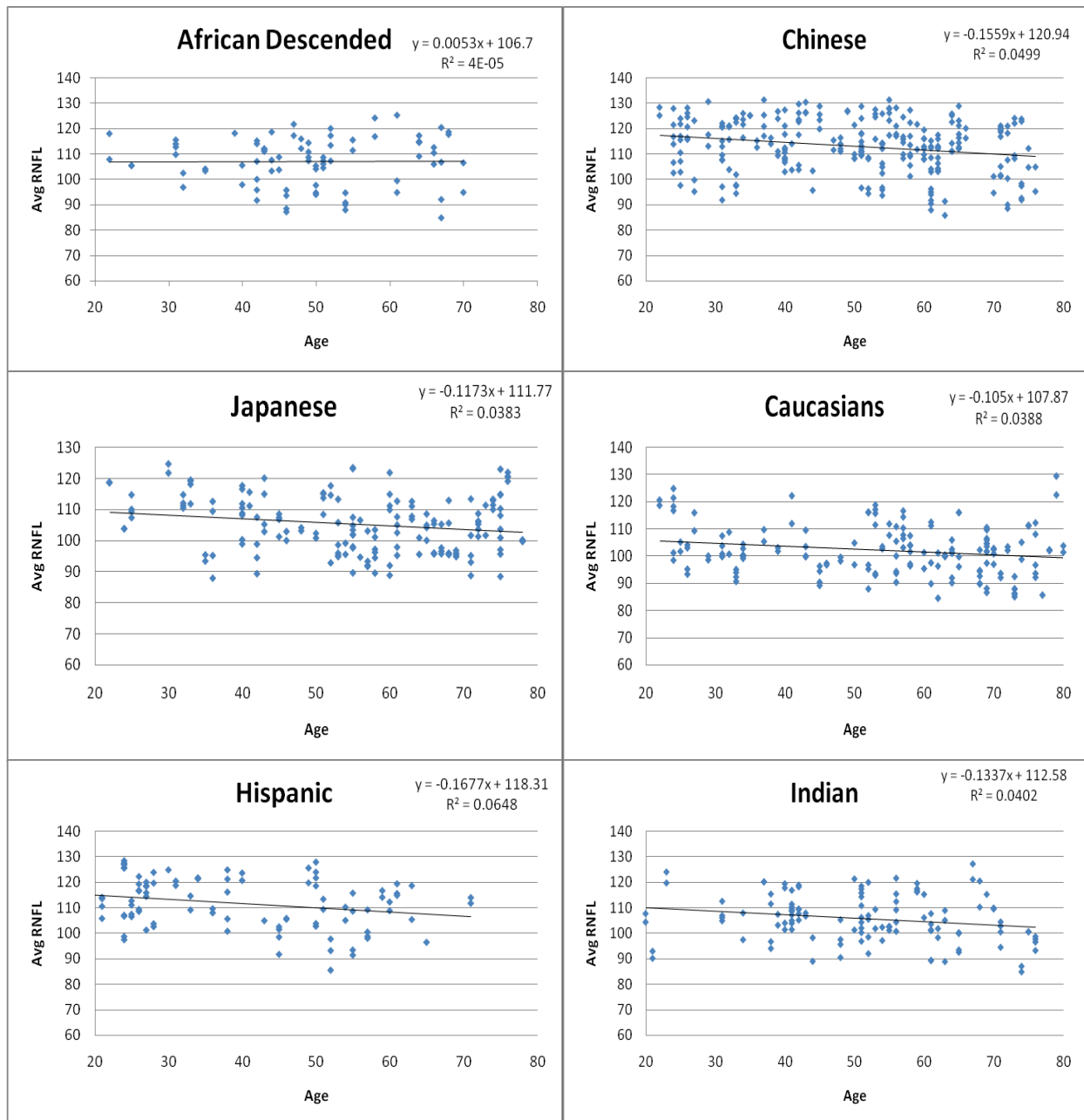
These figures show the relationship of age and RNFL thickness for each ethnic group in the normative database. RNFL thickness declines at a similar rate for all ethnicities, except for African Descended participants. However a statistical test found the slopes to not be significantly different, suggesting age affects all ethnicities similarly. A similar correaltion was found for optic disc size and RNFL thickness. This analysis found RNFL thickness increased similarly for all ethnicities with increasing optic disc size.

