SD-OCT derived characteristics of Bruch's Membrane Opening in a young adult Australian population.

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The optic nerve head (ONH) is the definitive site of ocular damage in glaucoma. To date, the vast majority of studies evaluating normal and disease-related structural variation in the ONH have utilised two-dimensional techniques (e.g. photo-based planimetry), which provide information about the surface morphology. However, recent work has shown that not only are conventional measurement techniques based on the clinically observable disc margin (DM), which is imprecise, but the underlying anatomy of the ONH also influences the risk of developing glaucoma.¹⁻³ The rationale for utilizing the clinically defined DM in ONH assessment is now being questioned because of advances in imaging technology that allow visualization of the sub-surface architecture.

One of the primary assumptions employed in studies of ONH morphology is that the clinically perceived contour of the DM represents an actual anatomic structure determined by an underlying ‘scleral’ connective tissue. Recent research has shown that this conventional clinical knowledge may be flawed for two reasons. DM anatomy is complex and involves Bruch’s Membrane, the end point of Bruch’s Membrane (Bruch’s Membrane Opening [BMO]) and the Border Tissues of Elschnig – not just the sclera. Consequently, it has been suggested that current neuro-retinal rim (NRR) measurements lack a solid anatomical foundation because: (1) the observed DM does not represent the anatomic structure that defines the border of the rim tissues as they pass through the ONH and, (2) neural tissue orientation within the ONH is not considered.^{2,3} The new generation of spectral-domain optical coherence tomography (SD-OCT) instrumentation overcomes these measurement limitations by providing anatomically and geometrically accurate BMO-based measurements of the NRR and related structures, thus enabling enhanced detection of open-angle glaucoma.¹

Few data are currently available regarding BMO-based ONH characteristics in normal populations. The primary aim of this study was to measure and describe these parameters in a large, young adult and healthy Australian population. Establishing normative profiles of BMO-based ONH anatomy will ultimately be essential in assisting the clinician in the diagnosis and monitoring of ONH disease, including glaucoma.

Methods

Participants

Participants were identified from the Western Australian Pregnancy Cohort (Raine) Study, a longitudinal prospective study established in Perth, Western Australia in 1989.⁴ Prenatal information (e.g., diet, exercise, work, and health) and ultrasound imaging were acquired at regular intervals during the pregnancies of 2,900 women enrolled until 1991. Subsequently, periodic follow-ups of their children were conducted and various clinical and general health (e.g., childhood milestones, height, weight, behavior, and illnesses) data recorded. Ocular health examinations at the 20-year follow-up of the cohort were conducted from 2010-12. All participants had a comprehensive ocular examination that included visual acuity assessment, anterior segment examination, corneal pachymetry, intraocular pressure (IOP) measurement, autorefractometry, and a mydriatic optic disc assessment. No participants had signs of glaucoma or other optic neuropathies. ONH imaging was performed using both SD-OCT (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) and Heidelberg retinal tomography (Heidelberg Engineering, Heidelberg, Germany) instrumentation to allow for comparison of anatomical parameters. Autorefractometry was conducted following cycloplegia in all subjects using Nidek ARK-510A (NIDEK Co.Ltd, Tokyo, Japan). The study adhered to the tenets of the Declaration of Helsinki. Ethics approvals were obtained from the

Human Research Ethics Committee of the University of Western Australia. Informed consent was obtained from all subjects after providing them with a detailed explanation of the study.

