CASE REPORT

The development of the Reference Database 2 for CIRRUS 6000

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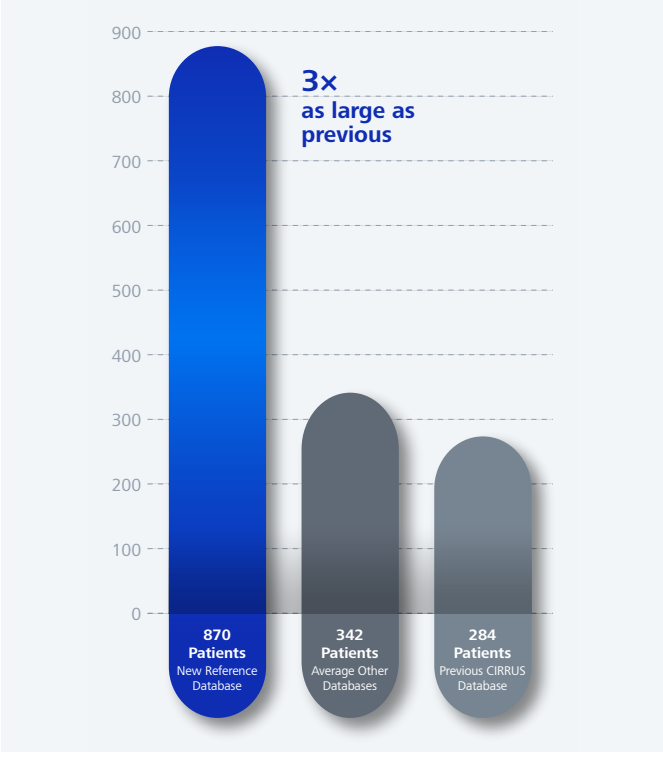
CIRRUS 6000 Reference Database 2

1.0 Introduction

Manufactured and distributed by Carl Zeiss Meditec, Inc. (CZMI), the CIRRUS High-Definition Optical Coherence Tomography (HD-OCT) is a spectral domain OCT (SD-OCT) instrument that uses a scanning beam of light called the superluminescent diode (SLD) to rapidly scan the eye. The CIRRUS HD-OCT model 6000 (CIRRUS 6000) is a class II medical device with 510(k) clearance from the FDA (K233933). It is a non-contact, high-resolution tomographic and biomicroscopic device used to image and measure anterior and posterior ocular structures, including the cornea, retina, retinal nerve fiber layer (RNFL), ganglion cell layer, inner plexiform layer (GCL-IPL), macula, and optic nerve head (ONH).



Expanded reference database for ZEISS CIRRUS 6000. Average values calculated from publicly available statistics as of April 2024.

The CIRRUS 6000 reference database 2 (RDB2) was developed to help clinicians assess and compare a patient's OCT measurements to a database of healthy subjects. RDB2 provides quantitative metrics to aid clinicians in differentiating between healthy and pathological conditions. It also assists clinicians in the diagnosis and management of ocular conditions. Specifically, RDB2 is a quantitative tool used for the comparison of RNFL thickness parameters, macular thickness parameters, GCL-IPL thickness parameters (actual layers measured are both the ganglion cell layer and inner plexiform layer), and ONH measurements to a database of healthy subjects.

Macular thickness is valuable in the detection and evaluation of various ocular conditions, including but not limited to diabetic retinopathy (DR), cystoid macular edema (CME), age-related macular degeneration (AMD), macular holes, pseudoholes, and central serous chorioretinopathy.[1-7] Ganglion cell thickness measurements are essential for evaluating glaucoma and monitoring glaucoma progression.[8-11] Similarly, ONH values and RNFL thickness measurements aid in the diagnosis and management of glaucoma[12-18] and other optic neuropathies.[19-21]

Creating a reference database with a diverse study population is crucial for representation of the general intended patient population. For RDB2, multiple investigational sites (eight sites) were selected across the United States, including the Midwest, Northeast, Southwest, and Western regions, to provide an extensive range of age, racial, and ethnic subgroups. The RDB2 distribution of ocular characteristics was also representative of the general population with respect to gender, refractive error, intraocular pressure (IOP) measurements, and axial length. Given the increased risk for ocular diseases among the geriatric population,[22-24] the study cohort was skewed towards the older age groups, where 40% of the study population was 60 years or older and 72% was 50 years or older. Overall, the RDB2 provides a comprehensive representation of the CIRRUS 6000 target population.

2.0 Purpose

Data was collected and analyzed for the RDB2 study to establish reference ranges for healthy eyes using regression analysis with reference limits at the 1st, 5th, 95th, and 99th percentiles for structural scans, including macular thickness parameters, GCL-IPL thickness parameters, the retinal nerve fiber layer (RNFL) thickness parameters, and optic nerve head (ONH) parameters. RDB2 reference limits for all OCT parameters, except optic disc area, were adjusted for age, then further adjusted for optic disc area for RNFL and ONH parameters.

3.0 Clinical Study Design

The RDB2 study was a prospective, multicenter cohort study conducted at eight (8) clinical sites across the United States.

3.1 Subject Population

The RDB2 subject population comprised healthy subjects 18 to 88 years of age (see Table 1).

3.2 Inclusion and Exclusion Criteria

To be included in the RDB2 study, subjects had to meet the criteria outlined in Table 1.

3.3 Subject Medical History

Investigators took medical and ophthalmic histories and conducted an ophthalmic examination on each subject before or during enrollment, which included the following qualifying procedures:

1. Best corrected visual acuity
2. Manifest refraction
3. Axial length measurement
4. Intraocular pressure measurement
5. Slit lamp examination of the anterior segment
6. Grading of the lens
7. Ophthalmoscopic evaluation and/or fundus photographs of the macula and ONH

Table 1 – Inclusion and Exclusion Criteria

Inclusion Criteria	■ 18 years or older ■ Able and willing to make the required study visits ■ Able and willing to give consent and follow study instructions ■ Able and willing to complete ophthalmic imaging

Exclusion Criteria	**Ophthalmic**
	■ Best corrected visual acuity worse than 20/40 on a Snellen or on a Snellen equivalent acuity chart in either eye
	■ Refractive error outside: –8.00D to +3.00D range, Astigmatism greater than -2D
	■ Glaucoma or glaucoma suspect diagnosis in either eye, including:
	  ■ Suspicious glaucomatous optic nerve appearance
	  ■ IOP > 21 mmHg in either eye
	  ■ History of unreliable/abnormal HFA 24-2 SITA Standard threshold visual field
	■ Any clinically significant vitreal, retinal, optic nerve or choroidal disease (small drusen are accepTable in subjects)
	■ Dense media opacity inhibiting adequate visualization of the retina
	■ History of ocular surgery (previous uncomplicated cataract and/or refractive surgery is acceptable)
	■ Any active infection of anterior or posterior segments
	■ Current use of ocular medication (topical lubricants, treatment for dry eyes and/or ocular allergies are acceptable)
	Systemic
	■ History of diabetes, leukemia, AIDS, dementia or multiple sclerosis
	■ A life threatening or debilitating disease
	■ Current or recent (within the past 14 days) use of an agent with photosensitizing properties by any route (e.g., Visudyne)
	■ Concomitant use of hydroxychloroquine and chloroquine

Table 2 – Demographic Summary for Subjects With Any Valid Scans

Factor Level	**Summary**
N (subjects)	870
Age (years)	
Mean (SD)	53.6 (15.1)
Median	56.0
Min, Max	[18.0, 88.0]
Age (by sampling categories)	
age 18-49	247/870 (28.4%)
age 50-88	623/870 (71.6%)
Age (by decade)	
age 18-29	87/870 (10.0%)
age 30-39	83/870 (9.5%)
age 40-49	77/870 (8.9%)
age 50-59	275/870 (31.6%)
age 60-69	237/870 (27.2%)
age 70 and older	111/870 (12.8%)
Gender n (%)	
Female	511/870 (58.7%)
Male	359/870 (41.3%)
Race n (%)	
Caucasian/White	474/870 (54.5%)
Black/African American	168/870 (19.3%)
Asian	160/870 (18.4%)
American.Ind/AK.Native	4/870 (0.5%)
Hawaiian/Pac.Islander	2/870 (0.2%)
Other	41/870 (4.7%)
Declines to State	21/870 (2.4%)
Ethnicity n (%)	
Not Hispanic or Latino	742/870 (85.3%)
Hispanic or Latino	105/870 (12.1%)
Declines to State	23/870 (2.6%)
Study Eye n (%)	
OD	438/870 (50.3%)
OS	432/870 (49.7%)