RNFL Variabiltiy Comparison by Database
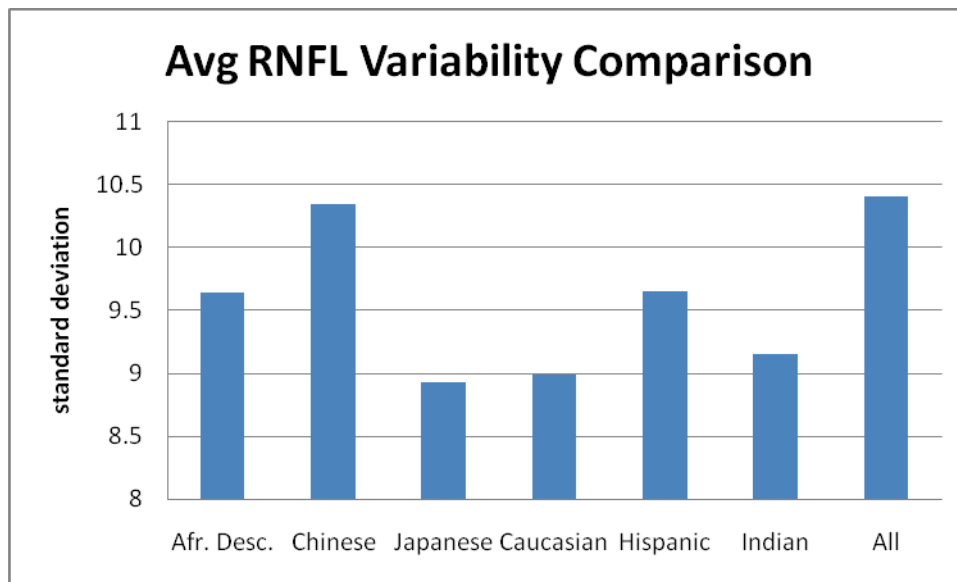
This figure plots the standard deviation of each normative database by ethnicity. Notice that when all data is combined (All column), the variability is actually greater than for each individual ethnic specific database. This is true even though there is a greater number of eyes in the combined data set. This shows the improvement of having separate normative databases for each ethnicity.
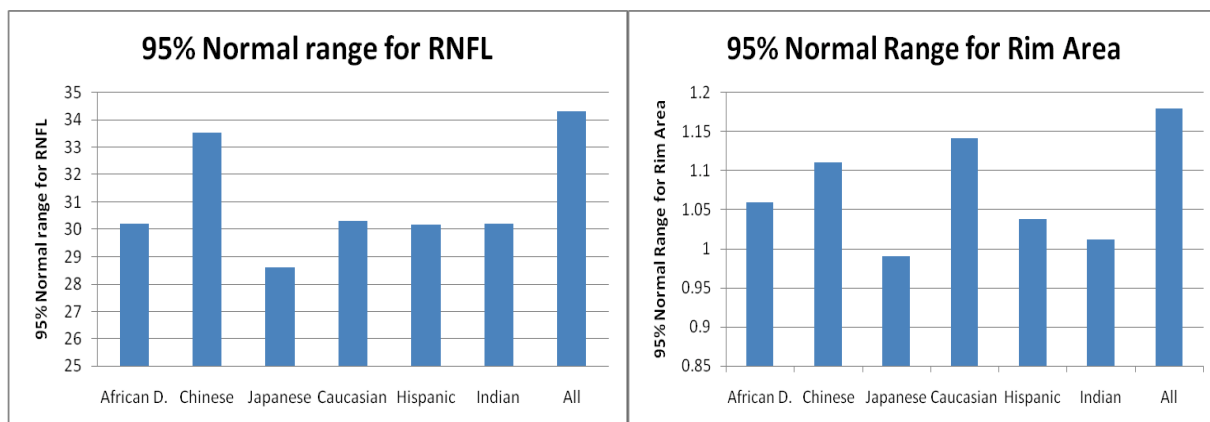
These figures furhter illustrate the reduced variability of separate, ethnic specific databases versus one combined database. The figutre on the left shows the 95% Normal range for RNFL thickness. Notice the normal range is greatest for the combined database (All). On the right, the same graph is shown for Rim Area. Again, the combined database shows the largest normative range.

Abnormal Cut-off (1%) for RNFL and **Abnormal (1%) Cut-off for Rim Area**
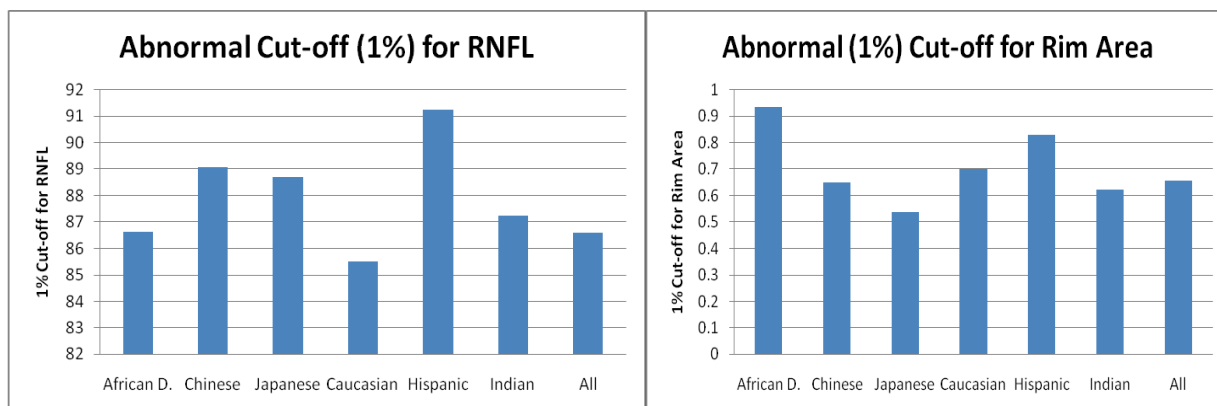
This final figure shows how the bottom 1% cut-off varies by database. The 1% cut-off is the point below which indicates an 'Outside Normal Limits' classification. This is generally interpreted as an abnormal result. Notice the cut-off changes substantially for each database. Using the combinede dataset would lead to more misclassifications than using the appropriate ethnic database.

Summary

The RTVue Fourier Domain OCT has a new, expanded ethnic specific databases in software version 4.0. Included in this software are 8 distinct databases to choose from including African Descended, Asian, Caucasian, Chinese, Hispanic, Indian, Japanese, and a combination of all ethnicities. In total, 861 eyes are included in these databases. Significant correlations were found for age and optic disc size as well as ethnicity. Each database automatically adjusts the normative range and cut-offs to account for both age effects and optic disc size effects. Significant differences were found for the various ethnicities, even after accounting for the effects of age and optic disc size. The normal range (variability) of the ethnic specific databases are smaller than the combined database with all individuals. This suggests using the appropriate ethnic specific database will increase the diagnostic accuracy of the results. This new database is the largest of any OCT device at this time.