SD-OCT Imaging and Image Processing

SD-OCT provides 3-dimensional imaging, denser sampling and enhanced imaging reproducibility compared to traditional time-domain OCT. SD-OCT utilizes frequency-based image acquisition, enabling 2- to 3-fold improved axial resolution and up to 50-fold increases in scan speed. For all participants, each eye was imaged using the Spectralis OCT with a standardized scanning protocol. A 49-line raster scan at 30 microns ($15^\circ \times 10^\circ$) centered on the optic disc (with tracking on) was performed in each eye, with 100 frames averaged to improve the image quality. Refraction and keratometry data were entered for all participants to correct for inter-individual ocular magnification effects. All scans were subjectively assessed for good signal strength and minimal motion artifacts. ONH scans were exported from Heidelberg Eye Explorer as PNGs with the y-scale set as 1:1 μm for analysis. We developed a customized script, coded in Matlab (Mathworks, Inc., Natick, MA, USA), to enable measurement of BMO-related parameters. The user interface allowed the trained observer (PS) to visualize and manually demarcate the positions of the BMO (two points per B-scan) and optic cup (if defined - two points per B-scan) (Figure 1). For each scan the innermost termination of the BMO was defined as the DM, with the cup margin bound by an approximately horizontal line connecting the two points and intersecting with the internal limiting membrane (ILM). In this way a reference plane was constructed such that structures above the plane and within the DM were defined as NRR, and below the plane, as optic cup. The BMO-based horizontal rim area (BMO-HRA) was defined as BMO disc area – cup area. The BMO-HRA was set to equal the BMO disc area in eyes whereby the cup was so shallow that the ILM did not cross the BMO reference plane. The BMO and ILM topographic outlines were reconstructed by calculating the position of the marked points on the x axis of the OCT image as a percentage of the total image width, and mapping them on the corresponding scan line of the fundus image. Once all the required B-scans were marked, the inbuilt Matlab function ‘roipoly’ was used to delineate the BMO disc and cup for area measurements. Linear dimensions were defined as the maximum horizontal and vertical diameters of the BMO disc and cup boundary. Parameters were adjusted for image magnification effects using the OCT x scaling (expressed as $\mu\text{m}/\text{pixel}$) found in the image information tab of Heidelberg Eye Explorer, such that area measurements were in mm^2 (BMO, cup and NRR) and linear measurements (horizontal and vertical BMO and cup) in mm.

Statistical Analysis

Data management and statistical tests were performed in the R statistical environment (R Development Core Team, 2014; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were described as the mean $\pm$ standard deviation (SD). We used the paired t-test and intra-class correlation to compare the similarity of sample distributions between right and left eyes. Linear regression models were used to estimate the effect of different variables (age, sex, ethnicity, height, mean axial length, mean spherical equivalent [SEQ] and BMO-HRA) on BMO area in both univariate and multivariable analyses. Unless otherwise specified all statistical tests were two-sided.

The inter-observer and intra-observer reproducibility of measuring BMO and NRR areas were evaluated by computing the intra-class correlation coefficient (ICC) from a

randomly drawn sample of 50 images manually delineated twice.⁵ The agreement between the SD-OCT derived and HRT-generated ONH area parameters were assessed by Bland-Altman analysis.⁶ The Bland-Altman plot allows comparison of SD-OCT and HRT by plotting the difference in the ONH area parameter from the two imaging instruments (vertical axis) against the average of the differences (horizontal axis).

Results

Data were available for 1344 subjects (2688 eyes), comprising 652 females (48.5%) and 692 males (51.5%) (Table 1). Participants were aged from 18 to 22 years (mean 20 years) with the vast majority (85.5%) Caucasian (5.6% - Chinese, 8.9% - Other). There was no difference in age between males and females (confidence interval [CI] for difference in means [-0.091 - 0.005], two-sample t-test $t(1342) = -1.77, p = 0.076$). BMO-based ONH parameter measurements are shown in Table 2. The inter-ocular ICCs were generally high (> 0.80) indicating parameter measurements between eyes were concordant and utilization of mean values in subsequent analyses, appropriate. Intra-grader repeatability was excellent with ICCs of 0.98 [0.97-0.99, $p < 0.001$] and 0.96 [0.92-0.98, $p < 0.001$] and the agreement between graders computed as 0.98 [0.96-0.99, $p < 0.001$] and 0.94 [0.90-0.97, $p < 0.001$] for BMO disc and NRR areas, respectively.

Mean BMO disc and NRR areas ranged from 0.94 to 4.06 mm² (mean 1.77 ± 0.38) and 0.94 to 3.99 mm² (mean 1.56 ± 0.31), respectively. The optic cup was defined in 1993 sets of images (74.1%) with the area ranging from 0.00 to 1.41 mm² (mean 0.21 ± 0.24). Mean values for C/D ratio and C/D area ratio were noted as 0.25 ± 0.19 and 0.11 ± 0.11 , respectively. When compared to the equivalent HRT measurements, SD-OCT derived measures differed significantly for all five ONH parameters (Table 2). Figure 2 shows the Bland-Altman plots comparing SD-OCT and HRT measurements of mean BMO disc (top), NRR (middle) and cup (bottom) area. The LoA (mean difference) were calculated as -0.95 mm^2 to 0.66 mm^2 (-0.14 mm^2), -0.72 mm^2 to 0.82 mm^2 (0.05 mm^2) and -0.44 mm^2 to 0.06 mm^2 (-0.20 mm^2) for the disc, NRR and cup areas, respectively.