Observations:
- 0 subjects under 18 years old
- 17 subjects 80 and older

SD = Standard Deviation

3.4 Study Sites

The following eight study sites were included in the RDB2 study (in alphabetical order):

- Fischer Laser Eye Center: 1801 19th Ave. SW, Willmar, MN 56201
- Illinois Eye Institute / Illinois College of Optometry: 3241 South Michigan Ave., Chicago, IL 60616
- Mann Eye Institute: 5115 Fannin St., Suite 1000, Houston, TX 77004
- Silicon Valley Eyecare: 770 Scott Blvd., Santa Clara, CA 95050
- SUNY College of Optometry: 32 West 43rd St., New York, NY 10003
- Turlock Eyecare: 1199 Delbon Ave., Turlock, CA 95382
- Visual Eyes Optometry: 5980 Stoneridge Dr., #110, Pleasanton, CA 94588
- ZEISS Innovation Center California: 5300 Central Parkway, Dublin, CA 94568

4.0 Clinical Study Results

4.1 Subject Enrollment

One thousand (1,000) subjects were enrolled at eight sites. Eight hundred seventy (870) subjects with qualified data were included in the analysis. See Table 2 (opposite) for a demographic summary of all qualified subjects and Table 3 (page 6) for a summary of the ophthalmic evaluation for all qualified subjects.

4.2 OCT Scan Types

All qualified subjects were scanned with the CIRRUS 6000. The operators obtained the following images from each subject:

- Macular Cube 200×200 scan
- Macular Cube 512×128 scan
- Optic Disc Cube 200×200 scan

Table 4 – Qualified Scans, by Scan Type

Scan status	**Macular Cube 200×200**	**Macular Cube 512×128**	**Optic Disc Cube 200×200**
Acceptable	826	831	854

Table 3 – Summary of Ophthalmic Evaluation for Subjects With Any Valid Scans

Factor Level	Summary
MRSE	
Mean (SD)	-0.8 (2.0)
Median	-0.25
Min, Max	[-7.75, 3.0]
Cylinder	
Mean (SD)	-0.6 (0.5)
Median	-0.5
Min, Max	[-2.0, 0.0]
BCVA	
20/15	21/870 (2.4%)
20/20	761/870 (87.5%)
20/25	74/870 (8.5%)
20/30	13/870 (1.5%)
20/40	1/870 (0.1%)
BCVA (logMAR[1])	
Mean (SD)	0.01 (0.04)
Median	0.00
Min, Max	[-0.12, 0.30]
IOP (mmHg)	
Mean (SD)	14.5 (3.1)
Median	14.0
Min, Max	[6.0, 21.0]
Axial length (mm)	
Mean (SD)	24.1 (1.1)
Median	24.0
Min, Max	[21.2, 28.4]
ONH, Horizontal Cup to Disc	
Mean (SD)	0.33 (0.12)
Median	0.30
Min, Max	[0.10, 0.80]
ONH, Vertical Cup to Disc	
Mean (SD)	0.33 (0.12)
Median	0.30
Min, Max	[0.10, 0.70]

NOTE: logMAR is converted from Snellen score using: $\text{logMAR} = \log_{10}(\text{SNELLEN}/20)$

4.3 Image Selection

Images were required to be sharp and clear, well-centered without missing data, and have a signal strength of six (6) or greater.

5.0 Statistical Analysis

By modeling the reference range values for OCT measurements of healthy eyes, RDB2 reference ranges can be compared to a patient's measurements to determine whether a patient's measurements fall within or outside this reference range. The subject's age and disc area are clinically important factors for determining the reference range values for OCT measurements of healthy eyes. Regression model analysis was used to estimate the reference range values, and the model was adjusted by age for all OCT parameters except optic disc area, then further adjusted for optic disc area for RNFL and ONH parameters. Ninety-five percent (95%) confidence intervals for each quantile limit were determined by bootstrapping.

The following conditional quantile regression model was used to derive the reference range values:

$$Q_\gamma(\tau|x)=\alpha+\beta x$$

- Q = Conditional quantile regression model
- γ = CIRRUS 6000 parameter
- x = subject's age and/or categorical disc area
- τ = 0.01, 0.05, 0.95, and 0.99
- α, β = model coefficients

To ensure that the estimated quantile regression lines did not cross, the method of Bondell (2010) was used.[25]

6.0 Summary of OCT Parameters

NOTE: "Ganglion Cell" represents GCL-IPL for all CIRRUS models.

6.1 Macular Parameters

A patient's macular thickness parameters can be quantitatively compared to the macular thickness reference range for healthy eyes.

Table 5 – Macular Thickness Parameters and Analyses With RDB Data

Measurement	Parameters	Analyses
Macular Parameters	Macular Thickness Average Macular Thickness Retinal Volume Cube (mm^2)	Macular Thickness Macular Change Panomap Single Eye Summary Wellness Report

The reference range for healthy eyes applies to the following measurements:

- Macular Thickness parameters: Average thickness parameters for the ILM - RPE tissue layer for each sector of the ETDRS grid. There are nine (9) sectors (see Figure 1).
- Average Macular Thickness parameters: Overall average thickness parameters for the ILM -RPE tissue layer over the entire scanned area.
- Retinal Volume Cube: Overall average volume for the combined ILM – RPE tissue layers over the entire scanned area.

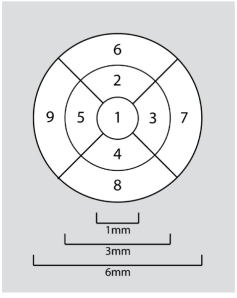


Figure 1: Early Treatment Diabetic Retinopathy Study (ETDRS) Grid

6.2 GCL-IPL Parameters

NOTE: "Ganglion Cell" represents GCL-IPL for all CIRRUS models.

Ganglion Cell Parameters

A patient's GCL-IPL parameters can be quantitatively compared to the GCL-IPL thickness reference range for healthy eyes.

Table 7 – GCL-IPL Thickness Parameters and Analyses With RDB Data

Measurement	Parameters	Analyses
GCL-IPL parameters	Average GCL + IPL thickness Average GCL + IPL thickness by sector GCL + IPL Deviation Map	Ganglion Cell OU PanoMap Wellness report

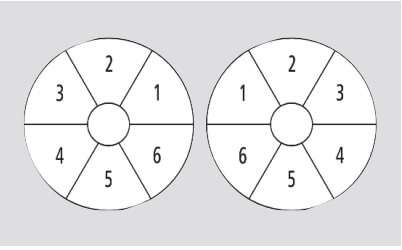


Figure 2: GCL + IPL thickness parameters grid

Table 6 – Summary of Variables for the Macular Cube 200×200

Type Variable	n	Mean (SD)	95% CI	Min	Max
Macular thickness parameters					
Central Subfield (µm)	826	257.31 (22.61)	[255.77, 258.86]	189.00	323.00
Inner Superior (µm)	826	321.48 (15.64)	[320.41, 322.54]	270.00	369.00
Inner Temporal (µm)	826	309.13 (15.46)	[308.07, 310.19]	257.00	352.00
Inner Inferior (µm)	826	317.33 (15.81)	[316.25, 318.41]	268.00	365.00
Inner Nasal (µm)	826	323.78 (16.88)	[322.63, 324.94]	269.00	381.00
Outer Temporal (µm)	826	259.51 (12.27)	[258.68, 260.35]	220.00	304.00
Outer Superior (µm)	826	276.81 (13.29)	[275.91, 277.72]	231.00	327.00
Outer Nasal (µm)	826	294.16 (15.37)	[293.11, 295.21]	246.00	342.00
Outer Inferior (µm)	826	265.16 (13.46)	[264.24, 266.08]	223.00	320.00
Average Cube thickness parameters (µm)	826	278.32 (12.55)	[277.46, 279.18]	237.00	319.00
Volume Cube (mm^3)	826	10.02 (0.45)	[9.99, 10.05]	8.50	11.50

The reference range for healthy eyes applies to the following measurements:

- Average GCL + IPL thickness, average of the six GCL-IPL sectors
- Average GCL + IPL thickness by sector, average thickness for each sector
- GCL + IPL Deviation Map

NOTE: The Minimum Thickness GCL-IPL parameter has been removed.

6.3 RNFL and ONH Parameters

A patient's ONH and RNFL parameters can be quantitatively compared to the ONH and RNFL reference range for healthy eyes.

NOTE: These reference range values are adjusted for age and optic disc area. Optic disc areas were categorized by tertiles into small (<1.58 mm^2), medium (1.58-1.88 mm^2), or large (>1.88 mm^2) disc area groups.

Table 8 – Summary of Variables for Macular Cube 200×200

Type Variable	n	Mean (SD)	95% CI	Min	Max
GCL-IPL thickness parameters					
Average thickness parameters (µm)	826	80.46 (6.36)	[80.02, 80.89]	61.00	100.00
Temporal Superior (µm)	826	79.60 (6.25)	[79.17, 80.03]	60.00	100.00
Superior (µm)	826	80.98 (6.73)	[80.52, 81.44]	59.00	102.00
Nasal Superior (µm)	826	82.16 (7.12)	[81.68, 82.65]	58.00	100.00
Nasal Inferior (µm)	826	80.49 (7.13)	[80.00, 80.97]	59.00	99.00
Inferior (µm)	826	78.84 (6.83)	[78.37, 79.30]	58.00	100.00
Temporal Inferior (µm)	826	80.71 (6.36)	[80.28, 81.15]	61.00	103.00

Table 9 – RNFL Thickness and ONH Parameters and Analyses with RDB Data

Measurement	**Parameters**	**Analyses**
RNFL Parameters	Average RNFL thickness Temporal Average RNFL thickness Superior Average RNFL thickness Nasal Average RNFL thickness Inferior Average RNFL thickness RNFL Symmetry RNFL Quadrants RNFL Clock Hours TSNIT Profile (RNFL thickness) RNFL Deviation Map	ONH/RNFL OU PanoMap Single Eye Summary Wellness Report
ONH Parameters	Rim Area (mm^2) Disc Area (mm^2) Average Cup-to-Disc Ratio Vertical Cup-to-Disc Ratio Cup Volume (mm^3) TSNIT Profile (Neuroretinal Rim Thickness)	ONH/RNFL OU PanoMap Single Eye Summary

RNFL Parameters

This study determined the reference range for healthy eyes for the following RNFL parameters:

- Average RNFL thickness
- Temporal Average RNFL thickness
- Superior Average RNFL thickness
- Nasal Average RNFL thickness
- Inferior Average RNFL thickness
- RNFL Symmetry
- RNFL Quadrants
- RNFL Clock Hours
- TSNIT Profile (RNFL thickness)
- RNFL Deviation Map

NOTE: RNFL symmetry values are calculated from both eyes; RNFL data was not included if only one eye was scanned.

ONH Parameters

This study determined the reference range for healthy eyes for the following ONH parameters:

- Rim Area (mm^2)
- Disc Area (mm^2)
- Average Cup-to-Disc Ratio
- Vertical Cup-to-Disc Ratio
- Cup Volume (mm^3)
- TSNIT Profile (Neuroretinal Rim Thickness)

Table 10 – Summary of Variables for Optic Disc Cube 200×200

Type Variable	n	Mean (SD)	95% CI	Min	Max
ONH					
Rim Area (mm^2)	854	1.30 (0.23)	[1.28, 1.31]	0.74	2.21
Average Cup-to-Disc Ratio	854	0.46 (0.17)	[0.45, 0.47]	0.06	0.74
Vertical Cup-to-Disc Ratio	854	0.44 (0.16)	[0.43, 0.45]	0.05	0.75
Cup Volume (mm^3)	854	0.13 (0.12)	[0.12, 0.14]	0.00	0.70
RNFL thickness parameters					
Average RNFL thickness parameters (µm)	854	93.19 (9.28)	[92.57, 93.81]	69.00	126.00
Temporal (µm)	854	64.04 (11.53)	[63.26, 64.81]	40.00	120.00
Superior (µm)	854	115.05 (15.92)	[113.98, 116.12]	72.00	162.00
Nasal (µm)	854	72.35 (11.54)	[71.58, 73.13]	41.00	115.00
Inferior (µm)	854	121.37 (16.08)	[120.29, 122.45]	72.00	188.00
Clock Hour 1 (µm)	854	105.56 (23.11)	[104.01, 107.11]	51.00	185.00
Clock Hour 2 (µm)	854	88.60 (18.10)	[87.39, 89.82]	43.00	160.00
Clock Hour 3 (µm)	854	60.73 (10.53)	[60.02, 61.44]	38.00	103.00
Clock Hour 4 (µm)	854	67.78 (13.79)	[66.85, 68.70]	37.00	129.00
Clock Hour 5 (µm)	854	100.12 (22.53)	[98.60, 101.63]	49.00	193.00
Clock Hour 6 (µm)	854	133.29 (26.17)	[131.53, 135.05]	45.00	229.00
Clock Hour 7 (µm)	854	130.69 (22.99)	[129.15, 132.23]	60.00	197.00
Clock Hour 8 (µm)	854	64.11 (15.16)	[63.10, 65.13]	32.00	151.00
Clock Hour 9 (µm)	854	51.09 (8.87)	[50.50, 51.69]	32.00	99.00
Clock Hour 10 (µm)	854	76.89 (15.44)	[75.86, 77.93]	43.00	135.00
Clock Hour 11 (µm)	854	123.18 (22.28)	[121.68, 124.68]	45.00	186.00
Clock Hour 12 (µm)	854	116.41 (26.43)	[114.64, 118.19]	51.00	205.00
RNFL Symmetry (%)[1]	725	0.88 (0.07)	[0.87, 0.88]	0.48	0.98

1. Note RNFL symmetry values are calculated from both eyes and was not included if only one eye was scanned.

6.3.1. RNFL and ONH Analysis Explanation and Limitations

Small Cup-to-Disc Ratios

For RDB2, the Average Cup-to-Disc Ratio and Vertical Cup-to-Disc Ratio will have a grey background when the ratio is below 0.25. The model used to fit the reference data does not apply to small Cup-to-Disc ratios.

OU Analysis

If a patient has a different disc area for each eye, different reference ranges may be applied to each eye (e.g., OD: large disc area reference range, OS: small disc area reference range). OU analysis takes the OD and OS disc areas and averages these values to determine the corresponding OU disc area category. Examples of parameters that use OU analysis include RNFL thickness, Neuroretinal rim thickness, TSNIT profiles, and RNFL symmetry.

Disc Area was not Associated with Age

In other studies, researchers classified disc sizes as small, medium, and large.[26-28] In this study we measured the disc area, which considers all meridians. The disc area values for the RDB2 study were:

- Less than 1.57 mm² (one-third of subjects)
- Between 1.57 and 1.88 mm² (one-third of subjects)
- Larger than 1.88 mm² (one-third of subjects)

NOTE: The info button adjacent to the "Disc Area" section on the CIRRUS 6000 ONH and RNFL OU Analysis indicates "ONH values are compared to reference samples with similar disc area. Consequently, disc area values are not compared to reference data and, therefore, are shaded gray in the summary table. The information below provides the range of disc area values observed in the reference population."

7.0 Discussion

RDB2 was developed for the CIRRUS 6000 and for this reference database, data was collected and analyzed to establish reference range values for healthy eyes by regression analysis for the reference limits at the 1st, 5th, 95th, and 99th percentiles for structural scans which included: macular thickness parameters, GCL-IPL thickness parameters, the RNFL thickness parameters, and ONH parameters.

7.1 Reference Range Value Covariates

The RDB2 reference limits for all OCT parameters, except optic disc area, were adjusted for age, then further adjusted for optic disc area for RNFL and ONH parameters.