Figure 3 shows the mean area distributions (in 0.25 mm² increments) for BMO disc area (top), NRR area (middle) and cup area (bottom), grouped by gender. All distributions demonstrated some degree of positive skewness, being most marked for mean cup area. The Shapiro-Wilks test indicated each distribution departed from normality ($p < 0.001$). Indeed, while this may be partly attributable to our large sample size, in this case the Central Limit Theorem works to advantage in making the parametric tests we have employed in the current study (t-test and linear regression) more robust to violations of this assumption.^{7,8} Regression residuals (e.g. Q-Q plots) were also assessed for normality.

Table 3 reports the results of the univariate and multiple regression analyses of factors associated with BMO disc area. In the multivariable analysis, BMO-HRA was significantly associated with disc area ($p < 0.001$) such that disc area increased by 0.93 mm² (95% CI [0.88 - 0.97]) for each 1 mm² increase in NRR area. Furthermore, in the multivariable analysis we noted a marginal effect of age, with ethnicity, axial length and SEQ more strongly correlated with the dependent variable. Compared to Caucasian subjects, being of Chinese or Other ethnicity was associated with larger BMO areas - 0.10 mm² and 0.06 mm², respectively. Longer eyes were similarly correlated with BMO area. For each 1 mm increase in axial length, BMO disc area increased by 0.06 mm² (95% CI [0.04 - 0.08]). Figure 4 shows the regression of BMO disc area on mean axial length. The coefficient of determination (R^2) of BMO disc area variation explained by axial

length was 3.5%. Figure 5 shows the regression of BMO-HRA on BMO disc area. The proportion of BMO rim area variation explained by BMO disc area was 59.5%.

Discussion

In this study we quantified BMO-based ONH parameters in a large, normal and predominantly Caucasian population using SD-OCT. Accurate delineation of the ONH margin is essential in determining unbiased estimates of NRR integrity (width, area, volume), which are important proxies for ganglion cell density - the cornerstone of glaucoma diagnosis and management. Emerging research utilizing SD-OCT has underscored the inherent subjectivity in clinically defining the DM compared to high-resolution in-vivo imaging that facilitates objective assessment of ONH parameters based on the BMO, a consistently identifiable anatomical landmark across individuals. By quantifying BMO-based anatomy, this work will be informative in establishing normative profiles of the sub-surface architecture.

After imaging the eyes of 1344 participants, we found that mean BMO disc area was 1.77 mm^2 , ranging from 0.94 mm^2 to 4.06 mm^2 . As the measurement of ONH parameters are technique dependent (a manifestation of the reproducibility issues intrinsic to this study), BMO-based parameterization produces mean values of disc size comparable to estimates within the lower range from other methods. Prior to the advent of ophthalmic digital imaging technologies over the past 15 years, planimetric evaluation was the standard approach in research hypotheses of the ONH, with disc size reported in multiple studies of Caucasian subjects to approximate 2.5 mm^2 and range from 2.1 mm^2 to 2.8 mm^2 .⁹⁻¹²

Subsequently, the widespread uptake of HRT and OCT imaging modalities has been transformative in allowing rapid and precise ONH evaluation; however, accuracy remained modest due to imaging limitations and inconsistencies in phenotype definitions across manufacturers. For example, in a 2005 study of 42 eyes, Hoffman et al. measured disc/NRR areas by Stratus OCT and HRT II as $2.31 \text{ mm}^2/1.37 \text{ mm}^2$ and $2.13 \text{ mm}^2/1.37 \text{ mm}^2$, respectively.¹³ Similarly, Lin and colleagues imaged 75 eyes (25 normal, 50 glaucomatous) and reported mean disc/NRR areas by Stratus OCT and HRT III as $2.77 \text{ mm}^2/1.12 \text{ mm}^2$ and $2.31 \text{ mm}^2/1.19 \text{ mm}^2$, respectively.¹⁴ In contrast, a smaller sample of normal eyes ($n=14$) produced disc size estimates of 1.89 mm^2 and 1.75 mm^2 from Stratus OCT and HRT II instruments, respectively.¹⁵ Such measurement variation, especially in NRR area, is in part due to the manner in which the reference plane is determined. The standard reference plane employed in the HRT software is located $50 \mu\text{m}$ posterior to the temporal ONH margin. In contrast, the reference plane in Stratus OCT is determined by drawing a line $150 \mu\text{m}$ anterior to the RPE. Consequently, these and other studies have cautioned against the interchangeable use of inter-instrument measurements in clinical practice because of their suboptimal agreement.^{16, 17} To that end, our observations of small but systematic biases in the measurements provided by SD-OCT and HRT similarly support this conclusion.