Age was used as a covariate because it is an important factor in the clinical assessment of the OCT parameters, as demonstrated in numerous studies evaluating age-related changes for RNFL thickness parameters, ONH values, macular thickness parameters, and ganglion cell layer thickness parameters.[8, 12, 29-37] Clinicians evaluate age as a risk factor for ocular diseases, including AMD and glaucoma, where incidence increases with increasing age.[38-42] The RDB2 study results showed that age had a statistically and clinically meaningful effect on many of the OCT parameters. Specifically, as age increases, the RDB values typically decrease for macular thickness parameters, GCL-IPL thickness parameters, RNFL thickness parameters, and ONH rim area, whereas ONH Cup Volume and Cup-to-Disc parameters typically increase. These findings confirm that the use of age as a covariate in the determination of the reference ranges is clinically important and appropriate.

Optic disc size evaluation is an important component for the evaluation of optic nerve parameters and RNFL thickness parameters,[28] and is especially important in glaucoma diagnosis. Studies showed that larger optic discs typically have thicker RNFL measurements. Literature also reveals that larger optic discs are associated with larger Cup-to-Disc ratios and optic disc rim area.[43-45] Optic disc area was used as a categorical variable as clinicians typically categorize optic disc size into small, medium, and large ONH size groups.[26-28, 44-45, 50-51] Similarly for this study, optic disc areas were categorized by tertiles into small, medium, or large disc area groups. The study results revealed that the optic disc area has a statistically and clinically significant effect on the optic disc parameters. As the optic disc area increases, the ONH measurements and RNFL thickness parameters generally typically also increase. This verifies that it was statistically and clinically meaningful to adjust for optic disc area and age for the ONH parameters and RNFL thickness parameters.

Study results revealed that the interaction of age and optic disc area did not have a statistically significant effect on the measurement values. Accordingly, RDB2 was not adjusted for the interaction between age and optic disc area.

7.2 Overlapping Confidence Intervals

For each of the RDB2 parameters, the 95% bootstrap confidence intervals for each quantile were also evaluated. The RDB quantile regression plot (see Figure 3) indicates that the confidence intervals did not overlap in the middle of each quantile. However, there was some overlap of confidence intervals between the 1% and 5% and 95% and 99% quantile limits at the youngest and oldest ages. It should be noted that the overlap was less in the intended population of 50 years of age and older. There was more overlap of the confidence intervals for the optic disc cube scan parameters than the macular cube scan parameters since the regression model for the ONH parameters and RNFL thickness parameters use both age and the three optic disc area categories as covariates while age was the only covariate used for the GCL-IPL and macular thickness parameters regression model.

When applicable, the CIRRUS analyses use the RDB2 models to modify the color code output and display the presence of overlapping confidence intervals when a measurement may fall within relevant overlapping confidence intervals of the 1% and 5% quantile limits (diagonal red hatch marks) or 95% and 99% quantile limits (horizontal pink hatch marks). These hatch marks provide more detailed information to assist the user's clinical assessments (see Figure 4 and Table 11). These hatch marks are displayed in the color code legend, RDB2 tables, and RDB2 maps for the RDB2 OCT parameters in the graphical user interface and the CIRRUS 11.7 software version IFU.

NOTE: Overlapping confidence intervals color code displays are only available for the OCT summary parameters and are not available for the deviation maps or TSNIT profiles.

NOTE: Refer to CIRRUS SW 11.7 IFU for GCL-IPL, RNFL, and ONH Parameter color keys.

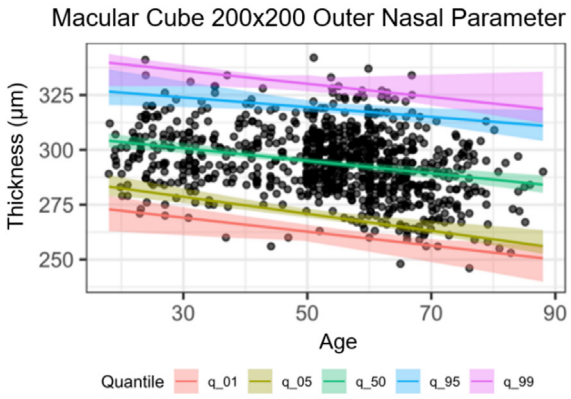


Figure 3 Quantile regression fits for the Macular Cube 200×200 Outer Nasal Parameter. Points are jittered horizontally for visualization. Shaded areas are 95% bootstrap confidence intervals from 10,000 bootstrap samples.

Table 11 – Color Key for Macular Thickness Comparison to the Reference Range for Healthy Eyes

Color code	Study population comparison
	The thickest 1% of measurements fall in the light red area. Measurements in light red are considered outside reference limits (light red > 99%, above reference limits).
	The thickest 5% of measurements fall within overlapping 95% confidence intervals of the 95% and 99% reference limits or above.
	The thickest 5% of measurements fall in the light yellow area or above. (95% < light yellow ≤99%, borderline above reference limits).
	90% of measurements fall in the green area (5% ≤ green and ≤95%).
	The thinnest 5% of measurements fall in the yellow area or below (1% ≤ yellow <5%, borderline below reference limits).
	The thinnest 5% of measurements fall within overlapping 95% Confidence intervals of the 1% and 5% reference limits or below.
	The thinnest 1% of measurements fall in the red area. Measurements in red are considered below reference limits (red <1%, below reference limits).

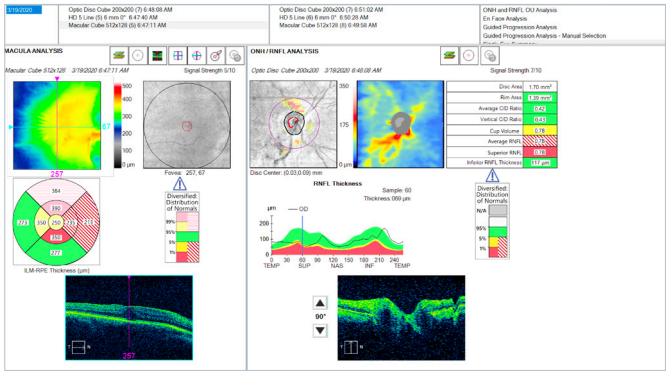


Figure 4: Example of overlapping confidence intervals of the 1% and 5% quantile limits (diagonal red hatch marks) and the 95% and 99% quantile limits (horizontal pink hatch marks).

7.3 Study Limitations

The reference range values for healthy eyes represent the general population. However, when interpreting the RDB2 data, the following study limitations should be considered, especially for the 1% and 99% limits:

Subjects

- Ages 18-88
- Refractive errors –8.00 D to +3.00 D range with Astigmatism less than -2D

NOTE: there is no RDB2 classification for patients < 18 years of age.

Age ranges with the fewest subjects

- 17 subjects aged 80-88
- Any patient over 88 years old will be compared with the reference database as if they were 88 years old

Factors That Affect the Reference Ranges

RDB2 reference limits for all OCT parameters, except optic disc area, were adjusted for age, then further adjusted for optic disc area for RNFL and ONH parameters. The RDB2 does not adjust for the following factors that may influence OCT measurements:

- Gender
- Axial Length
- Image Signal Strength
- Race
- Ethnicity
- Refraction

7.4 Diversified Reference Database 1 (RDB1) vs Reference Database 2 (RDB2)

When comparing RDB1[52-54] with RDB2, RDB2 includes a larger population with a larger subset of older subjects than RDB1. In addition, RDB2 uses optic disc area and age as covariates for RNFL measurements. RDB1 excludes extreme optic disc areas (optic disc areas less than 1.3 mm² or greater than 2.5 mm²), as only a small distribution of RDB1 study subjects had extreme optic disc areas. As a result, for patients with extreme optic disc areas, the RDB1 color-coded values for ONH parameters are not generated and the values are displayed with a grey color code. Specifically, Rim Area, Average Cup-to-Disc Ratio, Vertical Cup-to-Disc Ratio, Cup Volume, and the TSNIT Neuroretinal Rim Thickness profile have a grey background. With RDB2, there was a larger number of subjects and subsequently, a greater distribution of subjects in the extreme optic disc area ranges. Therefore, the RDB2 now allows for color code reference values for ONH parameters to be generated, even those with extreme optic disc areas. Additionally, the CIRRUS analyses use the RDB2 model to modify the color code output when a measurement may fall within relevant overlapping confidence intervals of the 1% and 5% quantile limits (diagonal red hatch marks) or 95% and 99% quantile limits (horizontal pink hatch marks). See Table 13 for a comprehensive comparison between the diversified reference database 1 (RDB1) and reference database 2 (RDB2).

The RDB1 data is not directly comparable to RDB2 data because they involve different study populations and different statistical analyses (e.g. In RDB2, the RNFL reference range values are adjusted for optic disc area in addition to age. In RDB1, the RNFL reference range values are adjusted only for age.)

Data acquired on the CIRRUS 400/4000/500/5000 uses RDB1 reference range values to compare macular thickness parameters, GCL-IPL thickness parameters, optic disc parameters, and RNFL thickness parameters. Data acquired on the CIRRUS 6000 uses RDB2 reference range values to compare macular thickness parameters, GCL-IPL thickness parameters, optic disc parameters, and RNFL thickness parameters (see Table 12). On the CIRRUS user interface (see Figure 5), select print preview from the print icon to view the source data. The header will list the device serial number and will show the device model the data was acquired on (CIRRUS model 400, 4000, 500, 5000, or 6000).

Table 12 – Applicable CIRRUS Models

RDB1	CIRRUS model 400, 4000, 500, 5000
RDB2	CIRRUS model 6000

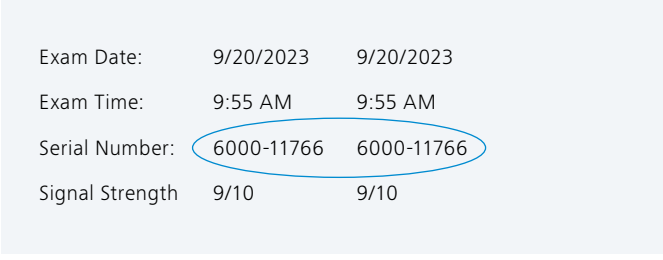


Figure 5: User interface print preview display

Guided Progression Analysis (GPA) is unrelated to RDB1 or RDB2. This analysis compares 3-8 exams from the most recent visits and evaluates changes in the thickness measurements over time to determine whether significant changes have occurred, without any reference database values. GPA data can be compared even if scans are acquired on different models, e.g., CIRRUS 5000 data and CIRRUS 6000 data can be compared within the same GPA report.

8.0 Conclusions

A second, more extensive reference database (RDB2) of healthy subjects was developed for the CIRRUS 6000. The RDB2 reference limits at the 1st, 5th, 95th, and 99th percentile points were established for macular thickness parameters, GCL-IPL thickness parameters, ONH parameters, and RNFL thickness parameters. These quantitative metrics allow for the comparison of a patient's OCT data with the largest OCT reference database (at the time of this report) of healthy eyes. RDB2 reference limits for all OCT parameters, except optic disc area, were adjusted for age, then further adjusted for optic disc area for RNFL and ONH parameters. Overall, the CIRRUS 6000 RDB2 provides a comprehensive representation of the CIRRUS 6000 target population and is a valuable and useful tool to facilitate clinical diagnosis and ocular health and disease management.

Table 13 – Comparison Between the Diversified Reference Database 1 (RDB1) and Reference Database 2 (RDB2)

	Diversified RDB1	**RDB2**
Applicable CIRRUS model	400/4000/500/5000	6000
Total enrolled eligible subjects	284	870
Subjects between 70-79 years old	28	94
Subjects 80 years and older	3	17
Age Range	19 to 84 years – Reference limits for > 84 years extrapolates age	18 to 88 years – Reference limits for > 88 years uses 88 years (i.e., fixed at 88)
Median age	46.5	56
Mean age	46.6	53.6
Min, max age	19, 84	18, 88
Race	43% Caucasian 24% Asian 18% African American 0% American Indian/ Alaska Native 0% Hawaiian/Pacific Islander 12% Hispanic 1% Indian 2% Other	54.5% Caucasian 18.4% Asian 19.3% African American 0.5% American Indian/ Alaska Native 0.2% Hawaiian/Pacific Islander 4.7% Other 2.4% Declines to state
Ethnicity	88% Not Hispanic 12% Hispanic (RDB1 included Hispanic under race)	85.3% Not Hispanic or Latino 12.1% Hispanic or Latino 2.6% Declines to state
Number of sites	7	8
Statistical model design	Linear or quantile regression	Quantile regression
Covariates: age only	■ Macular thickness parameters ■ GCL-IPL parameters ■ RNFL Parameters	■ Macular thickness parameters ■ GCL-IPL parameters
Covariates: age and disc area	■ ONH parameters NOTE: Disc area used continuous statistical analysis	■ ONH parameters ■ RNFL thickness parameters NOTE: Disc area used categorical statistical analysis
Optic disc areas	■ RDB color codes provided only for disc areas between 1.3 – 2.5 mm^2 (disc areas outside of this range have a grey color = no RDB color code values) ■ Cup-to-Disc Ratios ≤ 0.25 were excluded as the model used to fit the reference data is not applicable for small Cup-to-Disc ratios	■ No exclusion of extreme optic disc areas and all disc areas were used for ONH parameter limits ■ Cup-to-Disc Ratios ≤ 0.25 were excluded as the model used to fit the reference data is not applicable for small Cup-to Disc ratios
Color code display of OCT measurement parameters that may fall within relevant overlapping 95% CI of the quantile limits	■ CIRRUS analyses that utilize the RDB1 models do not display overlapping confidence intervals	■ CIRRUS analyses that utilize the RDB2 models are displayed as hatch marks when relevant to the measurement ■ Diagonal red hatch marks are displayed when a measurement may fall within relevant overlapping confidence intervals of the 1% and 5% quantile limits ■ Horizontal pink hatch marks are displayed when a measurement may fall within relevant overlapping confidence intervals of the 95% and 99% quantile limits

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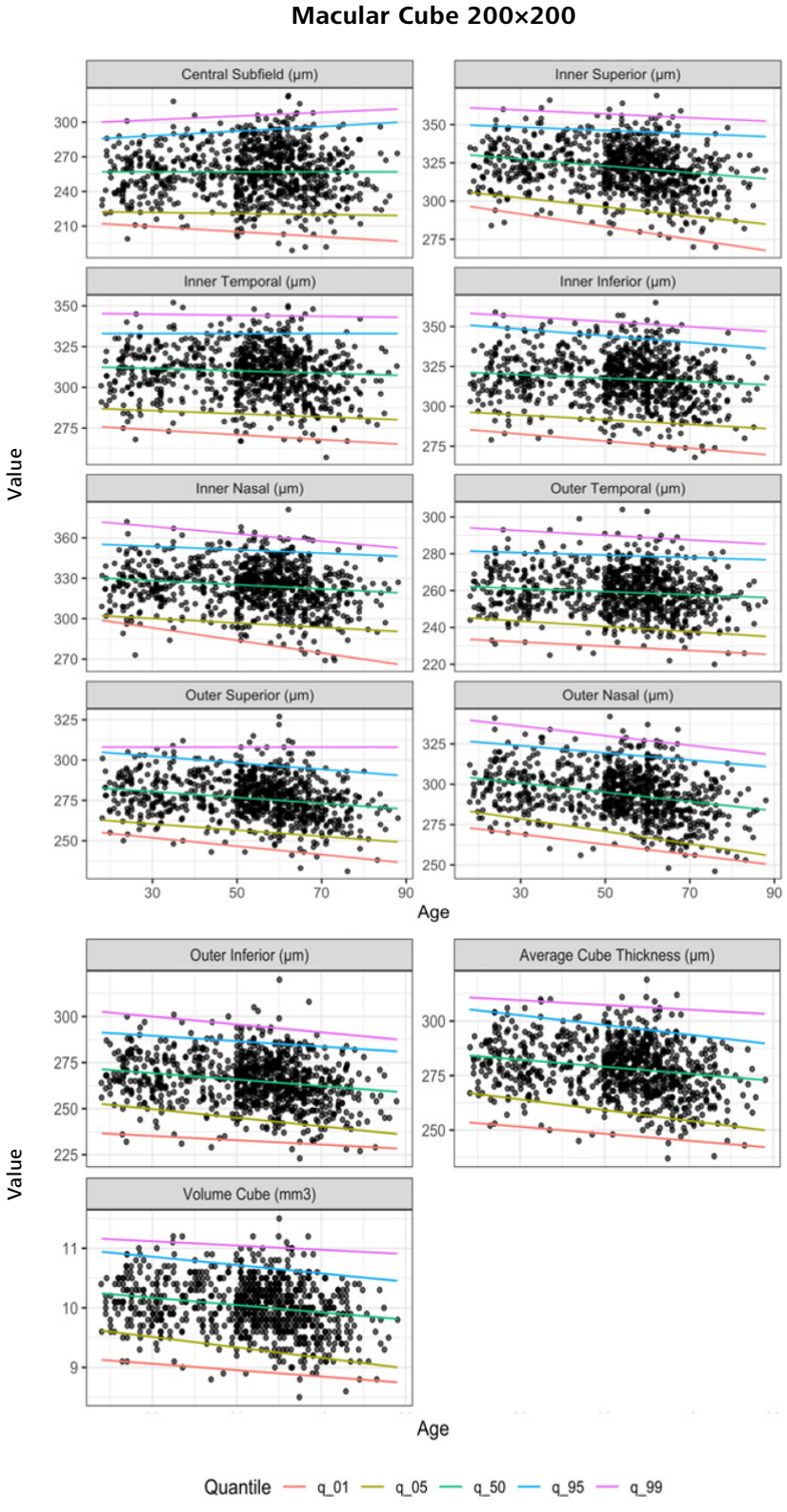
10.0 Appendix 1: Quantile Plots