Our finding of smaller BMO-based ONH parameters compared to their DM-based counterparts has been observed in previous studies.^{3, 18-20} In a sample of 149 eyes, Sharma et al. employed a custom automated segmentation algorithm to quantify BMO-based ONH anatomy using equivalent definitions to our own.¹⁸ Disc/NRR areas were determined to be $2.12 \text{ mm}^2/1.54 \text{ mm}^2$ and $1.82 \text{ mm}^2/1.20 \text{ mm}^2$ by stereo-photo planimetry and SD-OCT, respectively. It is not obvious why DM-based measurements should be systematically larger, but it may simply be a result of the differences in ease of

discrimination of associated contours. The BMO represents a consistently and accurately identifiable landmark, whereas reproducible delineation of the DM from topographic images is more difficult as it is dependent on the 3-dimensional architecture of BM and underlying border tissue, rather than a single structure.²¹ In addition, determination of the disc contour with HRT is known to be error-prone, as a spline curve is fit to the DM after an observer manually identifies points that lie on the border. Inter- and intra-individual differences in the surface morphology (colour, depth, etc.) may help to explain some of the difficulty in delineation and discrepancy in size measurements observed.

In our study regression analysis confirmed that the well-documented physiological association between NRR and ONH size¹¹ is equally relevant when measurements are based on the BMO. While the vast majority of our subjects were Caucasian we did note a small effect of ethnicity, with Chinese participants manifesting larger BMO-based disc areas. This has been supported in other studies utilizing both SD-OCT and planimetric assessment of the ONH.^{22, 23} After controlling for height and axial length we no longer observed any association between gender and BMO parameters (BMO disc area – males: mean $1.79 \pm 0.37 \text{ mm}^2$, females: mean $1.76 \pm 0.38 \text{ mm}^2$, $p = 0.18$). Indeed, large epidemiological studies of ONH morphology have found that mean optic disc area is on average larger in men than women.^{24, 25} Currently, there are few data reporting on equivalent effects for BMO-based parameters. In their analysis, Tun et al. observed that BMO-MRW (minimum rim width) was thicker in female subjects.²⁶ BMO-MRW is the linear complement of another surrogate of NRR area - BMO-MRA (minimum rim area) and would thus indicate a larger rim area. Clearly, more work needs to be undertaken to evaluate the relationships between BMO-based and other ocular and demographic variables.

This study has several limitations, the most significant being the availability of images restricted to those acquired using the raster scan protocol. Several recent studies have demonstrated the superior diagnostic performance of two new BMO-based parameters alluded to previously, the BMO-MRW and BMO-MRA.^{1, 3, 27, 28} BMO-MRW measures the minimum width of the NRR from BMO and differs from BMO-HRW in a salient manner. As the measurement is made perpendicular to the neural tissue, it accounts for the variable pathway of ganglion cell axons as they exit the ONH.³ This minimum distance, and its corresponding minimum area (BMO-MRA), approximate the smallest cross-sectional area that nerve fibres occupy, with the latter parameter potentially acting as a surrogate of nerve fibre density and thus an indicator of structural integrity for both diagnostic and research purposes in glaucoma.²⁸ In a study of 221 advanced glaucoma subjects, Gardiner and colleagues demonstrated that minimum NRR measurements from SD-OCT were better correlated to both structural (retinal nerve fibre layer thickness) and functional (perimetric mean deviation) parameters than NRR measurements within the BMO plane or based on the clinical DM.²⁸ Furthermore, Muth et al. have more recently proposed two additional BMO-based parameters, BMO-PRW (perpendicular rim width) and BMO-PRA (perpendicular rim area), which they have found to be as effective as minimum rim measurements in diagnostic capability.²⁹ The segmentation and computation of minimum NRR parameters necessitates SD-OCT image data acquired using the radial scan protocol which we did not have at the time of our data collection, but rather the horizontal rim area we measured was comparable with the conventional size measurements produced by planimetry or output by commercial HRT/OCT instruments. Our data were analyzed retrospectively following SD-OCT imaging (raster-based ONH scan) conducted as part of the standard Raine ophthalmic examination protocol. The updated software from Heidelberg allowing automated analysis of these

new parameters (radial ONH scan) was not available at the time of examination but will be conducted at follow-up.