Note: The 50th percentile reference limit is also modeled and shown in each of the following quantile plots.

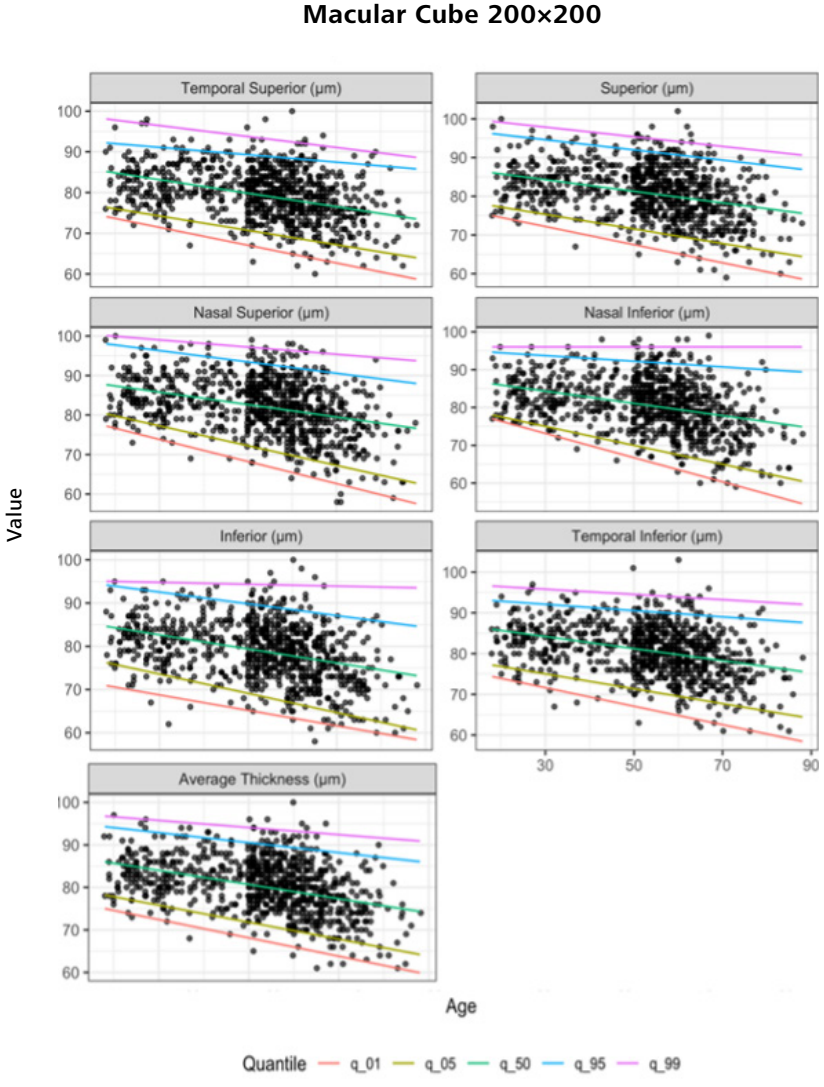
10.1 Macular Parameters

The macular thickness parameters regression fits for each quantile for the Macular Cube 200×200 scan.



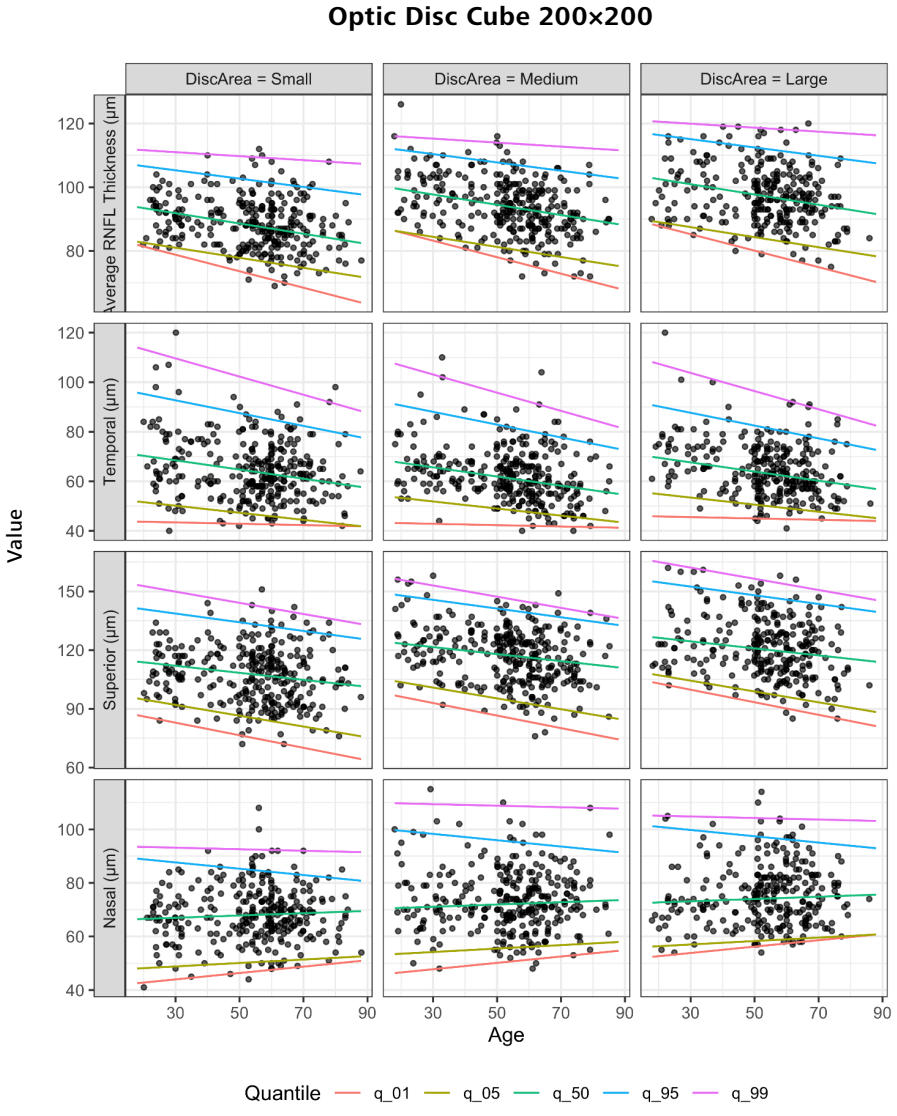
10.2 GCL-IPL Parameters

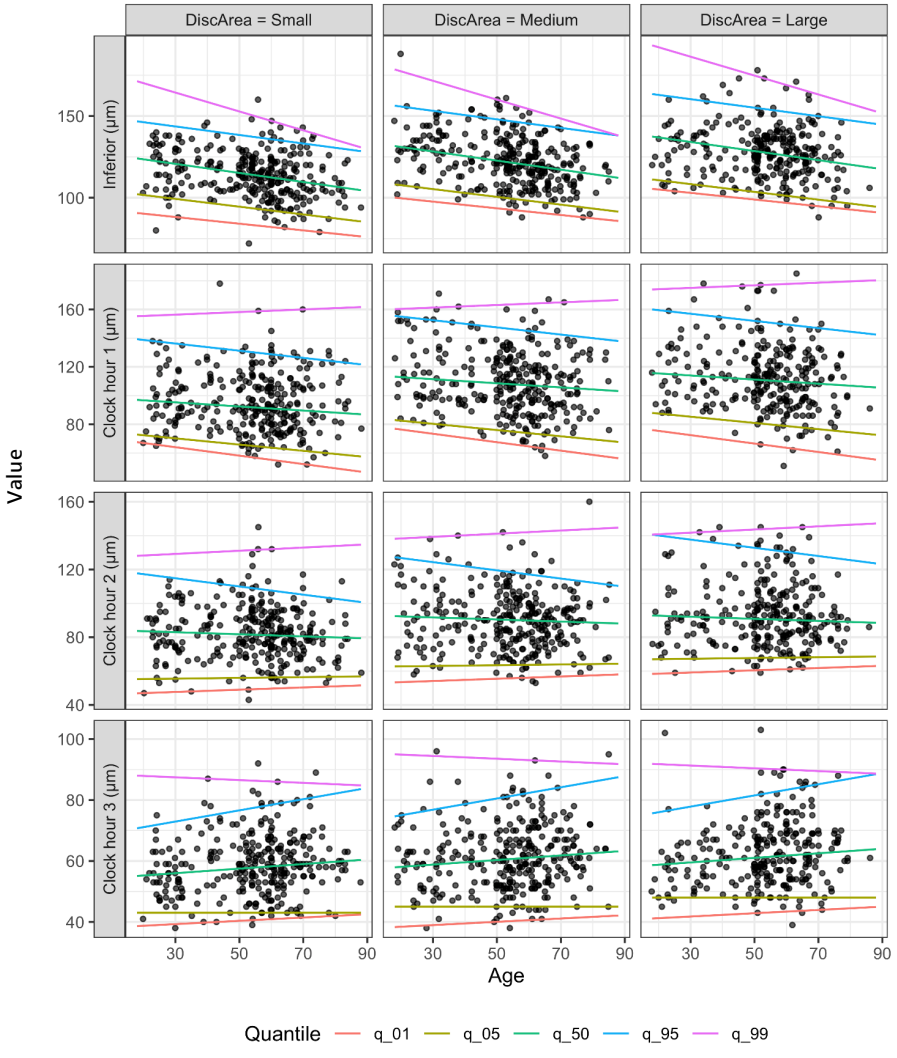
The GCL-IPL thickness parameters regression fits for each quantile for the Macular Cube 200×200 scan.



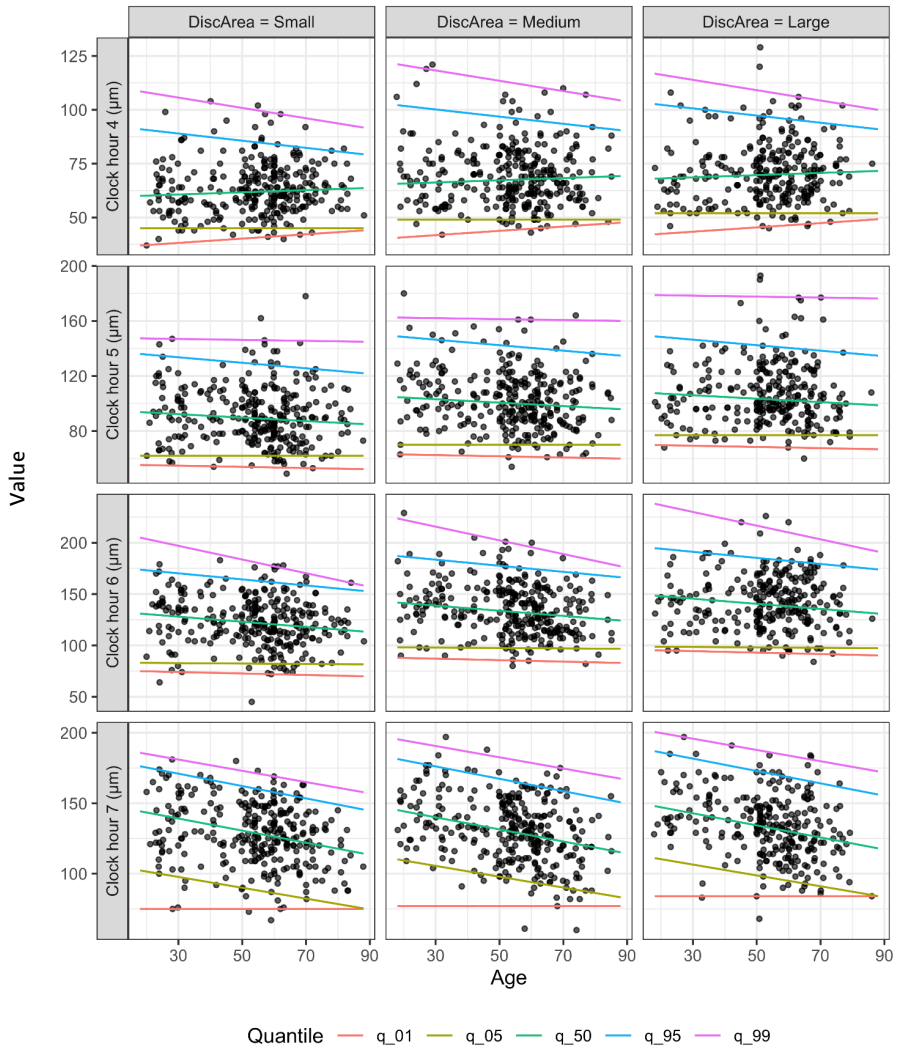
10.3 RNFL and ONH Parameters

The RNFL thickness and ONH parameters regression fits for each quantile for the Optic Disc Cube 200×200 scan.