The raster scan protocol also precluded accurate sectoral analysis of NRR variation and border tissue configuration. The border tissue of Elschnig is a fibrous tissue originating from the sclera and fusing with BM to enclose and separate the choroid from the ganglion cell axons as they exit the ONH. The border tissue anatomy may affect the clinicians perception of the DM position and is regionally variable within the ONH, most commonly characterized as internally or externally oblique relative to the underlying sclera.³ As the scan axis was not perpendicular to the tissues except at the 3 and 9 o'clock positions, we were unable to accurately assess border tissue configurations at other positions around the ONH. The most common configuration we observed was internally oblique, which accounted for almost 50% of all subjects, but this was highly variable and we noted it was not uncommon to observe different configurations along the primary scan axis (e.g. internally oblique temporally and externally oblique nasally). The internally oblique border tissue configuration has been previously noted by others to be most prevalent.^{21, 30} Finally, the age range of participants in this study was very narrow, limiting our ability to investigate possible associations of age with SD-OCT derived ONH characteristics.

The main strength of this study is the large sample size and that our cohort consisted of young and healthy subjects. To the best of our knowledge this is the first study of such magnitude to quantify BMO-based parameters of the ONH and will be useful for establishing normative profiles for clinical and research purposes. Future research into other factors genetic and environmental factors affecting BMO-based parameters will help improve understanding of diseases such as optic nerve hypoplasia, optic atrophy and glaucoma.

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Legends

Figure 1: Cross-sectional image of the optic nerve head (ONH) (right) showing manual demarcation of the Bruch's membrane opening (BMO) origin (top) with a reference line connecting the two points. The corresponding position of the BMO origin, mapped on the fundus image is shown on the left. For each B-scan the intersection (if present) of this plane with the internal limiting membrane (ILM) (bottom) determined the extent of the optic cup and neuro-retinal rim (NRR). Structures above the plane and within the disc margin (DM) were defined as NRR, and below the plane, as optic cup. The BMO-based horizontal rim area (BMO-HRA) was defined as BMO disc area – cup area. Once all relevant B-scans were marked, Matlab was used to reconstruct the BMO and ILM topographies on the fundus image and compute the scaled parameters.

Figure 2: Bland-Altman plots comparing mean Bruch's membrane opening (BMO) (top), rim (middle) and cup (bottom) areas between spectral domain optical coherence tomography (SD-OCT) and Heidelberg retinal tomography (HRT) measurements. Horizontal lines are drawn at the mean difference and at the limits of agreement (LoA), defined as the mean difference ± 1.96 times the standard deviation of the differences. Ideally, the mean difference will approach zero indicating no systematic bias in the measurement techniques. Similarly, the differences in measurements should lie within the LoA 95% of the time.

Figure 3: Histogram showing the distribution of mean Bruch's membrane opening (BMO) (top), rim (middle) and cup (bottom) areas for spectral domain optical coherence tomography (SD-OCT) derived measurements, grouped by gender.

Figure 4: Scatterplot of mean Bruch's membrane opening (BMO) rim and disc areas in 1344 normal subjects. Slope of the regression line (95% CI): $\beta = 0.63$ ($p < 0.001$), $R^2 = 59.5\%$.

Figure 5: Scatterplot of mean Bruch's membrane opening (BMO) disc area and axial length in 1344 normal subjects. Slope of the regression line (95% CI): $\beta = 0.08$ ($p < 0.001$), $R^2 = 3.5\%$.

Variables	Mean (Male, Female)	Standard Deviation (Male, Female)	Range
Sex, n	692 : 652		
Age (y)	20.1 (20.1, 20.0)	0.5 (0.5, 0.4)	18.3 – 22.1
Height (cm)	172.6 (179.0, 165.8)	9.6 (7.3, 6.5)	145.0 – 199.0
Weight (kg)	73.1 (78.8, 16.4)	17.1 (67.1, 15.8)	40.8 – 176.5
BMI (kg/m ²)	25.8 (25.4, 26.2)	11.0 (9.3, 12.6)	15.4 – 51.7
Axial Length (mm)	23.6 (23.8, 23.4)	0.9 (0.9, 0.9)	20.4 – 27.9
Spherical Equivalent (D)	-0.1 (-0.1, -0.2)	1.6 (1.5, 1.6)	-11.0 – 8.1

Table 1: Patient Clinical and Demographic Information.

Table 2: Bruch's membrane opening-based optic nerve head parameter measurements for spectral domain optical coherence tomography and Heidelberg retinal tomography.

Parameter	Right	Left	p Diff. in Means*	ICC [95% CI]	SD-OCT R/L Mean [Range]	HRT R/L Mean [Range]	p Diff. in Means*
BMO Area (mm ²)	1.77 ± 0.37	1.78 ± 0.41	0.162	0.85 [0.83 - 0.87]	1.77 ± 0.38 [0.94 - 4.06]	1.92 ± 0.50 [0.86 – 4.17]	< 0.001
Cup Area (mm ²)	0.21 ± 0.24	0.21 ± 0.26	0.568	0.85 [0.84 - 0.87]	0.21 ± 0.24 [0.00 - 1.41]	0.40 ± 0.31 [0.00 – 1.73]	< 0.001
Rim Area (mm ²)	1.56 ± 0.31	1.57 ± 0.33	0.175	0.87 [0.86 - 0.88]	1.56 ± 0.31 [0.94 - 3.99]	1.51 ± 0.37 [0.76 – 4.13]	< 0.001
C/D Area Ratio	0.11 ± 0.11	0.11 ± 0.11	0.715	0.89 [0.88 - 0.90]	0.11 ± 0.11 [0.00 - 0.53]	0.20 ± 0.11 [0.00 – 0.57]	< 0.001
C/D Ratio	0.25 ± 0.20	0.25 ± 0.20	0.026	0.85 [0.83 - 0.86]	0.25 ± 0.19 [0.00 - 0.70]	0.28 ± 0.20 [0.00 – 0.79]	< 0.001
BMO Ver. Diam. (mm)	1.53 ± 0.17	1.54 ± 0.18	0.121	0.80 [0.78 - 0.82]	1.53 ± 0.17 [1.06 - 2.33]		
BMO Hor. Diam. (mm)	1.53 ± 0.17	1.53 ± 0.18	0.148	0.83 [0.82 - 0.85]	1.53 ± 0.17 [1.14 - 2.38]		
Cup Ver. Diam. (mm)	0.40 ± 0.33	0.39 ± 0.34	0.159	0.85 [0.83 - 0.86]	0.40 ± 0.32 [0.00 - 1.31]		
Cup Hor. Diam. (mm)	0.46 ± 0.36	0.45 ± 0.37	0.170	0.85 [0.83 - 0.86]	0.46 ± 0.35 [0.00 - 1.54]		
BMO Shape Factor (V/H)	1.00 ± 0.08	1.01 ± 0.08	0.002	0.64 [0.60 - 0.67]	1.01 ± 0.08 [0.77 - 1.22]		
Cup Shape Factor (V/H)	0.85 ± 0.21	0.86 ± 0.21	0.912	0.33 [0.27 - 0.39]	0.86 ± 0.16 [0.38 - 1.50]		

BMO = Bruch's membrane opening

C/D = cup/disc

*Paired t-test

ICC – Intra-Class Correlation coefficient

Table 3: Univariate and multiple regression of age, sex, ethnicity, height, mean axial length, mean spherical equivalent (SEQ) and Bruch's membrane opening (BMO)-based rim area on BMO area.

		Univariate Analyses		Multivariate Analysis	
Variable		β (95% CI)	p Value	β (95% CI)	p Value
Age (yrs)		0.03 (-0.02 - 0.07)	0.30	0.03 (0.004 - 0.064)	0.03
Sex (ref: Female)	Male	0.03 (-0.01 - 0.07)	0.18	0.001 (-0.038 - 0.037)	0.97
Ethnicity (ref: Caucasian)	Chinese	0.14 (0.05 – 0.23)	0.003	0.10 (0.04 – 0.16)	0.001
	Other	0.04 (-0.03 – 0.12)	0.21	0.06 (0.01 – 0.10)	0.02
Height (cm)		0.002 (0.000 – 0.004)	0.03	0.001 (-0.001 – 0.002)	0.57
Mean Axial Length (mm)		0.077 (0.054 – 0.099)	< 0.001	0.06 (0.04 – 0.08)	< 0.001
Mean Spherical Equivalent (D)		-0.01 (-0.03 - 0.00)	0.03	0.03 (0.01 – 0.04)	< 0.001
Rim Area (mm²)		0.94 (0.90 - 0.99)	< 0.001	0.93 (0.88 – 0.97)	< 0.001

(a)

(b)

FIG, 2a

Mean SD-OCT BMO Cup Area - Mean HRT Cup Area (mm^2)

FIG. 2b

FIG. 3a

FIG. 3b

FIG. 3c

FIG. 4