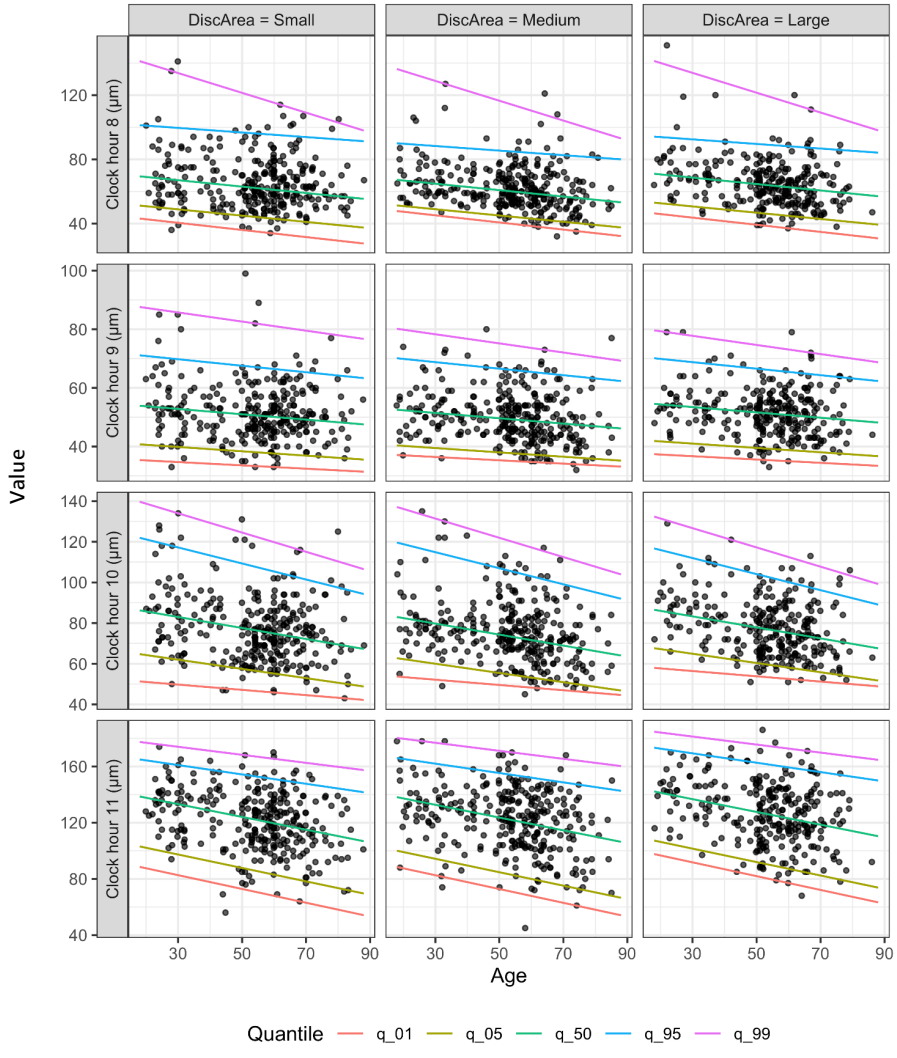




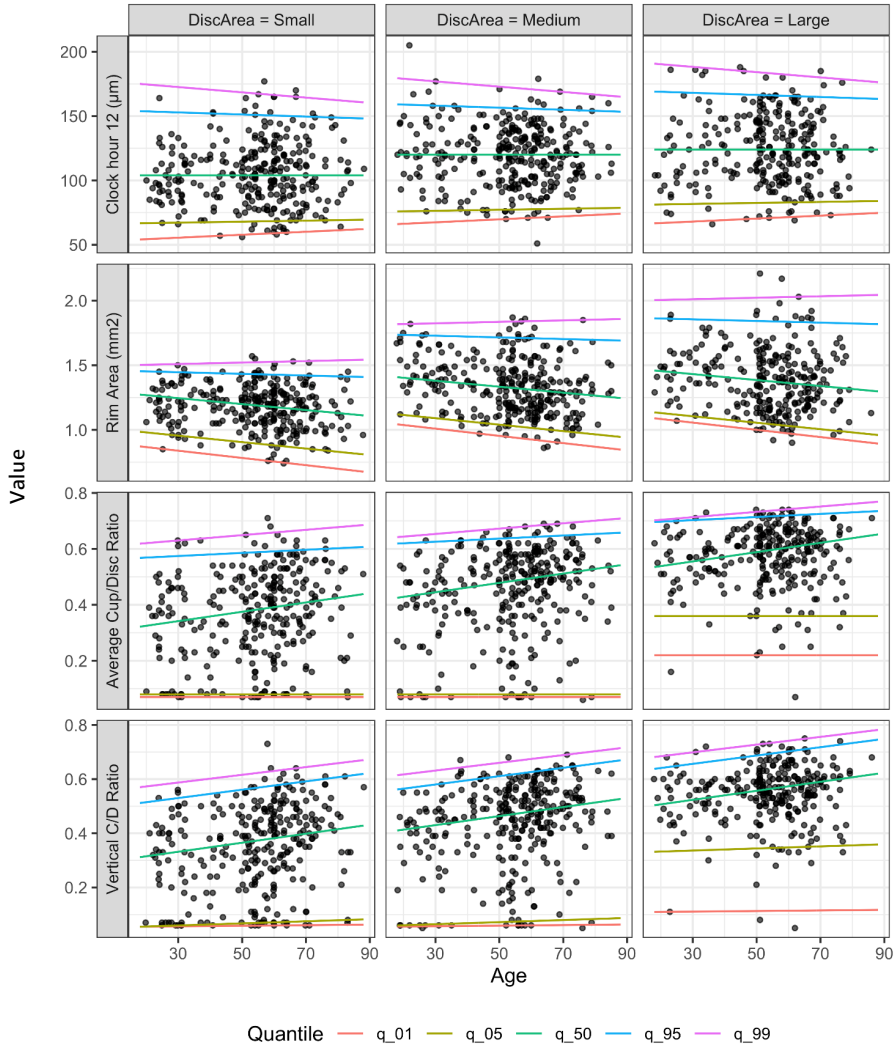
The RNFL thickness parameters regression fits for each quantile for the Optic Disc Cube 200×200 scan.



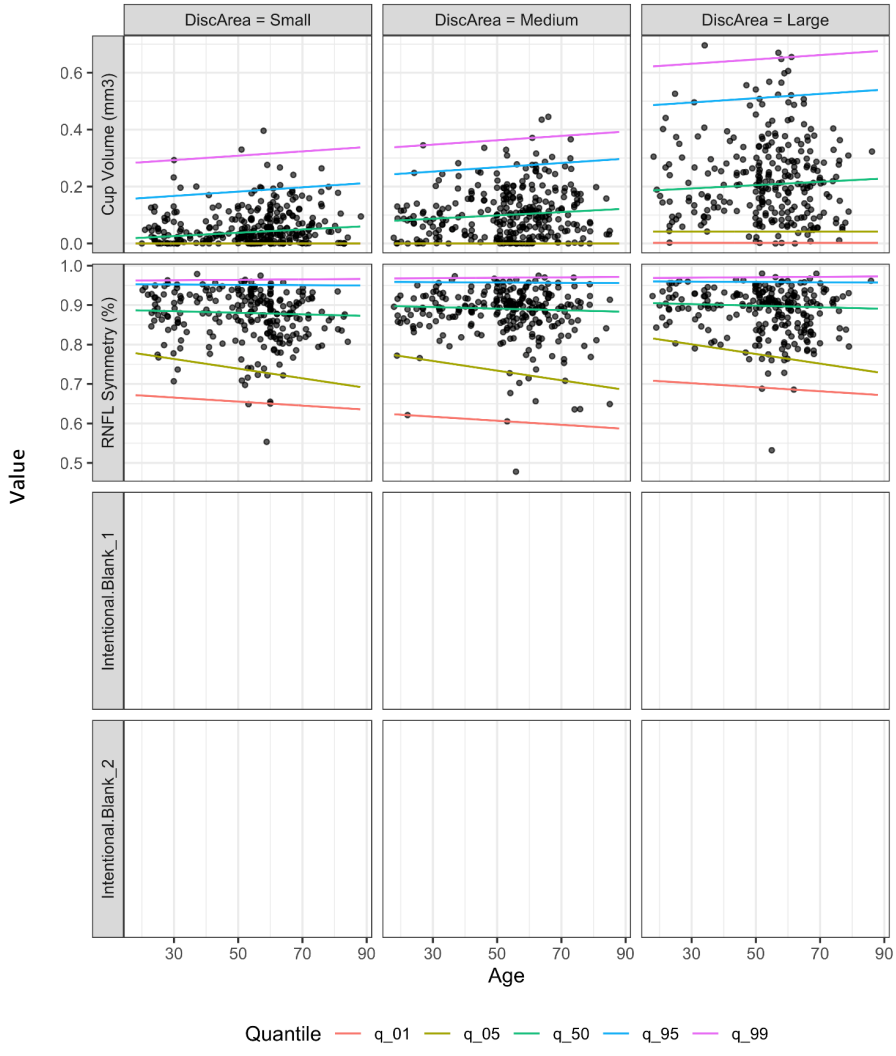
The RNFL thickness parameters regression fits for each quantile for the Optic Disc Cube 200×200 scan.



The RNFL thickness parameters regression fits for each quantile for the Optic Disc Cube 200×200 scan.



The RNFL thickness and ONH parameters regression fits for each quantile for the Optic Disc Cube 200×200 scan.



The RNFL thickness and ONH parameters regression fits for each quantile for the Optic Disc Cube 200×200 scan.

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